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ARTICLE

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# Intact sensorimotor gating in adult attention deficit hyperactivity disorder

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**Abstract**

Disrupted sensorimotor gating has been found in various neuropsychiatric conditions which are characterized by impaired attention, poor impulse control, dysfunctional dopamine neurotransmission, and neurodevelopmental deficits. We investigated sensorimotor gating by prepulse inhibition (PPI) of the acoustic startle eyeblink reflex in 23 young adults diagnosed with attention deficit hyperactivity disorder (ADHD) as children and still symptomatic at the time of testing and 29 age-matched healthy control subjects. Sensorimotor gating was assessed in a passive listening task at prepulse-to-startle probe intervals of 30, 60, 120, 240, and 480 ms, and subsequently at prepulse-to-startle probe intervals of 60, 120, 240, and 480 ms whilst participants were performing a two-tone auditory discrimination task on the prepulse. Consistent with increased neural maturity and partially remitted symptomatology, our results indicate intact sensorimotor gating for both tasks in adult ADHD with no comorbidity, independent of the subjects' gender and whether ADHD subjects were receiving ongoing stimulant treatment or not. Reduced PPI at 120-ms lead intervals, on the other hand, was recorded in a subset of 10 ADHD subjects who were taken off their prescribed regular stimulants for 24 h and tested in a randomized counterbalanced order for on *vs*. off medication. However, our data remained inconclusive as to whether this observation constitutes beneficial treatment or acute stimulant withdrawal effects on sensorimotor gating.

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**Key words**: Acoustic startle eyeblink response, attention, d-amphetamine, methylphenidate, prepulse inhibition.

## Introduction

Attention deficit hyperactivity disorder (ADHD) is a highly prevalent childhood onset neuropsychiatric condition with genetic, biological, and environmental aetiologies (Spencer *et al*. 2007). According to DSM-IV criteria (APA, 1994), the disorder is characterized by behavioural symptoms of inattention, hyperactivity, and impulsivity by the age of 7 yr. ADHD is associated with numerous morbidities, including oppositional defiant disorder, conduct disorder, mood disorders (both unipolar and bipolar), anxiety disorders, and learning disorders which substantially affect primary- and secondary-school performance as well as social development, particularly if undiagnosed and untreated (Biederman, 2005).

Growing evidence suggests that ADHD, once diagnosed in childhood, persists into adulthood and its profile changes with brain maturation. As the child grows older, inattention symptoms tend to endure whereas hyperactive and impulsivity symptoms tend to remit during adolescence (Biederman *et al*. 1993; Biederman, 2005; Faraone *et al*. 2000; Seidman *et al*. 1998, 2006; Spencer *et al*. 2007).

The changing clinical features of ADHD in adolescence and early adulthood affect diagnostic reliability, thus highlighting a lack of generally accepted biological markers of the disorder that are present throughout lifespan and which can assist with the detection of ADHD and treatment evaluation. In childhood, stimulant medication is commonly prescribed, such as d-amphetamine or methylphenidate hydrochloride, and often continues well into early

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adulthood, aiming to support tertiary education and training. However, stimulant pharmacotherapy continues to evoke some controversy (Barkley *et al*. 2003; Looby, 2008).

We investigated a psychophysiological measure of impaired automatic and controlled attention processing in young adults who had been diagnosed with ADHD as children. We tested all participants off-stimulant treatment and a subsample on their prescribed medication using prepulse inhibition (PPI) of the acoustic startle eyeblink response.

Here, PPI is operationalized as a decrease in the electromyographic (EMG) response to a startling auditory stimulus (S2) when it is immediately preceded by a brief tone or prepulse (S1) that does not elicit a motor response. PPI of the acoustic startle eyeblink response is well established as a measure of sensorimotor gating, a mechanism thought to protect the processing of S1 by inhibiting a response to S2 (Graham, 1975). In accordance with Graham's model, our previous work has shown increased PPI at longer S1–S2 intervals when using an active attention task (i.e. two-tone discrimination task on the prepulse) compared to a standard passive listening task in healthy adults (Stojanov *et al*. 2003).

