universität wien

DIPLOMARBEIT

Titel der Diplomarbeit

THE EFFECT OF ESTRADIOL ON SENSORIMOTOR GATING

Verfasserin

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Angestrebter akademischer Grad

Magistra der Naturwissenschaften (Mag. rer. nat.)

Wien, 2014

Studienkennzahl: A 298

Studienrichtung: Diplomstudium Psychologie

Betreuer: Dr. med. univ. Igor Riečanský, Ph.D.

Vorwort

An dieser Stelle möchte ich mich bei all jenen Personen bedanken, die mich bei der Erstellung dieser Diplomarbeit unterstützt haben und ohne die eine Realisierung nicht möglich gewesen wäre.

Mein Dank gilt zuerst natürlich meinem Betreuer Dr. Igor Riečanský sowie Dr. Christoph Eisenegger und dem gesamten Team, das bei der Datenerhebung in Bratislava einen wesentlichen Beitrag geleistet hat: Jan Seidel, Mgr. Rastislav Rovný, Mgr. Veronika Rohárikova, RNDr. Barbora Cimrova, PhD, Mgr. Jana Murinova, Matus Linsky und Stefan Bendzala.

Weiters haben erst finanzielle Förderungen der Universität Wien und der Aktion Österreich Slowakei sowie die bereitwillige Beteiligung zahlreicher Versuchspersonen diese Forschungsarbeit ermöglicht. Auch ihnen sei an dieser Stelle herzlich gedankt.

Ein besonders herzliches Dankeschön gilt weiters meinem Bruder Mag. Franz Raffaseder und meinem Verlobten Georg Grünauer, BSc., für das Korrekturlesen meiner Arbeit sowie für ihre Freundschaft und Unterstützung, die mir sehr viel bedeuten. Besonders mein Liebster Georg war und ist für mich immer eine große Stütze und eine Quelle der Kraft. Ich bedanke mich dafür, dass er während der Entstehung dieser Arbeit meine Launen wortlos ertragen hat und immer da war, wenn ich Anregung oder Ermutigung gebraucht habe.

Zuletzt möchte ich mich noch von ganzem Herzen bei meinen lieben Eltern bedanken, die mich in so vielerlei Hinsicht schon mein ganzes Leben lang unterstützen und mir auch dieses Studium ermöglicht haben. Ihr Rückhalt, ihre Liebe und ihr Vertrauen haben mich sehr geprägt und das Weiterkommen auf meinem Lebensweg unterstützt.

DANKE!

Eidesstattliche Erklärung

Ich erkläre hiermit an Eidesstatt, dass ich die vorliegende Diplomarbeit selbständig verfasst, andere als die angegebenen Quellen und Hilfsmittel nicht benutzt und mich auch sonst keiner unerlaubten Hilfe bedient habe. Ich versichere weiters, dass ich diese Diplomarbeit bisher weder im In- noch im Ausland in irgendeiner Form als Prüfungsarbeit vorgelegt habe.

Wien, 22. September 2014 Johanna Raffaseder

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Abbreviations

Ag/AgCl	silver chloride
ANOVA	analysis of variance
ANCOVA	analysis of covariance
BAS	behavioral activation system
BIS	behavioral inhibition system
BMI	body mass index
cf.	compare
E	extraversion
e.g.	for example
EMG	electromyogram / electromyographic
EMG-L	left eye EMG channel
EMG-R	right eye EMG channel
ER	estrogen receptor
FPS	fear potentiated startle
HAB	startle habituation
i.e.	that is
INPP	Institute of Normal and Pathological Physiology
ISI	interstimulus interval
ISR	initial startle reactivity
ITI	intertrial interval
N	neuroticism
PA	pulse-alone
PP	prepulse-pulse
PPA	prepulse-alone
PPF	prepulse facilitation
PPI	prepulse inhibition
2D:4D	second-to-fourth digit ratio
5-HT_{1A}	serotonin-1A receptor
8-OH-DPAT	8-hydroxy-dipropylaminotetralin

Abstract

Prepulse inhibition (PPI) of the acoustic startle reflex is an established measure of sensorimotor gating. Gating refers to an automatic cognitive filter mechanism which screens irrelevant sensory stimuli out of awareness. Deficient gating may therefore result in overstimulation and aberrant information processing and is considered to play a causal role in schizophrenia pathogenesis. Previous studies revealed that PPI in healthy women is reduced during the high-estrogen phase of the menstrual cycle. To explore the association between estradiol and PPI in more detail, we transdermally administered estradiol to 32 healthy adult males in a double-blind, placebo controlled cross-over study. In addition to PPI, prepulse facilitation, habituation and initial startle reactivity were assessed. Our data show that a single dose of 3 mg transdermally administered estradiol has no considerable influence on prepulse modulation, habituation and initial magnitude of the acoustic startle response.

