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Relationship of prepulse inhibition of the startle reflex to attentional and executive mechanisms in man

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Abstract

Prepulse inhibition (PPI) of the startle reflex at short lead intervals is thought to reflect the operation of a preattentive "sensorimotor gating" mechanism, which suggests that processing of the prepulse stimulus should not be modulated prior to its inhibitory effects on startle. To test this hypothesis, we examined whether PPI is affected following habituation to the prepulse. PPI was measured in two sessions associated with either the presence (habituation condition) or the absence (control condition) of prepulse repetition. There was a trend for prepulse repetition to reduce the effectiveness of that prepulse in inhibiting the startle response. We also explored the relationship of PPI to scores in tests of selective and sustained attention and planning ability. Overall PPI performance was correlated to performance indices of planning ability and there was a trend level correlation with scores in selective but not sustained attention tests. These preliminary results merit further investigation.

Keywords: Prepulse inhibition; Startle reflex; Habituation; Stroop; CANTAB; Healthy humans

1. Introduction

The startle reflex consists of contraction of the skeletal and facial musculature in response to a sudden intense stimulus, e.g. a loud noise. The startle reflex is a primitive, cross-species reflex mediated by a pontine-based, ear-to-spinal outflow, simple neural circuit that has been specified in animals by the work of Davis and colleagues (Lee et al., 1996). The blink reflex component of the startle response is a convenient measure of startle in man and refers to the electromyographic response of the orbicularis oculi muscles in response to a sudden intense stimulus (e.g. a loud noise) (Graham, 1975; Braff et al., 1978). It is well established that the amplitude of the startle reflex response is attenuated when the strong startle-eliciting stimulus is preceded 30–500 ms by a weaker stimulus, or prepulse. This phenomenon is termed prepulse inhibition (PPI) and has been observed across a wide range of stimulus intensities and modalities in animals (Hoffman and Ison, 1980,

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1992) and humans (Graham, 1975; Filion et al., 1998 for review). PPI varies with different prepulse intensities being generally more pronounced for more intense prepulses (Graham and Murray, 1977; Schwarzkopf et al., 1993; Blumenthal and Creps, 1994; Blumenthal, 1995), and it is most robust for 60- and 120-ms lead intervals (i.e. when the prepulse precedes the pulse stimulus by 60 or 120 ms). Graham (1975) proposed that PPI reflects the operation of an automatic preattentive sensory gating process that momentarily protects the processing of the prepulse from distractions such as a startling loud sound. PPI of the startle reflex is thus used as an operational neurobiological measure of a central process termed "sensorimotor gating" (Swerdlow et al., 1992).

The operation of a preattentive sensory gating mechanism is assumed to precede any general or selective attentional process, and thus there should be no attentional selection of sensory information for further processing prior to the operation of such a mechanism (Deutch and Deutch, 1964). Therefore, if the phenomenon of PPI reflects the operation of a preattentive "sensory gating" mechanism, independent from a selective attentional mechanism, then processing of the prepulse stimulus should not be modulated prior to its inhibitory effects on startle. Consequent to this idea is the hypothesis that PPI of the startle reflex should not diminish with prepulse habituation. Indeed, animal (Wu et al., 1984; Ison et al., 1973; Russo et al., 1975; Hoffman et al., 1969) and human [Abel et al., 1998; Lipp and Krinitzky, 1998; Schell et al., 2000] studies showed that repetitive preexposure to a prepulse does not produce any observable habituation of PPI of the startle reflex.

In the above studies, startle was measured over intermixed blocks of trials consisting of the startle stimulus alone and of the startle stimulus preceded by the prepulse, either following extended repetition of the prepulse or not. It is possible that habituation of PPI at the end of the phase of preexposure to the prepulse may have dissipated as a result of presentations of the startle stimulus (itself a potent dishabituating stimulus) at test. Gewirtz and Davis (1995) minimised the potential impact of dishabituation over the course of testing for PPI, using a relatively small number of startle stimuli presented at long regular intervals, interspersed among a much larger number of auditory prepulse-alone stimuli. These procedures unmasked a reduction of the effectiveness of an auditory prepulse in inhibiting the startle response, leading to the conclusion that PPI in the rat, is subject to the influences of general attentional mechanisms. The primary aim of this study was to examine whether PPI in human subjects, could habituate as a result of prepulse repetition, using a protocol based on the optimal procedures mentioned above.