Sensorimotor gating usually matures by the age of 8–10 yr when PPI reaches adult levels (Ornitz *et al*. 1986, 1991). Disrupted sensorimotor gating in children with ADHD has therefore been interpreted as neurodevelopmental immaturity when they also present with comorbidities for nocturnal enuresis (Ornitz *et al*. 1999) or Tourette's syndrome (Castellanos *et al*. 1996). Comorbidity confounds these findings, as could the effect of stimulant medication.

Hawk *et al*. (2003) compared methylphenidate and placebo effects on PPI during both passive listening and active attention tasks. These authors reported that 10- to 12-yr-old boys diagnosed with ADHD showed reduced PPI of the acoustic startle eyeblink response relative to healthy control subjects, with a lead interval of 120 ms, for attended but not ignored prepulses, following placebo administration. Methylphenidate selectively increased PPI to attended prepulses (S1–S2 interval of 120 ms) to a level comparable to that of the age-matched control group of boys who did not receive stimulants. This suggests an amelioration of attention deficit by methylphenidate administration. Stimulant challenge in healthy participants, on the other hand, temporarily disrupts sensorimotor gating 1–2 h after a single oral dose of 10–20 mg d-amphetamine (Hutchison & Swift, 1999; Kröner *et al*. 1999). However, stimulant effects on PPI in healthy subjects can depend on a range of factors, including personality and baseline levels of PPI (Bitsios *et al*. 2005; Hutchison *et al*. 1997).

We hypothesized that young adults who were diagnosed with ADHD as children, but still meeting DSM-IV diagnostic criteria for at least the inattention subtype at the time of testing in the current study, present with intact sensorimotor gating in a passive listening task while medication-free. Unlike their healthy age-matched controls, their PPI would not increase when asked to perform a two-tone discrimination task on the prepulse. We further hypothesized that stimulant medication would normalize sensorimotor gating in the ADHD group when recorded in the prepulse discrimination task.

## Materials and methods

### *Participants*

The research protocol was approved by the University of Newcastle Human Research Ethics Committee and the Hunter New England Area Research Ethics Committee. Participants gave written informed consent.

All participants were recruited from the local community through advertising. Twenty-three ADHD participants (mean age $20.5 \pm 3.7$ yr) meeting DSM-IV criteria (APA, 1994) for the combined ($n = 13$) or inattentive subtype ($n = 10$) and 29 healthy control subjects (19 female, mean age $21.2 \pm 3.7$ yr; 10 male, mean age $21.2 \pm 3.1$ yr) participated. Group comparisons were performed on a subsample of 23 age-matched healthy control participants (mean age $20.8 \pm 2.9$ yr) with a non-significant male bias of 16 in the ADHD group compared with 10 in the healthy control group ($\chi^2 = 3.19$, $p = 0.14$).

Lifetime diagnosis of ADHD and current symptoms were assessed with SCID for DSM-IV (First *et al*. 1997) and interviews conducted by a senior consultant psychiatrist with extensive clinical and research experience in child and adolescent as well as adult psychiatry. 'Borderline cases' were peer-validated and collateral information was sought (e.g. from parents) if required. No monetary incentives were given to participants other than reimbursement of travel costs. Exclusion criteria for all participants included a hearing condition, head injury/surgery or sustained period of unconsciousness, neurological disorder, major medical illness, lifetime drug and/or alcohol abuse/dependency as well as current drug or nicotine use, including prescribed medication other than stimulant treatment in ADHD participants, and personal or family history of psychiatric or psychological illness

(especially major depressive disorder, OCD, pathological gambling, schizophrenia, and schizotypal personality disorder).

### *Tasks*

The methods of the current study deviate from those suggested by Blumenthal and colleagues (2005) and are described by Stojanov *et al*. (2003). When using this modified procedure, Stojanov *et al*. (2003) reported increased PPI across a broader range of S1–S2 intervals with a maximum effect at 240-ms lead interval when performing a two-tone discrimination task on the prepulse compared to 120 ms in a passive listening task. These findings suggest that the 'attention effect' on sensorimotor gating involves an increase in PPI especially over longer S1–S2 intervals (i.e. up to 500 ms). Hence the present study assessed this 'attention by lead interval effect' by recording PPI for various S1–S2 intervals of up to 480 ms. In order to minimize habituation effects, we included only two trials per lead interval which our previous work (Stojanov *et al*. 2003) suggests provides sufficient power to detect relatively small group differences as well as prepulse-to-startle probe interval effects.