Keywords: Prepulse inhibition, Prepulse facilitation, Sensorimotor gating, Schizophrenia, Estradiol

Zusammenfassung

Sensomotorisches Gating wird üblicherweise anhand der Prä-Puls-Hemmung (PPI) des akustischen Schreckreflexes gemessen. Gating bezeichnet einen automatischen Filtermechanismus des Zentralnervensystems, der die Ausblendung unbedeutender sensorischer Reizinformationen ermöglicht. Störungen der Gatingfunktion führen demnach zu Reizüberflutung und fehlerhafter Informationsverarbeitung und tragen wesentlich zur Pathogenese von Schizophrenie bei. Bei gesunden Frauen zeigt sich eine reduzierte PPI in Zyklusphasen mit erhöhtem Östrogenspiegel. Die vorliegende Studie untersuchte den Zusammenhang zwischen transdermal appliziertem Östradiol und PPI in einer Doppelblindstudie an 32 gesunden Männern. Neben PPI wurden die Prä-Puls-Erhöhung (PPF), die Habituation der Schreckreaktion während einer Testsession und die Reaktion auf den allerersten Schreckreiz (Schreckreaktivität) untersucht. Die Ergebnisse zeigen, dass eine einmalige Verabreichung von 3 mg transdermalem Östradiol keinen signifikanten Einfluss auf PPI, PPF, Habituation und Schreckreaktivität hat.

Keywords: Prä-Puls-Hemmung, Prä-Puls-Erhöhung, Sensomotorisches Gating, Schizophrenie, Östradiol

1 Introduction

1.1 Sensorimotor gating (prepulse inhibition)

Gating in general refers to a basic cognitive filter mechanism, which "gates out" irrelevant stimuli so that attention can be focused on the most salient aspects of the environment (Braff, Geyer, & Swerdlow, 2001). Or, as Light and Braff (1999) put it:

> Under natural circumstances gating is conceptualized as being continuously active, contributing to our ability to modulate a continuous stream of sensory and cognitive information. Gating is necessary to navigate successfully in a stimulus-laden world, selectively allocate attentional resources to salient stimuli, and ignore redundant, repetitive, or trivial information. (p.32)

Effective gating helps to prevent sensory overload, whereas its breakdown may cause sensory inundation, cognitive fragmentation, disorganized thinking and possibly other psychotic symptoms (Braff & Geyer, 1990; Light & Braff, 1999). There are two commonly used conceptually related operational measures to assess gating of sensory stimuli: suppression of the P50 wave of auditory evoked potentials (often referred to as sensory gating) and prepulse inhibition of the acoustic startle response (PPI or sensorimotor gating) (Light & Braff, 2001).

PPI is a form of modulation or plasticity of the startle reflex (Graham, 1975), which in itself is an omnipresent reflexive reaction to strong exteroceptive stimuli (Geyer, Swerdlow, Mansbach, & Braff, 1990). Besides PPI the startle reflex demonstrates other forms of behavioral plasticity, e.g. habituation (Geyer & Braff, 1987) and fear potentiation (Brown, Kalish, & Farber, 1951). The startle reflex occurs in all mammals and consists of a contraction of the skeletal and facial muscles in response to a sudden, intense stimulus that may be presented across multiple modalities (e.g. visual, tactile and auditory) (Light & Braff, 1999). If this startle eliciting stimulus (the pulse) is preceded 30-500 ms by a relatively weak sensory event (the prepulse), the magnitude of the startle motor response (e.g. the eyeblink) is reduced or rather inhibited ("gated") (see Figure 1; Graham, 1975). This concept is called PPI and the construct measured is referred to as "sensorimotor gating" (Braff et al., 2001; Braff, 2010).

If the interval between the prepulse and the pulse (i.e. the interstimulus interval, ISI) exceeds 1000 ms the startle response is increased (see Figure 1), hence the term

prepulse facilitation (PPF) is used (as reviewed in Braff et al., 2001). In comparison with PPI, PPF is relatively less well-studied, with different authors suggesting PPF to either reflect sustained attention (Dawson, Schell, Swerdlow, & Filion, 2013) or a different aspect of the concept underlying PPI (Aasen, Kolli, & Kumari, 2005; Kumari, Gray, Gupta, Luscher, & Sharma, 2003).