The dominant theoretical interpretations of the phenomenon of PPI, at least at short lead intervals, is that it reflects (a) a "low-level" inhibitory mechanism that serves to protect processing of the prepulse (Graham, 1975) and also (b) a more general inhibitory process (sensorimotor gating). The latter is regarded as a critical component for intact cognitive processing that involves filtering out irrelevant sensory, motor, and cognitive information in the early stages of information processing (Braff and Geyer, 1990). Despite these widely accepted theoretical interpretations, the study of the relationship between PPI and more specific aspects of cognitive processing in normal subjects has received little empirical attention to date. One approach has been the investigation of the relationship of PPI to other measures of cognition, which share a similar "inhibition-based" theoretical interpretation. Indeed, such studies comparing PPI with the backward masking and negative priming (measures reflecting low-level inhibitory processes) and with the Wisconsin Card Sorting Test and Ego Impairment Index (neuropsychological and clinical measures reflecting high-level inhibitory processes) reveal several intriguing similarities (see Filion et al., 1999 for a review of this evidence). However, there are also important differences, which weaken the argument of a shared, common underlying inhibitory process (for a review of this evidence, see Filion et al., 1999) and leave this issue still inconclusive.

A secondary aim of this study was therefore to collect preliminary empirical evidence about the relationship of PPI to behavioral measures of attention, which are "inhibition-based" (Stroop Interference Test) and others, which are not (Rapid Visual Information Processing test) in the same group of normal subjects. This aim also extends in the collection of preliminary empirical evidence about the relationship of PPI to planning ability, a measurable aspect of cognition, central to many aspects of

complex behavior with which startle inhibition may share a common neurophysiological basis (see below). The Stroop colour/word Interference task requires the subject to inhibit the (habitual) response to the semantic value of the word and to (selectively) attend to its colour content, thus probing inhibition of habitual responses and attentional selection of processing (Mesulam, 1985; Bamford et al., 1989; McLeod, 1991; Laplante et al., 1992). Besides the possibility that both PPI and the Stroop task share a common underlying inhibitory mechanism, there is another reason for Stroop performance to correlate with PPI. Subjects with the best ability for attentional selection in the Stroop task may be more prone to attentional selection of the prepulse and thus more likely to present with greater startle inhibition. Clearly, attentional selection of the prepulse can increase PPI (Dawson et al., 1993, 2000; Filion et al., 1993, 1994; McDowd et al., 1993; Jennings et al., 1996; Hazlett et al., 1998; Schell et al., 1995, 2000), although this attentional selection to the prepulse is not necessary for PPI to occur (Blumenthal, 1999). On the other hand, the Rapid Visual Information Processing (RVIP) is a test that reflects the ability to sustain the function of the allocated processing resources to the task-at-hand, based more on the premises of alertness and vigilance (Sahakian et al., 1989) rather than an inhibitory mechanism and it is not therefore expected to relate with PPI. Finally, several lines of evidence suggest that similarly to the Wisconsin Card Sorting Test (Butler et al., 1991), there is a possible relationship between cognitive planning and PPI as they both depend on frontal lobe integrity, thus raising the possibility that both measures share a common underlying neurophysiological basis (see Filion et al., 1999 for discussion of this argument). Indeed, planning ability is impaired in groups of patients known for their PPI deficits [schizophrenia (Morris et al., 1995; Pantelis et al., 1997; Rushe et al., 1999; Joyce et al., 2002) and other frontostriatal syndromes (see Owen, 1997 for review)]. Functional neuroimaging studies in normal controls have shown that the frontal lobes are critically involved in planning behavior in these tests (see Owen, 1997 for review). Converging evidence from preclinical (see Koch and Bubser, 1994; Swerdlow et al., 1995a) and clinical studies (Hazlett et al., 1998; Hazlett and Buchsbaum, 2001; Hazlett et al., 2001) support the importance of the functional integrity of the prefrontal cortex to PPI modulation.

2. Methods

2.1. Subjects

Twenty male subjects, all medical students, were recruited. Following oral and written information and demonstration of apparatuses, each volunteer underwent a physical and psychiatric screen using the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998) and a hearing test and gave their written informed consent. Exclusion criteria were history or presence of major medical illnesses, major past or current axis I disorders, past or current neurological disorders, head trauma, use of prescribed or recreational drugs, hearing threshold at 1 kHz >20 dB[A]. None of the subjects were excluded based on the above criteria; however, four subjects were excluded based on a startle response of less than 50 units (122 μV) as assessed in the preliminary session (see Procedure). The remaining 16 subjects (20–36 years, mean age±S.D.: 26.9±4.6) participated in the study. All were right-handed and had estimated IQs (derived from Raven's Standard Progressive Matrices) >130. Nine subjects were non-smokers, three smoked less than 10 cigarettes a day, and four smoked 15–20 cigarettes a day. Subjects were regular caffeine and occasional social alcohol consumers. The study was approved by the Ethics Committee of the University of Crete.