Auditory stimuli were generated using the NeuroScan Stim System (NeuroScan Inc., USA) and were played bilaterally over Telephonics headphones (TDH-39P; USA), against a constant 55-dB (sound pressure level; SPL) white background noise. The task consisted of 23 acoustic startle stimuli (rectangular white noise, 115-dB SPL, 50-ms duration) presented with or without a prepulse in an alternating sequence with a variable inter-stimulus interval of 5–9 s. Ten startle stimuli were preceded by a prepulse tone (1 kHz, 70-dB SPL, 20-ms duration including 5-ms rise/fall time) at lead intervals of 30, 60, 120, 240, or 480 ms (two trials per interval), and were presented in a pseudo-randomized order. The task commenced with presentation of three startle stimuli not preceded by a prepulse. These responses were not included in further analyses. Participants were instructed to listen to the stimuli but make no overt response.

The task was repeated under 'attend prepulse' instructions using a two-tone prepulse discrimination task. Of the 19 acoustic startle stimuli presented in this task, eight were preceded by a prepulse at lead intervals of 60, 120, 240, or 480 ms (the 30-ms prepulse condition was omitted). The prepulse was either a target (1.4 kHz) or non-target (0.8 kHz) tone (70-dB SPL, 50-ms duration including 10-ms rise/fall time), presented with equal randomized probability. Participants were required to respond to the target prepulse as quickly as possible, using a button press response (Neuroscan Stim response pad).

### *Procedure*

Participants were tested twice, 1 wk apart, with ADHD participants recorded on and off their regular stimulant treatment (i.e. after 24-h washout period). Participants were assigned to a counterbalanced order, to control for retest by medication interaction effects.

Following screening procedures, participants were fitted with EMG electrodes. During the recordings, participants were instructed to keep eye movements to a minimum by focusing on a spot in a landscape photograph. The passive listening tasks were presented first in order to reduce unintentional attending or responding to prepulse stimuli. Prior to commencement of the prepulse discrimination task, participants were presented with a practice run of a randomized sequence of 10 target and 10 non-target stimuli, and their responses were monitored to ensure they were discriminating correctly.

### *Data recording and processing*

Bipolar silver/silver chloride electrodes were positioned above the orbicularis oculus muscle of the participant's left eye to record the acoustic eyeblink response. Impedances were set to $<5$ kΩ. EMG was recorded at a sampling rate of 1000 Hz and with a bandpass filter of 1–1000 Hz.

Rectified startle response was averaged over an epoch that extended from 50 ms prior to stimulus onset to 200 ms after stimulus onset, relative to a baseline of 50 ms prior to acoustic startle stimulus onset. Mean startle amplitude was defined as a reflexive response within a 35–140 ms post-stimulus response window as determined by the onset and offset of the EMG response curve derived from the population average of all baseline startle responses. For each participant, startle amplitude measures were averaged across all startle responses that were not preceded by a prepulse (baseline) and across the two trials for each prepulse lead interval in the passive listening task and for the target and non-target tones in the two-tone prepulse discrimination task, respectively. PPI was calculated for each lead interval as percentage change units

$$[(\text{prepulse} - \text{baseline})/\text{baseline}] \times 100,$$

with negative values representing PPI of the acoustic startle reflex (Dawson *et al*. 1993).

### *Statistical analysis*

The distributional properties of all dependent measures of PPI were tested (i.e. skewness and kurtosis) prior to parametric statistical analyses. All statistical analyses used repeated-measures or mixed-design ANOVA. Differences in baseline startle responses (without prepulse) were assessed with group (13 non-medicated ADHD subjects, 10 medicated ADHD subjects after 24-h washout, and 23 age-matched healthy control subjects) and gender as between-subjects factors, and task conditions (i.e. passive listening *vs*. prepulse discrimination task) as a within-subjects factor. The overall effect of prepulse lead intervals and task conditions as within-subjects factors was assessed with groups (as defined above) and gender as between-subjects factors, excluding the 30-ms lead interval condition from the passive listening task. Retest effects were assessed separately for each task in 29 healthy subjects with gender as between-subjects factor, and prepulse lead intervals and session as within-subjects factor.