In humans, the magnitude of the acoustic startle reflex is typically assessed by measuring the electromyogram (EMG) of its blink component over the orbicularis oculi muscle (Graham, 1975; Blumenthal et al., 2005). Prepulse-to-pulse intervals of 30-240 ms are typically utilized and maximal inhibition typically occurs with intervals of approximately 120 ms (as reviewed in Braff, 2010). Since PPI is also observed at ISIs of 30 or 60 ms – intervals too short to be considerably influenced by the volitional distribution of attentional resources – PPI is considered a preattentional process (Swerdlow, Braff, & Geyer, 2000). Accordingly, the protection of processing hypothesis states that preattentional mechanisms are activated by the prepulse which in turn inhibit the pulse processing (Kohl, Heekeren, Klosterkötter, and Kuhn; 2013). More precisely, while information processing resources are directed at the prepulse, any other incoming information (i.e. the pulse) is attended to at a reduced level, thereby protecting the processing of the information contained in the weak initial stimulus (Graham & Murray, 1977). Thus, sensorimotor gating is considered a protective mechanism that regulates environmental inputs by screening out interfering stimuli and therefore allowing an individual to focus on important events (Braff et al., 1978). Consequently, deficits in the ability to avoid, gate or filter out such irrelevant stimuli may cause sensory over-stimulation, which may lead to aberrant salience and cognitive fragmentation, which are considered to play a causal role in several mental disorders, most notably schizophrenia (Braff & Geyer, 1990; Geyer et al., 1990).

1.2 PPI in mental disorders

It is well established that PPI is reduced in people suffering from schizophrenia (e.g. Braff et al., 1978; Geyer et al., 1990; Kumari, Aasen, & Sharma, 2004; Braff, Light, & Swerdlow, 2007; Takahashi et al., 2008), which can be considered one of the most consistent and robust findings in schizophrenia research. Moreover, deficient PPI is considered a possible schizophrenia endophenotype, i.e. a marker of increased risk of the disorder (Light & Braff, 1999; Cadenhead, Swerdlow, Shafer, Diaz, & Braff, 2000), as PPI is also reduced in healthy biological relatives of schizophrenia patients (Cadenhead et al.,

2000; Kumari, Das, Zachariah, Ettinger, & Sharma, 2005; Takahashi et al., 2010) and people with schizotypal personality disorder (Cadenhead, Geyer, & Braff, 1993; Cadenhead et al., 2000).

However, PPI deficits are not specific to schizophrenia. Evidence for sensorimotor gating deficits has also been reported to occur in obsessive compulsive disorder, Huntington's disease, Gilles de la Tourette's syndrome, post-traumatic stress disorder and attention deficit/hyperactivity disorder (as reviewed in Braff et al., 2001; Braff, 2010; Kohl et al., 2013). Braff (2010) argued that all these disorders are characterized by a deficit of gating in sensory, motor or cognitive domains.

1.3 Sex differences in PPI and schizophrenia

There is convincing evidence for sex differences in PPI, with lower PPI observed in women than in men (e.g. Swerdlow et al., 1993, 1997, 2006; Kumari et al., 2003, 2004, 2008; Bannbers, Kask, Wikström, & Sundström-Poromaa, 2010). Such a difference has already been reported in 8-year-old children (Ornitz, Guthrie, Sadeghpour, & Sugiyama, 1991). Furthermore, PPI varies with the menstrual cycle in women. Both cross-sectional (Swerdlow et al., 1997; Jovanovic et al., 2004) and within-subjects studies (Jovanovic et al., 2004; Kumari et al., 2010) observed higher PPI during the early follicular phase relative to the (mid-)luteal phase. Interestingly, PPI in follicular phase women does not seem to differ significantly from PPI in men (Ludewig et al., 2003; Jovanovic et al., 2004), but women in the luteal phase differ from both those groups (Jovanovic et al., 2004). The sex difference and menstrual cycle variability in PPI have been attributed to variations in sex steroid levels, primarily estradiol (cf. Jovanovic et al., 2004; Swerdlow et al., 1997). Swerdlow et al. (1997) for example reported reduced PPI levels at the time of the preovulatory peak estrogen levels, i.e. cycle days 10-15.