2.2. Materials

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. The equipment and methodology used for testing the acoustic startle response in humans has been described in detail elsewhere (Braff et al., 1992). Acoustic stimuli in all sessions were administered binaurally through headphones (model TDH-39-P, Maico, Minneapolis, MN). Acoustic startle (pulse) stimuli at all times consisted of 50-ms bursts of 115 dB[A] broadband noise with nearly instantaneous rise

time (0.2–1 ms) over a continuous background noise of 69 dB[A]. Prepulses consisted of 20 ms bursts of 82 dB[A] white noise (i.e. 13 dB[A] above background) with nearly instantaneous rise time (0.2–1 ms). Prior to the presentation of any stimuli, there was a 5-min acclimation period of 69 dB background noise, which continued throughout the session.

2.3. Procedure

Initially, all 20 subjects participated in a preliminary session used for training, matching and neuropsychological testing. First, five acoustic startle-eliciting stimuli were administered the average of which was used to determine initial startle reactivity. Any subjects presenting with a startle reactivity of less than 50 digital units were excluded at this point. As mentioned above (see Subjects), four subjects were excluded due to this criterion. Previous startle habituation studies have shown that PPI decreases as startle response habituates (Blumenthal, 1996, 1997; Lipp and Krinitzky, 1998), an effect linked to the "law of initial values" (Wilder, 1976; Blumenthal, 1997). With this conservative definition of startle responders (initial reactivity <50 digital units), we tried to obviate an unwanted floor effect later in the experimental sessions, and enhance sensitivity in detecting a genuine prepulse repetition-related reduction of PPI. Following assessment of initial startle reactivity and exclusion of four "non-responders", the remaining 16 subjects received a block of three pulse-alone and three prepulse-pulse stimulus trials in a randomised order, to calculate PPI of the startle reflex. The 16 subjects were then assigned to two groups (A and B) of eight subjects each, with similar group mean levels of startle and PPI using a "rolling average" strategy (Swerdlow et al., 2001). The two matched groups were then allocated to sessions/conditions according to a balanced, cross-over, single-blind design. This session ended with subjects performing the neuropsychological tests (see Neuropsychological testing).

One to three days later, each one of the two matched groups of subjects participated in two 50-min testing sessions 10 days apart, having been instructed to maintain their normal patterns of caffeine and nicotine consumption based on reported effects of caffeine (Swerdlow et al., 2000) and nicotine withdrawal (Kumari and Gray, 1999) on PPI. One session was associated with the elicitation of the acoustic startle response at regular intervals, interspersed among a much larger number of prepulse alone stimuli (habituation condition), and the other with identical elicitation of the acoustic startle response at regular intervals, interspersed among background noise alone (control condition). The two groups, A and B, differed only in the order in which they were exposed to the two conditions.

Fig. 1 represents diagrammatically the sequence of stimulus presentations and the inter-stimulus intervals across time. In order to establish a steady baseline of startle, subjects received 10 startle stimuli presented at regular 15 s intervals prior to any test for PPI. Following this, the 16 subjects received eight identical pairs of startle stimuli presented at regular intervals (see Fig. 1). One startle stimulus of each of the eight pairs was preceded by the auditory prepulse (at a 50 ms interstimulus interval) and the other was not. For half of the subjects (four subjects from group A and four subjects from group B), the first startle stimulus of each of the eight trial pairs was always preceded by the auditory prepulse and the second was not, and the reverse stimulus sequence was true for the remaining half of subjects. Counterbalancing the stimulus sequence within-subject would have required each subject to be exposed to each one of the two conditions (habituation and control) twice. This would increase the number of sessions to four (two for each condition), thus increasing the risk for an unwelcome learning effect resulting in within- and possibly even between-session habituation of the startle response. Fig. 1 shows that, following the first startle stimulus of the first trial pair, subjects received repeated presentations of the auditory prepulse during the session associated with the habituation condition. Fifteen prepulse stimuli were presented between each pair of startle stimuli and three prepulse stimuli were presented between the two startle stimuli of a pair. The prepulses were presented at irregular intervals with a mean interstimulus interval of 15 s. This procedure was continued until the final pair of startle stimuli had been presented. Therefore, the session associated with the habituation condition contained a total of 126 presentations of the auditory prepulse alone. The only difference between the habituation and the control condition was the auditory prepulse

