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Increased prepulse inhibition of the acoustic startle response is associated with better strategy formation and execution times in healthy males

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Abstract

Prepulse inhibition (PPI) refers to the attenuation of the amplitude of the startle reflex in response to sudden intense stimuli (pulse) if preceded by a weaker sensory stimulus (prepulse). PPI reflects the ability to filter out irrelevant information in the early stages of processing so that attention can be directed to more salient environmental features. Inhibition at this early stage of information processing appears modulated by the prefrontal cortex in a "top-down" fashion and this may account for the normal inter-individual variability in PPI and in cognitive performance.

PPI data were calculated from 82 healthy male subjects who were also tested in problem solving (Stockings of Cambridge; SoC), spatial working memory (SWM) and 5-choice reaction time (RT) tests from the Cambridge Neuropsychological Test Automated Battery. Correlations between PPI scores and cognitive test variables were examined. In addition PPI scores were divided in quartiles which were used as grouping factors in examining cognitive test performance.

Compared to individuals in the lowest quartile those in the highest had (a) shorter execution but not reaction times on the 5-choice RT, (b) shorter subsequent but not initial thinking times in the SoC where they also solved more problems correctly with the minimum number of moves, and (c) better strategy but not errors scores in the SWM.

Our findings suggest that greater PPI is associated with superior abilities in strategy formation and execution times. We suggest that this is due to more efficient early information processing.

Keywords: Sensorimotor gating; Strategic processing; Executive function; Prefrontal function; CANTAB

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1. Introduction

Prepulse inhibition (PPI) refers to the attenuation of the amplitude of the startle reflex in response to sudden intense stimuli (pulse) if preceded by a weaker sensory stimulus (prepulse). A common interpretation is that PPI reflects a general inhibitory process, termed sensorimotor gating, which involves filtering out irrelevant information in the early stages of processing so that attention can be directed to more salient environmental features (Braff et al., 1978; Braff & Geyer, 1990). PPI varies with different prepulse intensities being generally more pronounced for more intense prepulses (Graham & Murray, 1977; Schwarzkopf, McCoy, Smith, & Boutros, 1993; Blumenthal & Creps, 1994; Blumenthal, 1995), and it is most robust for 60- and 120-ms lead intervals. Graham (1975) proposed that PPI reflects automatic preattentive processes but did not exclude the possibility of higher level cognitive processes being involved. Accumulating evidence suggests that inhibition even at this early stage of information processing is indeed modulated by cognitive processes controlled in a "top-down" fashion by the cortex (Hazlett, Dawson, Schell, & Nuechterlein, 2001). This effect has been repeatedly demonstrated with different versions of "attention-to-prepulse" paradigms where subjects show increased PPI to prepulses they are instructed to attend compared to those ignored (Jennings, Schell, Filion, & Dawson, 1996; Filion, Dawson, & Schell, 1998; Schell, Wynn, Dawson, Sinaii, & Niebala, 2000). A cortical contribution is also supported by increased frontal and parietal cortical activation in human functional imaging studies using attentionally modulated (Hazlett et al., 1998, 2001) and passive PPI paradigms (Kumari et al., 2003). In the later study, functional magnetic resonance imaging was used to examine

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the neural correlates of PPI using airpuff stimuli as both the prepulse and the pulse. In healthy participants, PPI was associated with increased activation bilaterally in the striatum, extending to hippocampus and thalamus, right inferior frontal gyrus and bilateral inferior parietal lobe/supramarginal gyrus.

An additional and important characteristic of PPI is that it shows significant inter-individual variability (Hamm, Weike, & Schuoo, 2001), which has been associated with behavioral features such as novelty seeking in some but not all studies (Hutchison, Wood, & Swift, 1999; Swerdlow et al., 2002) but has not been examined in terms of possible associations with measures of executive function.

