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# Deficient prepulse inhibition of the startle reflex in schizophrenia using a cross-modal paradigm

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ABSTRACT

*Objectives:* To investigate whether the typically reported deficient sensorimotor gating in patients with schizophrenia using unimodal paradigms can also be detected by a cross-modal paradigm which made use of an electrocutaneous-acoustic coupling of stimuli.
*Methods:* Twenty-one male schizophrenia patients took part in a prepulse inhibition (PPI) paradigm with an electrocutaneous prepulse and an acoustic startle-eliciting pulse. Their results were compared with those from nineteen healthy males.
*Results:* As expected, the patients showed significantly lower PPI than controls. No associations were found between measures of illness severity and PPI.
*Discussion:* To the best of our knowledge, this is the first study showing reduced PPI in patients with schizophrenia by using an electrocutaneous-acoustic prepulse-pulse combination. Hence, this study gives further evidence of a modality-independent sensorimotor gating deficit in schizophrenia. Furthermore, as PPI was also lower than usual in controls using unimodal paradigms, results are interpreted in favour of longer processing times of the electrocutaneous prepulse, which probably led to a shorter perceived stimulus onset asynchrony (SOA) in the brain.

## 1. Introduction

The human startle response is a reflexive contraction of the skeletal and facial muscles in response to a sudden, intense stimulus and is regarded as a defensive rather than an orienting response (Braff, 2010). The strength of the human eye blink reflex is assessed as a subcomponent of the whole body startle reflex using electromyography (EMG) of the orbicularis oculi muscles. PPI of the startle reflex is the phenomenon that the startle magnitude as a result of a startle-eliciting stimulus (or "pulse", e.g. a sound of approximately 118 dB) is decreased whenever a less intense and non-startling stimulus (or "prepulse", e.g. a sound of approximately 85 dB) is presented just before the intense stimulus. PPI can, among others, be modulated by the interval that separates the prepulse and pulse stimuli, with the maximum inhibition usually occurring between 100 and 120 ms (Graham & Murray, 1977; Stitt, Hoffman, & DeVido, 1980). Hence, it is regarded a useful tool to investigate information processing, more specifically, a measure of sensorimotor gating because the eye-blink reflex is based on a muscle contraction (Braff & Geyer, 1990; Braff, 1993).

For schizophrenia patients, there is ample evidence that PPI is reduced compared to healthy individuals when using unimodal paradigms (Braff et al., 1978; Graham, 1975; see Braff, Geyer, & Swerdlow, 2001; Braff, 2010; Takahashi et al., 2011 for reviews).

Previous studies have shown that PPI also occurs with other than acoustic stimuli, particularly stimuli from the tactile and nociceptive modality have been studied, both in healthy control subjects (Blumenthal, Burnett, & Swerdlow, 2001; Kumari, Antonova, & Geyer, 2008) and schizophrenia patients (Bolino et al., 1994; Kumari et al., 2003) by using either electrical stimulation or airpuffs. There is also evidence that PPI can be induced by using cross-modal paradigms in healthy individuals from studies using acoustic prepulses and tactile pulses (Hoffman, Cohen, & Stitt, 1981; Flaten, Firan, & Blumenthal, 2016; Sanes & Ison, 1979; Stitt et al., 1980), studies using tactile prepulses and acoustic pulses (Blumenthal & Gescheider, 1987;

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**Table 1**
Demographic and clinical characteristics.

| | Healthy controls | Medicated patients | Med.-free patients |
|---|---|---|---|
| N | 24 | 17 | 6 |
| Age, mean (SD) | 25.67 (4.90) | 39.13 (7.65) | 27.33 (9.00) |
| Medication | – | 1 x typical, 3 x clozapine, 11 x other atypical, 2 x combination of typical and atypical | – |
| PANSS positive, median (min, max, IQR)[a] | | 15 (11, 25, 11) | 17.5 (14, 25, 6.5) |
| PANSS negative, median (min, max, IQR) | | 17 (7, 31, 12) | 25 (16, 27, 9.5) |
| PANSS general, median (min, max, IQR) | | 30 (20, 51, 18.75) | 41 (33, 44, 5.75) |
| PANSS total, median (min, max, IQR) | | 60 (38, 100, 37.5) | 83 (63, 93, 16.5) |

*Note:* PANSS scores for the medicated sample are based on n = 16 because values for one subject were missing.
[a] Min = minimum value, max = maximum value, IQR = interquartile range.

Blumenthal & Tolomeo, 1989; Elden & Flaten, 2003; Hill & Blumenthal, 2005; Perlstein, Simons, & Graham, 2001) and studies using visual prepulses and electrocutaneous (Rossi et al., 1995) or acoustic (Oranje, Geyer, Bocker, Kenemans, & Verbaten, 2006) pulses. Typically, the efficiency of those cross-modal pairings in eliciting PPI was lower compared to unimodal conditions. Yet, up to now there is only one cross-modal study in schizophrenia patients: Braff, Grillon, and Geyer (1992) reported reduced PPI in schizophrenia patients compared to healthy controls with acoustic prepulses and either tactile (airpuffs) or acoustic pulse stimuli.