Since the order of task conditions was not counterbalanced (i.e. the prepulse discrimination task always followed the passive listening task) and the number of lead intervals differed between task conditions (i.e. the 30-ms lead interval was not presented in the prepulse discrimination task), PPI group differences were assessed separately for the passive listening and prepulse discrimination task with groups (as defined above) and gender as between-subjects factors and lead intervals as a within-subjects factor.

From the sample of 23 participants with ADHD, medication effects were tested in a subset of 14 (ten male, four female) ADHD participants. Of those, 10 participants (eight male, two female) had been on stable regular stimulant treatment (i.e. six on d-amphetamine and four on methylphenidate) for several years. These participants were recorded 2 h after taking their regular medication and also asked to volunteer for a recording following a 24-h medication washout period. Another four participants (two male, two female) were only taking their prescribed stimulant sporadically. They were also asked to volunteer for a recording about 2 h after taking their usually prescribed medication (i.e. two on d-amphetamine and two on methylphenidate). Order of recordings (i.e. on *vs*. off medication) was counterbalanced and randomized. Medication effects were assessed (1) in all ADHD subjects separately for both task conditions with medication status as between-subjects factor, lead interval as within-subjects factor and mean baseline startle amplitude as covariate (Bitsios *et al*. 2005); and, (2) with medication status and recording order as within-subjects factors for those ADHD participants who were tested on and off stimulants with treatment status (i.e. taking prescribed medication regularly *vs*. sporadically) as between-subjects factor.

Wilks' statistics were employed for within-subjects effects and power ($\eta^2$) was calculated for non-significant results. *t* tests were used to examine significant effects across factors with more than two levels. $\alpha$ was set at $p < 0.05$ (two-tailed probability).

## Results

Individual reflexive baseline (without prepulse) startle eyeblink responses ranged from 11.6 to 117.2 $\mu$V *vs*. a mean resting noise level of $2.7 \pm 1.8\,\mu$V (range $< 6.1\,\mu$V). Baseline startle responses did not differ between groups or gender ($F < 1.0$, $\eta^2 < 0.06$). Baseline startle responses were larger for the prepulse discrimination task than for the passive listening task [$65.3 \pm 19.5$ *vs*. $57.7 \pm 18.2\,\mu$V; $F(1, 49) = 9.4$, $p = 0.004$]. This effect was not modulated by group or gender.

Prepulses significantly reduced the startle response [$F(3, 46) = 12.1$, $p < 0.001$] and there was significantly increased PPI when performing the prepulse discrimination task [$F(1, 48) = 4.1$, $p < 0.05$; Fig. 1]. Task condition tended to interact with lead interval [$F(1, 46) = 4.6$, $p = 0.06$]. *Post-hoc* comparisons confirmed PPI for lead intervals of 60, 120, and 240 ms in the passive listening task ($t > 3.1$, $p < 0.005$) and for all lead intervals in the prepulse discrimination task ($t > 3.1$, $p < 0.005$).

There was no group difference in PPI; neither in the passive listening ($F < 1.0$, $\eta^2 = 0.05$) nor in the prepulse discrimination task [$F(1, 46) = 1.6$, $\eta^2 = 0.24$; Fig. 1], nor gender effects ($F < 1.0$, $\eta^2 < 0.12$), nor significant interactions of group [$F(6, 84) < 1.2$, $\eta^2 < 0.12$] or gender with lead intervals [$F(3, 42) < 1.6$, $\eta^2 < 0.29$] in both task conditions.

While PPI did not differ between the two sessions when recorded in the passive listening task ($F < 1.0$, $\eta^2 = 0.05$), PPI was smaller in the retest session when recorded in the prepulse discrimination task in healthy subjects [$F(1, 26) = 6.7$, $p = 0.015$]. *Post-hoc* tests confirmed significantly reduced PPI of $-6.4\%$ (S.E.M. $= 10.3\%$) in the 480-ms lead interval condition at retest *vs*. $-37.2\%$ (S.E.M. $= 7.9$) at the first test session ($t = -2.5$, $p = 0.02$). There were no gender effects on test/retest performance ($F < 1.0$, $\eta^2 < 0.08$).