In an earlier preliminary report on 30 healthy males, we reported on the relationship between individual variability in PPI and performance on a complex reaction time test, the 5-choice reaction time (RT), and in a task of planning ability, the Stockings of Cambridge (SoC), both from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (http://www.cantab.com; Sahakian & Owen, 1992; Giakoumaki, Bitsios, & Frangou, 2006). In the 5-choice reaction time, participants have to choose on a touch sensitive screen a target stimulus out of an array of 5. Longer movement latencies are considered indicative of less efficient allocation of attentional resources and in our study movement latencies were longer the lower the PPI. In the SoC participants are asked to move a number of coloured balls to match a target pattern. Initial and subsequent thinking time reflect the time taken to plan the first and subsequent moves. Subsequent but not initial thinking time was longer the lower the PPI suggesting that individuals with lower PPI had to revise their strategy during the task. In this study we aimed to replicate and expand these preliminary findings. Here, we include a third task from the CANTAB battery, the spatial working memory (SWM) subtest to allow us to examine two further dimensions of executive function, strategy and working memory. These three tests are known to rely on the integrity and efficiency of prefrontal cortical function (Owen, Downes, Sahakian, Polkey, & Robbins, 1990; Owen, Morris, Sahakian, Polkey, & Robbins, 1996; Stuss et al., 2005). We used the same passive PPI paradigm in both studies as we specifically wanted to examine how early information processing may relate to frontally mediated cognitive functions. We chose an 80 ms prepulse–pulse interval, since longer intervals (above 100 ms) are susceptible to active selective attention effects (Filion et al., 1998; Böhmelt, Schell, & Dawson, 1999) and 80 ms intervals give more robust PPI results compared to shorter (30 and 60 ms) intervals, in the experience of our lab when a 75 dB prepulse is used. Our hypothesis was that better perceptual processing as reflected in greater PPI will be associated with enhanced performance in upstream cognitive functions.

2. Methods

2.1. Subjects

The study was approved by the Ethics Committee of the University of Crete and all participants gave their written informed consent. Participants were recruited by advertisement amongst university students based on the following criteria: male gender, right-handed, no history of any major medical or neurological disorders, no personal or family (up to second degree) history of major DSM-IV axis I disorders, no history of head trauma, no use of prescribed or recreational drugs, hearing threshold of 1 kHz >20 dB and initial startle reactivity >122 μV/U. Females were not included in order to minimize heterogeneity due to the sexual dimorphism of PPI (Aasen, Kolli, & Kumari, 2005) and its normal fluctuation during the menstrual cycle (Swerdlow, Hartman, & Auerbach, 1997). Participants were seen on a single day when all the assessments described below took place.

2.2. Clinical assessment

All participants underwent physical and psychiatric assessment using the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998) and a hearing test. All subjects completed urine toxicology screening amphetamine, cannabis, opiates, methamphetamine, benzodiazepines, barbiturates and cocaine.

2.3. Startle and PPI measurements

A commercially available electromyographic startle system (EMG SR-LAB, San Diego Instruments, San Diego, CA, USA) was used to examine the eyeblink component of the acoustic startle response. Acoustic stimuli were administered binaurally through headphones (model TDH-39-P, Maico Minneapolis, MN).

Electromyographic recordings were taken while subjects were seated comfortably in an armchair, instructed to relax and stay awake. The eyeblink component of the startle reflex was indexed by recording EMG activity of the orbicularis oculi muscle directly beneath the right eye, by positioning two miniature silver/silver chloride electrodes filled with Signa gel electrolyte paste (Parker Laboratories Inc., New Jersey, USA). The ground electrode was attached behind the right ear on the mastoid. Resistance was kept lower than 10 kΩ. EMG activity was band-pass filtered (100–1000 Hz) and 60-Hz notch filtered, digitized, and 250, 1 ms readings, were recorded starting at startle stimulus onset. A background of 70 dB broadband white noise was present throughout the recording period. Pulses consisted of 40 ms 115 dB white noise tones and prepulses consisted of 20 ms 75 dB white noise tones presented at a 80 ms lead interval, over a 70 dB background noise. We chose a weak prepulse (75–5 dB above background) on the basis of its putative ability to discriminate better than an intense prepulse between subjects with different levels of startle inhibition by a prepulse. The recording period began with a 3 min acclimation period in which the background noise was present. The recording period consisted of 18 trials. The inter-trial interval varied between 15 and 25 s (average 20 s). The total length of recording was approximately 9 min. There were six pulse-alone trials at the beginning of the recording session, in order to elicit the acoustic startle response and the average of the six responses was used to determine initial startle reactivity. These were followed by six pulse-alone trials (baseline startle) and six prepulse–pulse trials in a pseudorandom order. Peak startle amplitude within 150 ms from the startling stimulus was determined. Trials with excessive baseline activity in the 20 ms prior to stimulus delivery were excluded to minimize the possible impact of voluntary and spontaneous eyeblink activity on startle measures (Graham, 1975). Subjects were excluded if they had more than one-third of total trials (6 out of 18) discarded or if they had three or more (out of six) prepulse–pulse trials discarded. Based on these criteria, four subjects were excluded because of PPI measures rendered unreliable due to many excluded trials. In the remaining sample of 82 subjects, less than 3% of all trials were excluded based on these criteria and no subjects had more than one (out of six) prepulse–pulse trials discarded.