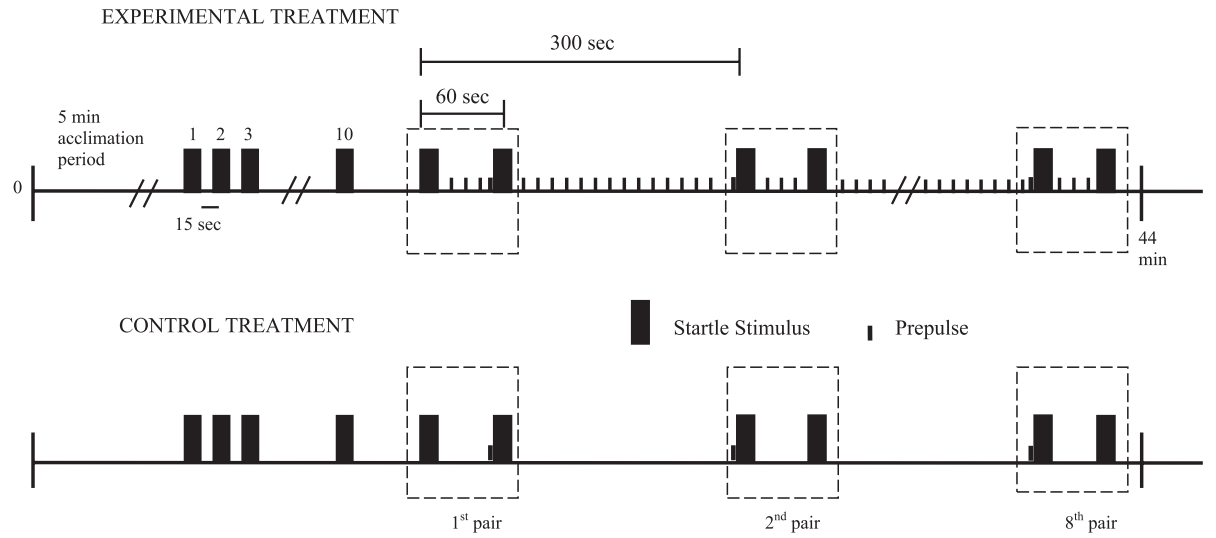

Fig. 1. Diagrammatic representation of procedures for testing of prepulse inhibition.

repetition in the habituation condition, vs. background noise alone in the control condition.

2.4. Neuropsychological testing

2.4.1. Stroop Interference Test (SIT)

The standardised version of this test was used (Golden, 1978). The administration and scoring procedures are described in detail elsewhere (Bondi et al., 2002). Briefly here, subjects were asked in three consecutive 45-s periods, first to read the names of colours written in black ink, then to name the colour of patterns and, finally, to identify the colour of ink that is mismatched to a word (e.g. the word *red* printed in blue ink is identified as *blue*). These procedures result in a Word (W), a Colour (C) and a Colour–Word (CW) score. The increase in time taken to identify the colour of the incongruent word list results in fewer correct responses in the 45-s period and is referred to as Stroop *interference*. Interference scores were calculated as the difference between the C–CW scores. The greater the C–CW difference, the greater the interference effect and the worse the performance in this test.

2.4.2. CANTAB tests

Cambridge Neuropsychological Test Automated Battery (CANTAB) is a set of neuropsychological test batteries developed by Robbins, Sahakian and co-workers (Morris et al., 1986) and standardised in a large group of normal subjects (Robbins et al., 1994; 1998). The tests in these batteries are non-verbal, administered with the aid of a high-resolution touch-sensitive screen (Advantech), with continuous and sensitive adjustment of levels of difficulty, obviating floor and ceiling effects. Their administration has been extensively described elsewhere (Owen et al., 1990, 1991, 1993). The CANTAB tests employed were:

Rapid Visual Information Processing (RVIP). Subjects were asked to detect consecutive target sequences of digits presented at the rate of 100 digits per minute for 4 min and responses are registered by a button press. Main performance measures include: total hits (number of targets correctly detected), total misses (number of undetected targets), total false alarms (number of responses made in the absence of targets). From these, calculations of sensitivity (A′ : tendency to detect target sequences) and response bias (B″ : tendency to respond regardless of target sequence) are possible, derived from Signal Detection Theory (Sahgal, 1987, Swets, 1996), which take both hit probability and false alarms into consideration.

Stockings of Cambridge (SoC). This is a modified, computerized version of the Tower of London (Owen et al., 1990). Subjects were 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 two- and three-move and harder four- and five-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, as well as number of moves required by the subjects to rearrange the balls, and problems solved in minimum moves were recorded. Poor performance [e.g. in hypofrontality (Joyce et al., 2002)] in this test is usually revealed for the difficult four- and five-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 opposite is true for high performance in this task.