The influence of estradiol on PPI is further supported by studies of women during pregnancy and in menopause – physiological conditions associated with severe hormonal fluctuations. In pregnancy, high levels of estradiol and progesterone during the late phase decline rapidly within 48 h after parturition. Kask, Bäckström, Gulinello and Sundström-Poromaa (2008) found that PPI is lower during the late phase of pregnancy and early postpartum (1st postpartal day) compared to the late postpartum phase (4th postpartal day), when estradiol and progesterone levels have already declined. Concerning menopause, Kumari et al. (2008) found sex differences in PPI to vanish when tested in postmenopausal women and age-matched men.

Furthermore, Kumari (2011) reviewed sex differences in PPF, namely healthy young women showing more PPF than men and also greater PPF during the luteal relative to the follicular phase. As to that, Kumari and colleagues repeatedly suggested that gender differences in human sensorimotor gating represent a shift of the inhibition/facilitation curve in the direction of facilitation in women relative to men (Kumari et al., 2003; Aasen et al., 2005; Kumari et al., 2010).

Sex differences in illness onset, prognosis, course and treatment are well-established in schizophrenia (Aleman, Kahn, & Selten, 2003; for reviews see Angermeyer & Kühnz, 1988; Abel, Drake, & Goldstein, 2010; Kulkarni, Hayes, & Gavrilidis, 2012; Markham, 2012) – a disorder strongly associated with PPI deficits (see section 1.2). It was hypothesized that estrogens might exert an age-dependent protective effect in women (Häfner, 2003), i.e. raising the vulnerability threshold for illness outbreak between puberty and menopause (estrogen protection hypothesis) (Riecher-Rössler & Häfner, 1993). This protection hypothesis has been supported by the findings that estradiol plasma levels negatively correlate with both the therapeutically required dose of antipsychotic medication (as reviewed in Kumari, 2011; Begemann, Dekker, van Lunenburg, & Sommer, 2012) and symptom severity (Riecher-Rössler, Häfner, Stumbaum, Maurer, & Schmidt, 1994) as well as promising results from intervention studies that used estradiol in hormone replacement therapy (Kulkarni et al., 2008, 2010). In addition, Riecher-Rössler and Häfner (1993) postulated the hypothesis of hypoestrogenism in schizophrenia, which is based on numerous reports about later age of menarche, menstrual irregularities, anovulation, reduced fertility and reduced estradiol blood levels in schizophrenia patients (see Riecher-Rössler & Kulkarni, 2011 for review).

1.4 Interactions between estradiol and PPI

Estrogens are a group of substances, including estrone, 17 β-estradiol and estriol, which bind to estrogen receptors (Azcoitia, Arevalo, De Nicola, & Garcia-Segura, 2011; Turgeon, McDonnell, Martin, & Wise, 2004). The two major estrogen receptors ER-α and ER-β are expressed in various regions of the prefrontal cortex, hypothalamus and especially the limbic system, including the hippocampus and the amygdala, in a variety of species (Österlund & Hurd, 2001; Brann, Dhandapani, Wakade, Mahesh, & Khan, 2007). In men estradiol is synthesized from testosterone by the enzyme aromatase (cf. Nelson & Bulun, 2001; Brann et al., 2007), but its levels are low compared to women (cf. Eisenegger, von Eckardstein, Fehr, & von Eckardstein, 2013; Riecher-Rössler et al., 1994).

While estradiol was classically considered a sex hormone, regulating the female reproductive cycle as well as the development and maintenance of female reproductive tissues (Kenneth, 1982), its neuroprotective, neurotrophic and antipsychotic actions are nowadays a point of intense research interest. Besides exerting effects on brain differentiation during development (Goldstein et al., 2002), estradiol affects brain structure (Pletzer et al., 2010) and behavior (cf. McEwen, Akama, Spencer-Segal, Milner, & Waters, 2012). Hence, estradiol is a "neuroactive steroid" with influence on signaling pathways within the CNS (Rupprecht, 2003). However, the mechanisms through which estradiol might exert its influence on PPI remain elusive.