2.4. Cognitive assessment

We used three subtests of Cambridge Neuropsychological Test Automated Battery (CANTAB) (Sahakian & Owen, 1992) namely, 5-choice reaction time (5-choice RT), Stockings of Cambridge (SoC) and spatial working memory (SWM). These are non-verbal tests which were administered with the aid of a high-resolution touch-sensitive screen (Advantech) and/or a response key to all subjects in the same order.

The SWM tests spatial working memory and spatial strategy (Owen et al., 1990). Subjects are required to search through an increasing number (two, three, four, six, and eight) of boxes shown randomly arranged on the screen, until they find a single token that, at any one time, is hidden in one of the boxes. The key instruction is that once a token has been found within a particular box, then that box should never be used again to hide a token. On each trial, every box is used once to hide a token such that the total number of tokens to be found corresponded to the number of boxes on the screen. Errors are scored according to the number of occasions on which a subject returns to open a box in which a token has already been found. An efficient strategy for completing this task is to follow a predetermined search sequence, beginning with a particular box and then returning to start each new sequence with that same box as soon as a token has been found. The extend to which this repetitive searching pattern is used as a strategy for approaching the problem is estimated from the number of search sequences starting with the same box, within each of the more difficult 6- and 8-box problems. The total of these scores provides a single measure of strategy for each subject, with a high score (many sequences beginning with a different box) representing low use of the strategy and vice versa.

The SoC is a modified, computerized version of the Tower of London (Owen et al., 1990; Owen, Sahakian, Semple, Polkey, & Robbins, 1995). Subjects are asked to compare two different arrangements of "balls" in "socks" (one presented on the top half of the screen, the other on the bottom) and rearrange, in the minimum possible number of moves, the balls in the lower half of the screen such that their positions match the target arrangement in the upper half. The test presents the subject with easy 2- and 3-move and harder 4- and 5-move problems. Subjects are asked to plan the complete sequence of moves required to solve the problem prior to their first move. Initial thinking time (ITT) prior to execution of the first move, subsequent thinking time (STT) for the execution of all subsequent moves, and problems solved in minimum moves are recorded. Poor performance in this test is usually revealed for the difficult 3-, 4- and 5-move problems; it translates into shorter ITT (less time planning), and/or longer STT (more time executing the solution) with more mean moves and less perfect solutions.

The 5-choice RT measures visual attention (Chari, Shaw, & Sahgal, 1996) in trials where subjects must release a home button (reaction time) and then touch whichever of five target stimuli has been indicated on the touch-screen (movement time). Outcome measures used were 5-choice reaction (i.e. the time taken to release the home button) and movement latencies (i.e. the time taken from button release to screen touch).

2.5. Data analysis

Percentage PPI (%PPI) was calculated using the formula $[(\text{Amplitude}_{\text{pulse-alone}} - \text{Amplitude}_{\text{prepulse–pulse}})/\text{Amplitude}_{\text{pulse-alone}}] \times 100$. With the exception of 5-choice reaction time, the distribution of all the other neuropsychological outcome variables deviated from normality based on the Kolmogorov–Smirnov test. PPI scores were divided in quartiles, which were used as grouping factors in examining cognitive test performance using ANOVA or the Kruskal–Wallis tests as appropriate. Since group comparisons were planned and hypothesis driven we did not consider Bonferroni correction of the threshold of statistical significance was necessary. Significant findings were followed-up by pair-wise group comparisons using the Mann–Whitney test. Correlations between %PPI and cognitive outcome variables were examined using spearman's or pearson's correlation coefficients as appropriate.