2.5. Data reduction and analysis

The EMG signal from two subjects was corrupted due to equipment failure during recording and for this reason, data reduction and analysis refer to the remaining 14 subjects. To assess changes in startle behaviour over the course of a session, the mean startle amplitude on startle stimulus-alone trials and prepulse-startle stimulus trials was calculated for the group of 14 subjects. The differences between startle stimulus-alone and prepulse-startle stimulus trials were calculated separately for each pair of startle responses that were separated by 60 s. PPI was defined as %change from baseline (%PPI) using the standard formula [(startle stimulus-alone−prepulse-startle stimulus)/startle stimulus-alone)]×100. Data from the first four and the last four trial pairs of the session associated with the habituation condition were collapsed into two blocks (one block for the first and one block for the last half of the session). Data from the session associated with the control condition were also collapsed in an identical manner. A mixed-model, three-way analysis of variance (ANOVA), with the order in which subjects were exposed to the two conditions as a between-subject factor, and condition and block as within-subject factors, were used to analyse the collapsed startle stimulus-alone and %PPI data. Similarly to the study of Gewirtz and Davis (1995), PPI was also defined as the raw difference in startle response amplitude between startle stimulus-alone and prepulse-startle stimulus trials, which entered a separate analysis of variance with the same factorial design as above. Because raw PPI may depend on variations in startle response amplitude in the startle stimulus-alone trials, we controlled for the latter with analysis of covariance of the raw PPI data taking the startle stimulus-alone data as the covariate. Pearson correlation coefficients were used to explore the relationships between %PPI and neuropsychological test scores.

3. Results

The mean scores on startle stimulus-alone and prepulse-startle stimulus trials and PPI expressed as the difference between the two scores (raw PPI) as

Table 1
Data summary of startle reflex

Session segment	First half		Last half		Entire session	
	H	C	H	C	H	C
Startle stimulus	96.9 (14.2)	100.6 (12.9)	87.6 (11.7)	99.3 (17.7)	92.2 (12.7)	100.0 (14.5)
Prepulse-startle	61.6 (10.2)	72.3 (12.2)	83.0 (15.3)	64.7 (10.6)	72.3 (12.2)	68.5 (11.0)
Raw PPI	35.3 (07.3)	28.3 (05.4)	04.6 (07.6)	34.6 (11.3)	19.9 (05.3)	31.5 (06.7)
%PPI	29.7 (05.1)	23.2 (07.0)	02.2 (12.3)	20.7 (05.9)	13.4 (06.2)	21.4 (05.2)

H: habituation condition; C: control condition.
Mean amplitudes (±S.E.M.) of startle stimulus alone, prepulse-startle stimulus trials and PPI expressed as their differences and %, per segment of session.

well as %change from baseline (%PPI) are shown in Fig. 2 and Table 1.

Since within each trial pair, half of the subjects always received the startle stimulus-alone trial first followed by a prepulse-startle stimulus trial and this sequence of stimuli was reversed for the other half of the subjects, we checked for an effect of stimulus sequence on startle amplitude in the pulse alone trials. However, a mixed-model ANOVA with stimulus sequence (two levels) as the between- and condition and block as the within-subject factors did not reveal any significant main effects or interactions (all F's<2, all p values >0.1). Analysis of variance of the startle stimulus-alone data from the group of 14 subjects, with the order in which they were exposed to the two conditions as the between- and condition and block as the within-subject factors, showed no significant order (F=1.06, df=1,12; p>0.1), condition (F=2.17, df=1,12; p>0.1) or block (F=1.35, df=1,12; p>0.1) main effects and no significant interactions [order×condition: F=2.02, df=1,12; p>0.1, order×block: F<1, condition×block: F<1, order×condition×block: F=2.31, df=1,12; p>0.1).

Fig. 2 shows that PPI was less pronounced in the habituation compared to the control condition, and