ADHD subjects who were tested for on- *vs*. off-stimulants showed no medication effects on PPI in the passive listening task when controlling for mean

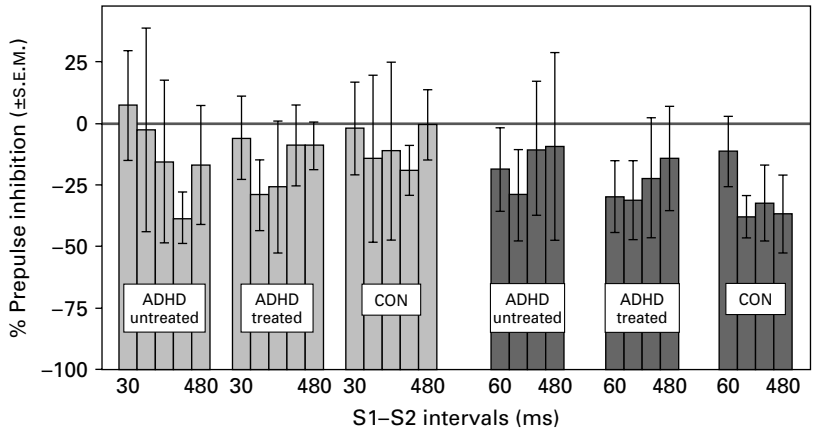


**Fig. 1.** Group-averaged % prepulse inhibition (PPI ± S.E.M.) recorded from 13 ADHD subjects not receiving ongoing stimulant treatment at the time of testing ('untreated'), 10 ADHD subjects receiving ongoing stimulant treatment ('treated') and tested following a 24-h medication washout period, and 29 age-matched healthy control subjects (CON). PPI was recorded at prepulse-to-startle probe intervals (S1–S2) of 30, 60, 120, 240, and 480 ms while participants performed a passive listening task (□, *left*), and at lead intervals of 60, 120, 240, and 480 ms while they performed a two-tone discrimination task on the prepulse (■, *right*). The grey horizontal line represents mean baseline startle response with negative values indicating PPI and positive values indicating prepulse facilitation. Across groups, PPI was confirmed for lead intervals of 60, 120, and 240 ms in the passive listening task and for all lead intervals in the prepulse discrimination task. PPI did not differ between groups in either condition, indicating intact sensorimotor gating in adult ADHD, regardless of treatment status and attention condition.

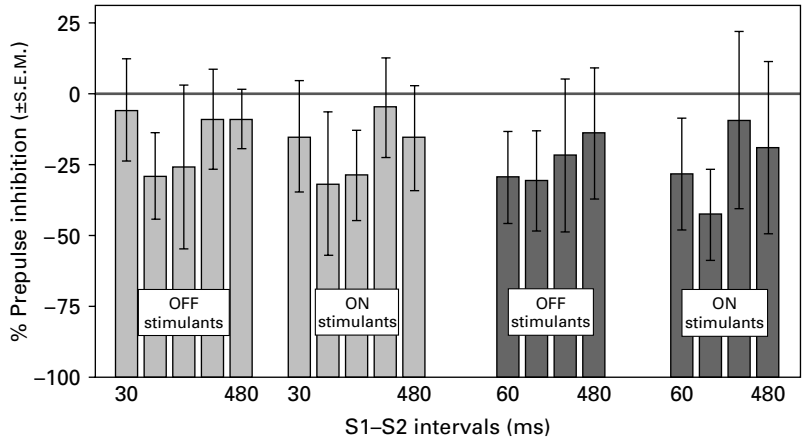


**Fig. 2.** Group-averaged % prepulse inhibition (PPI ± S.E.M.) recorded from 14 ADHD subjects tested on- and off-stimulant medication. PPI did not differ for on- *vs*. off-stimulant medication, indicating no effect of stimulants on sensorimotor gating in adult ADHD. (See text for potential stimulant withdrawal effects in a subsample of 10 ADHD subjects.) Passive task (□, *left*); discrimination task (■, *right*).