3. Results

Eighty-two participants were included out of the 98 who volunteered. Twelve subjects were excluded because of positive urine drug screens and four on the basis of excessive EMG baseline activity. Forty-eight participants were non-smokers and 34 smoked 10–20 cigarettes a day. All subjects were regular caffeine (1–2 cups/day) and occasional alcohol consumers (<4 units/week). Table 1 shows the profile of the PPI groups following quartile splits. There were no group differences in initial startle reactivity, baseline startle, age, years of education, body weight and smoking status.

Pearson correlation coefficients between %PPI, baseline startle, initial reactivity showed expected correlations between baseline startle and initial startle reactivity ($r = 0.84$, $p < 0.001$). PPI was unrelated to initial startle reactivity or baseline startle ($r = 0.09$ and 0.08, respectively, $p > 0.1$).

Table 1
Mean (±S.D.) %PPI, initial reactivity, baseline startle, and age, years of education, body weight and smoking status for each group following quartile splits

	Quartile 1 (lowest PPI group) (*n* = 20)	Quartile 2 (*n* = 21)	Quartile 3 (*n* = 21)	Quartile 4 (highest PPI group) (*n* = 20)	*F*-value	*p*-value
%PPI_75	−21.19 ± 31.43	14.99 ± 05.15	29.51 ± 05.81	57.20 ± 14.82	68.95	=0.000
Initial reactivity (μV)	371.36 ± 233.65	329.81 ± 221.84	326.54 ± 169.55	420.60 ± 179.75	<1	>0.1
Baseline startle (μV)	298.80 ± 236.65	276.52 ± 237.99	254.02 ± 159.99	318.51 ± 181.65	<1	>0.1
Age (years)	23.60 ± 03.94	23.19 ± 03.37	24.57 ± 03.49	23.90 ± 04.28	<1	>0.1
Education (years)	16.16 ± 02.54	16.05 ± 02.72	17.32 ± 03.24	16.37 ± 02.52	<1	>0.1
Body weight (kg)	82.58 ± 10.13	77.91 ± 07.82	81.68 ± 09.31	80.16 ± 09.83	01.02	>0.1
Smokers/non-smokers	8:12	10:11	9:12	10:10		

Table 2
Mean (±S.D.) of the cognitive performance scores of each neuropsychological test in the four percentile PPI groups

	Quartile 1 (*n* = 20)	Quartile 2 (*n* = 21)	Quartile 3 (*n* = 21)	Quartile 4 (*n* = 20)
Spatial working memory test				
Strategy	31.22 ± 04.02	31.81 ± 04.76	30.24 ± 04.79	27.95 ± 04.76
Total errors	11.22 ± 11.43	13.33 ± 13.81	12.52 ± 12.31	10.80 ± 13.73
Stockings of Cambridge test				
Mean initial thinking time (ms)	8663.28 ± 4735.17	8049.37 ± 5058.07	7775.89 ± 3456.23	6043.68 ± 2975.55
Mean sub thinking time (ms)	1230.10 ± 1221.87	978.76 ± 1691.95	579.98 ± 532.45	472.02 ± 420.79
Problems solved in minimum moves	08.89 ± 01.99	09.57 ± 01.57	09.76 ± 01.61	10.60 ± 01.27
Reaction time test				
5-Choice movement time	382.21 ± 76.58	381.59 ± 79.17	344.20 ± 73.91	309.55 ± 77.61
5-Choice reaction time	343.73 ± 56.96	336.11 ± 46.32	333.86 ± 45.63	344.29 ± 38.35

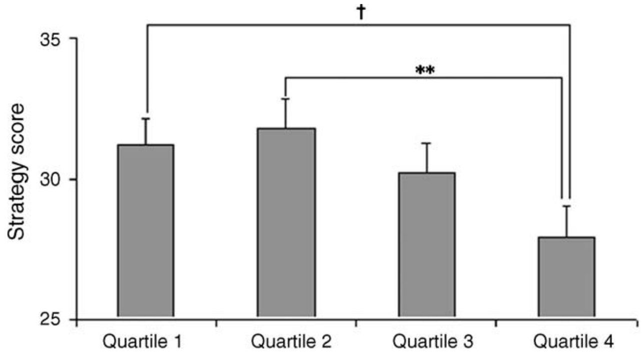

Fig. 1. Strategy scores from the SWM test across the four groups following quartile splits on PPI scores. Columns represent group means and bars represent S.E.M. Pair-wise group comparisons were performed using the Mann–Whitney test. $^{\dagger}p = 0.08$; $^{**}p = 0.007$.