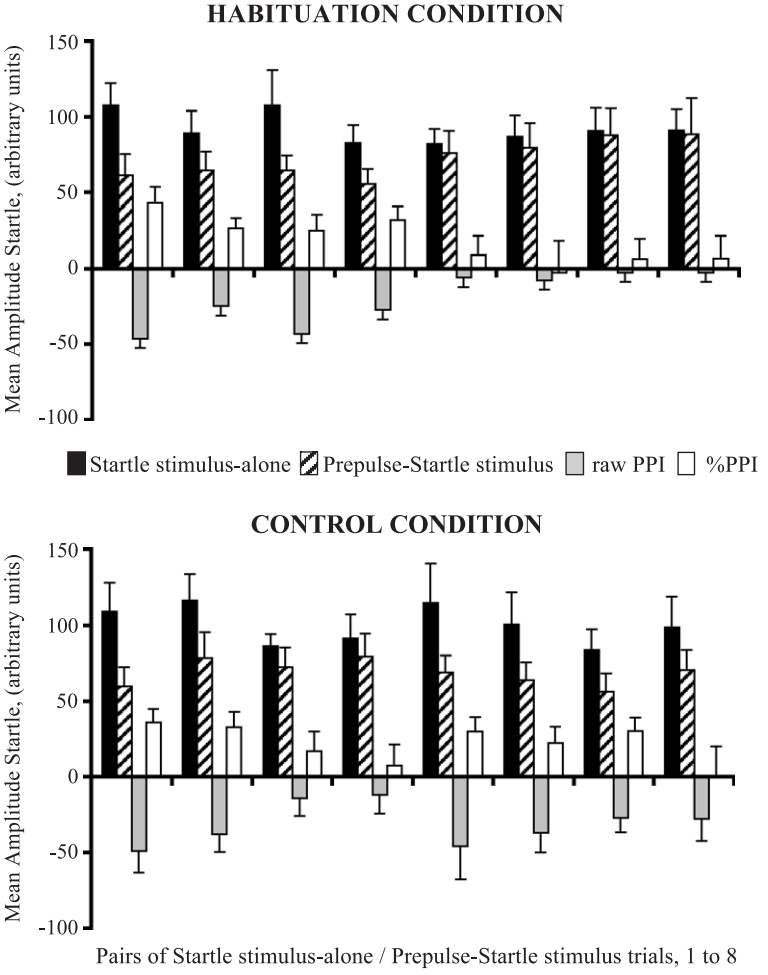

Fig. 2. Level of prepulse inhibition (±S.E.M.) to an auditory prepulse, measured intermittently over the course of repetitive exposure to the auditory prepulse (habituation condition—top panel) or to background noise alone (control condition—bottom panel).

this effect was more marked in the last four trial pairs of the session associated with the habituation condition. Analysis of variance of the %PPI data, using the same factorial design as above, showed a significant block (F=5.57 df=1,12; p<0.05), but not order (F<1) or condition (F=2.34, df=1,12; p>0.1) main effects. There was only a trend for the important condition×block interaction (F=3.23, df=1,12; p=0.098). The order×condition, order×block and the three-way interactions were not significant (F=2.25, df=1,12; p>0.1, F<1, and F<1 respectively). Pearson correlation coefficients between %PPI and startle stimulus-alone magnitude (mean data collapsed for the entire session) showed that mean %PPI was unrelated to overall startle reactivity (control condition: r=0.12, habituation condition: r=−0.11).

Analysis of variance of the raw PPI data, with the same factorial design as above, revealed a significant condition (F=8.82, df=1,12; p<0.05) and block (F=7.24 df=1,12; p<0.05), but not order (F<1) main effects. There was a significant order×condition interaction (F=5.15, df=1,12; p<0.05) but only a trend for the important condition×block interaction (F=3.82, df=1,12; p=0.074). The order×block and the three-way interactions were not significant (F's<1). ANCOVA of the raw PPI data taking the startle stimulus-alone data as the covariate showed a trend level significant effect of the regression in the case of order (F=4.74, df=1,11; p=0.052) and a significant effect of the regression in the case of the condition×block interaction (F=13.29, df=1,11; p<0.005). Following this analysis, the main effects of condition and block remained significant (F=5.50, df=1,11; p<0.05 and F=4,87, df=1,11; p=0.05, respectively), while the order×condition interaction was no longer significant (F=2.97, df=1,11; p>0.1). Finally, the remaining interactions including the important condition×block interaction remained non-significant (F=3.71, df=1,11; p=0.08).

Seven out of the fourteen subjects were smokers. To test for any effects of smoking habits, separate mixed model analyses of variance were performed on the startle stimulus-alone and PPI (percentage and raw scores) data with smoking (two levels) as the between- and condition and block as the within-subject factors. None of these analyses revealed any significant main effects of smoking or smoking×condition, smoking×block or a three-way interaction (all F's<1.1, all p values >0.1).

To test whether there was any reduction in the magnitude of PPI across sessions, comparisons were conducted between the first measurement of PPI (percentage and raw scores) of each session. These comparisons did not reveal any significant differences between prepulse inhibition in the first and second sessions.