For stimulus processing, it is known that processing times differ between sensory modalities: For example, it is known that the overall processing time of acoustic stimuli is shorter than that of visual stimuli. This is due to faster transduction times in the ear and a shorter distance from the ear to the auditory cortex (King, 2005). Processing times of electrocutaneous, i.e. nociceptive, stimuli are also longer than of acoustic stimuli (Flaten et al., 2016).

In the current study we investigated the stimulation efficiency of an electrocutaneous prepulse combined with an acoustic startle-eliciting pulse in healthy controls as well as in patients with schizophrenia. We expected to find significantly lower PPI in patients compared to controls as this was found with both unimodal and cross-modal paradigms before (see Braff et al., 2001 for a review). We also reasoned that a cross-modal pairing of stimuli should result in a lower PPI for both patients and controls as electrocutaneous prepulses have proven to be less effective in evoking PPI compared to acoustic ones in unimodal paradigms (Flaten et al., 2016).

This study was part of a larger project investigating somatosensory (electrocutaneous stimuli) P50 suppression in healthy individuals (Bak, Glenthøj, Rostrup, Larsson, & Oranje, 2011) and schizophrenia patients (Bak, Rostrup, Larsson, Glenthøj, & Oranje, 2014).

## 2. Methods

### 2.1. Subjects

The study was approved by the Committee for Biomedical Research Ethics, Copenhagen, taking into account the ethical principles stated in the Declaration of Helsinki (Amendment of Washington, 2002). After written and oral information had been given, written informed consent was obtained from all subjects before enrolment in the study. To reduce variance we included only male participants as it is described that women have lower levels of PPI than males in both healthy people (Swerdlow et al., 1993) and schizophrenia patients (Kumari, Aasen, & Sharma, 2004). Additionally, women's PPI levels are affected by the menstrual cycle (Swerdlow, Hartman, & Auerbach, 1997).

Twenty-four healthy male volunteers (mean age: 25.67, SD = 4.90) were recruited through an advertisement on the internet, all from the Copenhagen area. Absence of any psychiatric disorder as well as alcohol or drug abuse was ensured by the use of Schedule for Clinical Assessment in Neuropsychiatry, version 2.1 (SCAN, Wing et al., 1990). Moreover, the healthy volunteers did not have a first-degree relative with a DSM-IV diagnosis and none of them had ever received psychopharmacological medication, nor had they participated in any electrophysiological experiment before.

Twenty-three schizophrenia patients (mean age: 35.91, SD = 9.49) were recruited either by advertisement in the community mental health centre, or were referred to us by their practitioner. Psychopathology was assessed with the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987), and the diagnosis was confirmed with the SCAN. Fulfilled DSM-IV criteria for substance dependence was an exclusion criterion. Seventeen patients received antipsychotic treatment at the time of participation: one with first-generation antipsychotics, three with clozapine, eleven with other second-generation antipsychotics, and two with a combination of first- and second-generation antipsychotics. Six patients were free of any medication, defined as having received no antipsychotics in the last three months preceding study participation. Twelve patients and five healthy controls were smokers ranging from 5 to 25 cigarettes a day. PANSS scores of one patient were missing. Thus, PANSS scores of 22 patients are reported.

Details regarding healthy control participants and both patient groups are summarized in Table 1.

### 2.2. Experimental design and tasks

Prior to the test session a urine sample of all participants was screened for cannabis, cocaine, opiates, and amphetamines (Syva® RapidTest d.a.u® 4). In order to minimize potential effects of caffeine and/or nicotine, all subjects were asked to refrain from drinking beverages that contained caffeine prior to the assessments on a test day, and from smoking an hour before meeting at the laboratory.

Subjects were seated comfortably in a sound insulated room (40 dB), situated adjacent to the control room. They were instructed to sit still and stay awake. The paradigm was presented via Presentation® software (Neurobehavioral Systems®, Albany, CA, USA; soundcard: Creative soundblaster®5.1, 2008 Creative Technology Ltd, Singapore). The electrocutaneous stimuli were presented by an electrical stimulator (Digitimer®, model DS7A, Hertfordshire, UK). Acoustic stimuli were presented binaurally through stereo insert earphones (Eartone® ABR, 1996–2008 Interacoustics A/S, Denmark, C and H Distributors Inc., USA).

In our bimodal PPI paradigm we used a short (5 ms) weak electrocutaneous stimulus applied over the median nerve of the left forearm as prepulse. The intensity was set at 80% of the electric current that was needed to activate the subject's thenar reflex. As such, the electric stimulation could be felt but was not painful according to participants' reports. The intensities ranged from 2 to 8.4 mA, with a mean of 4.9 mA (SD = 1.6) for both patients and healthy controls. The startle-eliciting stimulus consisted of a sound (white noise) with an intensity of 118 dB and a duration of 20 ms, instant rise and fall.

The assessment of PPI started with three minutes of acclimation to a background noise (70 dB white noise), which was presented continuously during the paradigm. The actual experiment consisted of one block with 24 pseudo-randomized (not more than two trials of the same