The means and standard deviations of the cognitive performance scores of each neuropsychological test in the four percentile PPI groups are shown in Table 2.

3.1. SWM test

In the entire group, %PPI correlated negatively with strategy ($\rho = -0.27$, $p = 0.01$) but not total errors score ($\rho = -0.07$, $p = 0.49$). There were significant group differences in strategy score (Kruskal–Wallis $x^2 = 7.48$, d.f. = 3, $p = 0.05$) but not error scores (Kruskal–Wallis $x^2 = 0.43$, d.f. = 3, $p = 0.93$). Pair-wise group comparisons using Mann–Whitney revealed that strategy score of the quartile with the highest PPI (quartile 4) was significantly smaller from strategy score of quartile 2 while its difference from quartile 1 was at a trend level (see Fig. 1 and legend).

3.2. SoC test

In the entire group, %PPI correlated negatively with subsequent thinking time ($\rho = -0.31$, $p = 0.004$) and positively with the number of problems solved in minimum moves ($\rho = 0.35$, $p = 0.001$). There was no correlation with initial thinking time ($\rho = -0.17$, $p = 0.12$). There were significant group differences in subsequent thinking time (Kruskal–Wallis $x^2 = 7.95$, d.f. = 3, $p = 0.04$) and the number of problems solved in minimum moves (Kruskal–Wallis $x^2 = 8.81$, d.f. = 3, $p = 0.03$) but not initial thinking time (Kruskal–Wallis $x^2 = 5.97$, d.f. = 3, $p = 0.11$). Pair-wise group comparisons revealed that subsequent thinking time of the quartile with the lowest PPI (quartile 1) was significantly longer from the quartiles with the highest PPI (quartiles 3 and 4) (see Fig. 2 and legend). These comparisons also revealed that the highest PPI quartile 4 had significantly more problems solved correctly with minimum moves compared to quartiles 1 and 2 (see Fig. 2 and legend).

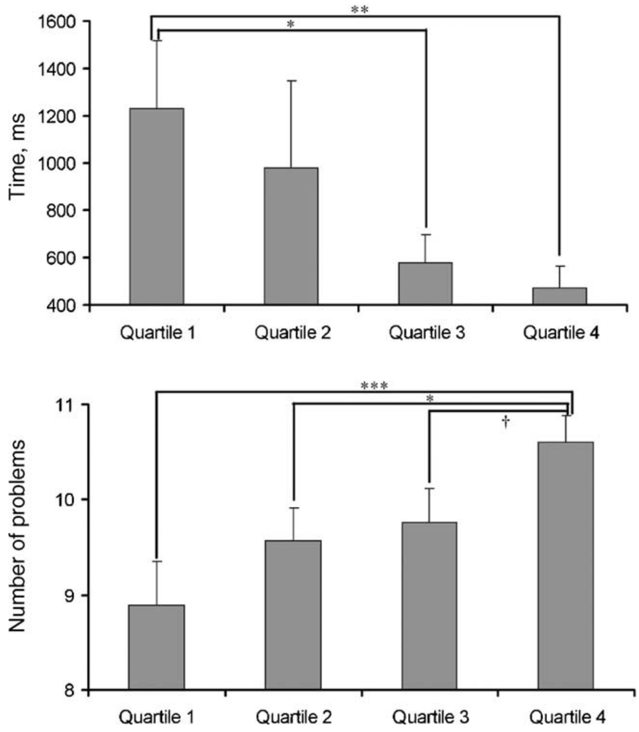

Fig. 2. Subsequent thinking times (top) and problems solved correctly in the minimum moves (bottom) from the SoC test across the four groups following quartile splits on PPI scores. Columns represent group means and bars represent S.E.M. Pair-wise group comparisons were performed using the Mann–Whitney test. $^{***}p = 0.006$; $^{**}p = 0.009$; $^{*}p = 0.03$; $^{\dagger}p = 0.097$.