3.1. Relationship between %PPI and neuropsychological scores

The group mean scores (±S.D.) in the most relevant performance measures of the neuropsychological tests are shown in Table 2. Data for the CANTAB tests were within the normal range for subjects' age based on large population studies [SoC: Robbins et al. (1998), Joyce et al. (2002); RVIP: normative data available within CANTAB]. Performance on the SoC showed the usual pattern related to difficulty level, seen in other published studies (Baker et al., 1996; Robbins et al., 1998; Dagher et al., 1999; Joyce et al., 2002). The group means of the rest of the neuropsychological tests and subtests and their intercorrelations are not reported here but are available on request. In general, Pearson correlation coefficients revealed that poorer performers tended to be more

Table 2
Data summary of neuropsychological test measures

	Mean (±S.D.)
STROOP	
Interference score	22.36 (08.03)
RVIP	
Tendency to detect targets (0 to 1)	0.94 (0.05)
Tendency to respond (−1 to 1)	0.84 (0.53)
Stockings of Cambridge	
Four-move problems	
Initial thinking time (ms)	10,077.30 (5070.96)
Subsequent thinking time (ms)	1005.82 (998.03)
Mean moves	4.77 (1.10)
Five-move problems	
Initial thinking time (ms)	16,028.16 (7992.1)
Subsequent thinking time (ms)	218.43 (292.59)
Mean moves	5.46 (0.63)

impulsive, spending less time in planning ahead the solutions (shorter ITTs) but more time to complete each subsequent move (longer STTs), employing more mean moves and reaching less perfect solutions. The opposite was true for the best performers.

For each of the 14 individuals, the mean %PPI in the habituation condition was calculated by averaging the %PPI from each one of the eight trial pairs and the same procedure was followed for the control condition. Comparison of mean %PPI in the habituation vs. the control condition with one-way ANOVA did not reveal a significant difference between the two conditions (F=1.09, df=1,26; p>0.1) and, therefore, %PPI data were collapsed across both conditions. The relationship between the overall %PPI values obtained in the group of 14 subjects and their neuropsychological test variables was explored using Pearson's correlation coefficients. These analyses revealed only a trend level significant negative correlation between overall %PPI and SIT scores (r=−0.50, df=14; p=0.068) and a significant positive correlation between overall %PPI and five-move STT (r=0.62, df=14; p<0.02) but not five-move ITT (r=0.25, df=14; p>0.1). None of the RVIP measures correlated significantly with overall %PPI (data not shown).

Because %PPI in the second half of the habituation condition was reduced compared to the first half of this condition (one-way ANOVA: F=5.95, df=1,26; p<0.05), separate Pearson's correlations were performed between neuropsychological test variables and %PPI in the first as well as the second half of the habituation condition. These analyses revealed only a significant positive correlation between overall %PPI in the first half and five-move STT (r=0.53, df=14; p<0.05).

In order to test whether neuropsychological test performance could predict more or less PPI habituation in the session associated with prepulse repetition, we identified subgroups of good and poor habituators via a median split on the amount of %PPI habituation (defined as the difference between mean %PPI in the first vs. the last half of the session associated with prepulse repetition). The groups of good and poor habituators were compared to each other for performance in all neuropsychological test variables with separate one-way ANOVAs. These analyses, however, did not reveal any significant group effect for any neuropsychological variable.

4. Discussion

Our procedures designed to minimise startle habituation were successful. Indeed, there was no evidence of startle response habituation over the course of a session, or any differences in startle response as a function of condition. Analysis of the prepulse inhibition data either as percentage or as raw scores revealed a block main effect suggesting habituation of PPI in the last half of the session; however, there was only a trend for the critical condition×block interaction, regardless of the PPI measure (raw or percentage) used. A significant condition×block interaction would be the critical finding to demonstrate PPI habituation specific to the prepulse repetition condition. This effect might have been more robust had we designed a longer session containing more presentations of the prepulse [8 trial pairs with 126 prepulse presentations in the present study vs. 11 trial pairs with 180 presentations in the animal study of Gewirtz and Davis (1995)]. However, pilot studies had shown that subject fatigue and dysphoria were prohibitive to such an ideal design. The analysis of the raw PPI data revealed a condition main effect, which was significant even after the baseline was taken as a covariate, suggesting that overall there was less prepulse inhibition in the prepulse repetition condition. This significant condition main effect revealed with raw PPI analysis was not found with the %PPI analysis. These discrepancies in the different PPI measures are very hard to interpret but it is interesting that similar discrepancies have also been observed in previous studies employing both PPI measures (Karper et al., 1996). One potential source for the present discrepant findings might be the different abilities of these measures to control for baseline differences.