baseline startle amplitude ($F<1.0$, $\eta^2<0.12$). When performing the prepulse discrimination task, PPI differed across lead intervals for on- *vs*. off-stimulants [$F(1, 11)=5.7$, $p=0.03$, Fig. 2] independent of recording order ($F<1.0$, $\eta^2=0.11$). However, this was dependent on whether subjects were receiving ongoing stimulant treatment or not [$F(3, 8)=4.5$, $p<0.04$]. *Post-hoc* comparisons indicated reduced PPI in the 120-ms lead interval condition ($t=-2.3$, $p<0.05$) when subjects with ongoing stimulant treatment were tested following a 24-h washout period *vs*. on their regular medication.

## Discussion

Our procedure produced robust measures of PPI at lead intervals of 60, 120, and 240 ms in the passive listening task and 60, 120, 240, and 480 ms in the

prepulse discrimination task (Stojanov *et al*. 2003); while baseline startle responses and PPI were larger when recorded in the prepulse discrimination task compared to the passive listening task, indicating attention modulation effects which interacted with neither group nor gender.

In contrast to Hawk *et al*.'s report (2003) of impaired sensorimotor gating in boys aged 10–12 yr with ADHD when recording PPI in response to attended *vs*. ignored tones, we found no difference in sensorimotor gating between healthy control and ADHD subjects in our adult sample (Fig. 1). This observation was independent of gender and task condition and appears consistent with declining ADHD symptom expression in adolescence and early adulthood, particularly impulsivity and hyperactivity (Biederman *et al*. 1993, 2000; Hart *et al*. 1995), and neural maturity (Ornitz *et al*. 1986). However, our study lacked statistical power to further analyse PPI differences between ADHD subtypes (i.e. with and without hyperactivity symptoms).

Our sample is also unique for adult ADHD since potential comorbidities are different to those in children (Biederman *et al*. 1993). This was taken into account in the current study when excluding participants with a history of psychotic spectrum disorders (including schizotypal personality disorder or family history of schizophrenia), obsessive–compulsive disorders, neurological conditions, nicotine and other substance use disorders, etc., which are likley or have been shown to affect sensorimotor gating (see Braff *et al*. 2001 for review). Hence our findings indicate intact sensorimotor gating in young adults with ADHD with no or very little comorbidity. Gender effects on sensorimotor gating have also been reported previously (e.g. Aasen *et al*. 2005; Swerdlow *et al*. 1993), however, they were not observed in the present study.

PPI did not differ between recording sessions in the passive listening task but was smaller in the repeat session when recorded in the prepulse discrimination task in healthy subjects. This finding suggests some prehabituation effect (Schell *et al*. 2000) and was taken into account by counterbalancing the order of on- and off-stimulant recordings when assessing medication effects on PPI in ADHD participants.

We did not detect any differences in sensorimotor gating performance between stimulant-treated and untreated ADHD subjects (Fig. 1). However, we found reduced PPI at 120-ms lead intervals when ADHD subjects were taken off their regular stimulant treatment and performing the prepulse discrimination task, suggestive of some beneficial stimulant effects on sensorimotor gating. This observation was independent of order effects. On the other hand, our sample of four ADHD subjects was too small to detect any stimulant challenge effects on sensorimotor gating in untreated ADHD subjects. This, together with a report of disrupted sensorimotor gating in rodents when withdrawing from d-amphetamine (Peleg-Raibstein *et al*. 2006), limit the interpretation of this observation.

While we were able to randomize and counterbalance on- *vs*. off-stimulant recordings, our study was open label and did not control for stimulant treatment *per se*. As such, our findings in relation to stimulant effects on sensorimotor gating need to be interpreted with caution and should be adequately tested in a randomized, controlled stimulant treatment trial. Conversly, the lack of any PPI differences between healthy control subjects and off-stimulant recordings in stimulant-treated and untreated ADHD subjects seems to be a robust finding and suggests largely intact sensorimotor gating in a cohort of adult ADHD with no or very little comorbidity.

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## Statement of Interest

None.

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