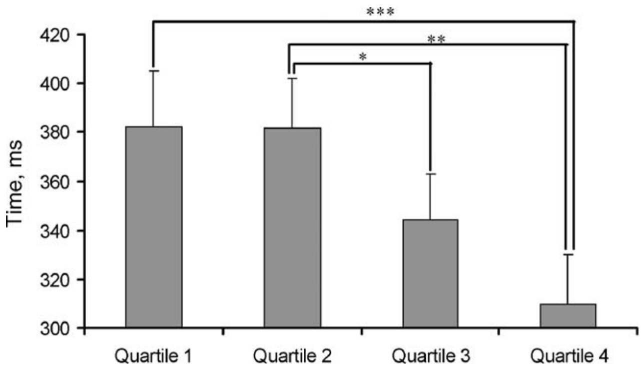

Fig. 3. 5-Choice movement time from the RT test across the four groups following quartile splits on PPI scores. Columns represent group means and bars represent S.E.M. Pair-wise group comparisons were performed using the Mann–Whitney test. $^{***}p = 0.009$; $^{**}p = 0.01$; $^{*}p = 0.027$.

3.3. RT test

In the entire group, %PPI correlated negatively with 5-choice movement time ($\rho = -0.40$, $p = 0.002$) but there was no correlation with reaction time ($r = -0.09$, $p = 0.51$). There were significant group differences in 5-choice movement (Kruskal–Wallis $x^2 = 10.99$, d.f. = 3, $p = 0.01$) but not reaction time ($F < 1$). Pair-wise group comparisons revealed that 5-choice movement time of the quartile with the highest PPI (quartile 4) was significantly shorter from the quartiles with the lowest PPI (quartiles 1 and 2) and also that 5-choice movement time of quartile 3 was shorter from that of quartile 2 (see Fig. 3 and legend).

4. Discussion

We found that in healthy males, increased PPI indexed better strategy formation and execution time. Specifically, in the

SWM task individuals' ability to form appropriate search strategies became better the higher their PPI. No association was found for error scores, which index individuals' working memory function. This finding is particularly interesting in the light of the findings of Owen et al. (1996) of a double dissociation between memory and "executive" function in working memory tasks in patients with specific brain lesions. Frontal lobe lesions produced significant impairment in patients' ability to generate search strategies, even at the least challenging level of task difficulty and this impairment was found to relate to the inefficient use of a particular searching strategy while patients who had temporal lobe lesions or had undergone amygdalo-hippocampectomy showed significant working memory deficits that were unrelated to any particular searching strategy.

In the SoC higher PPI was associated with shorter subsequent thinking times and more problems solved with the minimum number of moves. No association was found with initial thinking time. Relative prolongation of subsequent but not initial thinking time may reflect either a tendency to act before a plan is fully formed or to produce less efficient strategies (Owen et al., 1990). Consequently participants with lower PPI may need to pause during the task to reassess their solutions. As shown by Owen et al. (1990) as well as Newman, Carpenter, Varma, and Just (2003), complex (trials involving moves of 3 and above) but not simple problem solving depends on the integrity of the frontal lobes and therefore our findings suggest that a higher level of PPI is associated with more effective prefrontal function.

Lower PPI subjects were also generally slower than higher PPI subjects in their 5-choice movement but not in 5-choice reaction time in the RT task. In the 5-choice RT, reaction time indexes initiation of movement and can be seen as conceptually similar to initial thinking time in the SoC. Movement time refers to execution time (from movement initiation until target selection) and is considered to reflect the efficiency of allocation of attentional resources in this complex visual task. If lower PPI reflects a relative inefficiency in information processing (noise versus target stimulus) then the increased execution time may represent an adaptive mechanism to prevent responding to noise (Stuss et al., 2005).

Our results suggest that improved earlier information processing as indexed by greater PPI is associated with superior abilities in strategy formation and associated execution times. Passive PPI is considered a measure of early, preattentive perceptual processing. The observed association between PPI levels and strategic rather than simple perceptual processing is open to two interpretations. Efficient perceptual processing may facilitate associative upstream transformation of sensory inputs and their integration into optimal plans of action. Alternatively, "top-down", inattentive control of early perceptual processing may be part of efficient strategy formation and may reflect enhanced prefrontal function. It is not possible to distinguish between these two interpretations based on the data presented here. To examine this further we plan to examine the relationship between higher cognitive function and PPI to very short lead intervals (<60 ms) considered purely "preattentive" as well as longer intervals (between 500 and 1200 s) that are thought to engage higher cognitive functions such as sustained (Dawson, Schell, Swerdlow, & Filion, 1997) or selective attention (Anthony, 1985). In addition, we propose to investigate whether individuals with superior strategy functions also produce higher PPI in "attention-to-prepulse" paradigms.

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