In summary, there was modest evidence showing that repetitive exposure of a 13 dB above background prepulse can reduce the effectiveness of that prepulse in inhibiting the startle response, although this appears to be a marginal effect. PPI is known to decrease as startle response habituates (Blumenthal 1996, 1997;

Lipp and Krinitzky 1998), but since there was no evidence of startle response habituation over the course of the session, this effect cannot be attributable to a time-dependent decrease in the magnitude of startle response in general. The animal study of Gewirtz and Davis (1995) showed that only an auditory prepulse with a low signal-to-noise ratio (2.5 dB above background noise) could undergo habituation in its ability to inhibit the startle response and that this effect was not observed with a loud, 13 dB above background prepulse such as the one used in the present study. One reason for this discrepancy may be that the influence of attentional processes on PPI is greater in human subjects which may reduce attention to the prepulse as a result of repetitive presentation of that prepulse, faster than experimental animals do. Another reason for this discrepancy may be the use of background noise alone as the control treatment in our study, instead of repetitive exposure to a light prepulse as in the study of Gewirtz and Davis (1995). Indeed, in the animal study (Gewirtz and Davis, 1995—Experiment 1), exposure to another repetitive event (light prepulse) as the control treatment may have masked a small effect of the exposure to the event under study (13 dB above background auditory prepulse), unless PPI was tested under conditions of marginal stability (i.e. with a very weak 2.5 dB above background prepulse). Finally, cross-species differences, such as increased sensitivity of the experimental animals to prepulse intensity, may have been responsible for this discrepancy. Indeed, while in their study a 2.5 dB above background prepulse inhibited the startle response by over 30% early in the session (Gewirtz and Davis 1995—Experiment 2; Fig. 3), our pilot studies (2.5 dB at 50 and 60 ms prepulse–pulse intervals) and other human studies (Swerdlow et al., 1995b: 2 dB prepulses at 60 ms interval, Cadenhead et al., 1999: 8 dB prepulses at 30 ms interval) showed absent or unreliable PPI of the startle response.

In agreement to the findings of Gewirtz and Davis (1995), reduction of PPI following prepulse repetition appears to be a short-term habituation of prepulse inhibition because there was no evidence that the reduction persists from one session to the next. Indeed, the level of PPI exhibited by the subjects at the beginning of the first session was similar to that at the start of the second session.

We found a trend level (p=0.068) negative correlation between overall %PPI and Stroop Interference scores. Given that a low score in the Stroop Interference test indicates efficient cognitive inhibition (ability to inhibit the habitual tendency to respond to the semantic value of the word and to selectively attend to its colour content), this trend suggests that subjects with the best cognitive inhibition and selective attention tended to have more startle inhibition by a prepulse. However, the weak association between Stroop and PPI performance found in the present study was not seen in a previous one using a larger sample (Swerdlow et al., 1995b), although important between-studies procedural differences (e.g. design of session) cannot be excluded as contributing to this discrepancy. Even though such an association makes some theoretical sense in that both PPI and the Stroop test share a similar "inhibition-based" interpretation, caution is required in the interpretation of this association for two reasons. Firstly, although it is conceivable that subjects with the best ability for attentional selection in the Stroop task may have been more prone to attentional selection of the prepulse and thus more likely to present with greater startle inhibition, this explanation is hard to reconcile with evidence showing that short lead intervals such as the 50 ms used in the present study are too brief to be accessible to the volitional allocation of attentional resources (Böhmelt et al., 1999). Secondly, if increased attentional selection of the prepulse was the critical factor underlying the relationship between PPI and Stroop performance, then it could be predicted that subjects with the best Stroop performance would be the least likely to reduce their attention to the prepulse in the session associated with prepulse repetition, and as a consequence, they would be those with the least reduction in PPI. However, the median split comparisons of good and poor habituators did not confirm the prediction that Stroop (or any other neuropsychological test) performance can be a predictor of PPI habituation later in the session associated with the habituation condition. More research is required into the relationship between Stroop performance and PPI, especially at lead intervals longer than the 50 ms used in this study.

In contrast to the Stroop, there was no association at all between PPI and performance in the

RVIP a test of sustained attention and vigilance. This finding ties in well with evidence showing that PPI remained stable even when baseline startle and levels of arousal were reduced by the sedative drugs clonidine and diazepam (Abduljawad et al., 1997). It is encouraging that measures of performance in the planning task correlated with startle inhibition, although the positive correlation between STT in the five-move task and PPI is very hard to interpret. Firstly, it seems counterintuitive because it suggests that subjects with the worse performance in the planning task had the greatest amount of PPI, and secondly, it is not obvious why these correlations did not extend to the four-move task, or why there were no analogous correlations between PPI and ITT.

In conclusion, although these results should be treated as preliminary and clearly need to be replicated in larger samples, they show modest evidence that PPI may not be totally independent of general attentional mechanisms. They also suggest that the general inhibitory process reflected in PPI may be shared by other inhibition—but not alertness/vigilance-based tests. It must be emphasised, however, that the present results also confirm the stability of short lead prepulse inhibition. Indeed, even under a highly specific set of circumstances (i.e. guarding against dishabituation and maintaining a fairly steady level of baseline startle), PPI habituation was marginal.

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