As reviewed in Kulkarni et al. (2012) estradiol has been reported to interact with the dopaminergic, serotonergic and glutaminergic systems, and is also found to modulate $GABA_A$ receptors by acting as functional antagonist at 5-hydroxytryptamine type 3 receptors ($5\text{-}HT_3$) (Rupprecht, 2003). Some of these interactions are similar to that of traditional and atypical antipsychotic drugs (Horacek et al., 2006). In humans and rats, Gogos and colleagues repeatedly examined the relationships between estradiol, dopamine receptor antagonists (e.g. apomorphine and haloperidol), serotonin-1A ($5\text{-}HT_{1A}$) receptor agonists (i.e. 8-hydroxy-dipropylaminotetralin [8-OH-DPAT] or buspirone) and PPI (Gogos & van den Buuse, 2004; Gogos, Nathan, Guille, Croft, & van den Buuse, 2005; van den Buuse & Gogos, 2007; Gogos, Kwek, Chavez, & van den Buuse, 2010). They found that estradiol treatment prevented PPI deficits induced by 8-OH-DPAT, buspirone or apomorphine. Furthermore, in an autoradiographic study in rats, these authors found that estrogen treatment reversed a significant reduction of dopamine transporter binding in the nucleus accumbens and increased dopamine D_2 receptor densities in the nucleus accumbens and caudate nucleus in ovariectomized rats (Chavez et al., 2010). They concluded that estrogen is more likely to affect dopaminergic than serotonergic functions, but as the findings seem at odds with the previously reported drug effects (i.e. antipsychotic action) on PPI they further acknowledged that even though estradiol clearly interacts with dopaminergic functions, the direction, specificity and extent of the interaction may depend on many factors and further research is needed to disentangle the relationship.

Considerable research also focused on the relationship between estradiol and glutamate (Zlotnik et al., 2011; Tsesis et al., 2013; see Wieck, 2011 for review). It has been found that ERs couple to metabotropic glutamate receptors (i.e. mGluR5 and mGluR3) and may initiate mGluR signaling independent of glutamate (Grove-Strawser, Boulware, &

Mermelstein, 2010; Meitzen & Mermelstein, 2011). This has been proposed as an important mechanism by which estradiol modulates neuron physiology (Meitzen & Mermelstein, 2011) and the glutamatergic function in the hippocampus and other brain regions (as reviewed in Wieck, 2011). There is further evidence that the glutamate levels in the hippocampus might in turn be negatively correlated with striatal dopaminergic activity (Stone et al., 2010). This mode of action further underlines the connections drawn between PPI, estradiol and schizophrenia (cf. sections 1.2 and 1.3) as increasing lines of evidence suggest schizophrenia's complex etiology to be associated with strong interconnected abnormalities in dopamine and glutamate transmissions (Laruelle, 2014; Goff & Coyle, 2001).

1.5 Objective and hypothesis

As reviewed in the preceding sections, there is evidence for reduced estrogens in schizophrenic female patients on the one hand, while, on the other hand, reduced PPI was reported to be associated with phases of high estrogens in healthy women. Therefore, the current study was designed to directly test the association between estradiol and sensorimotor gating in a homogenous sample of healthy adult males. The main hypothesis was that the administration of an estradiol gel, in comparison to placebo, would modify the efficiency of sensorimotor gating, as indexed by more or less PPI. Given previous findings we also expected that estradiol increases PPF.

2 Methods

2.1 Study design

This study was designed as a double-blind, placebo controlled crossover experiment. All subjects were tested twice with the two days of measurement separated by at least one week. On one testing day the participants received an estradiol gel (3 mg; Divigel®, Orion Pharma AG, Zug, Switzerland), while on the other day they received the same amount of a placebo gel. Order of gel administration was randomized and counterbalanced. The estradiol and the placebo gel used for the experimental manipulation were indistinguishable in appearance, density and odor. The prepulse modulation of the startle reflex was measured at four different prepulse lead intervals (inducing either PPI or PPF; see section 2.7). Data of all dependent variables (i.e. PPI, PPF, ISR and HAB; see section 2.8) was assessed at two different EMG recording sites (see section 2.6). Prepulse

lead interval, EMG recording channel and applied substance constituted within-subject factors.

2.2 Participants

For this study, young healthy males were recruited via online announcements and local advertisements. Responders were asked to complete an online survey (including the 12-item General Health Questionnaire [GHQ-12; Goldberg & Williams, 1988; Sarkova et al., 2006] and screening questions about their use of psychoactive substances as well as anamnestic questions based on the M.I.N.I. International Neuropsychiatric Interview [Sheehan et al., 1998]) and were invited to an initial test session (see section 2.3.1) to verify the study requirements: (I) male sex, (II) right-handed, (III) nonsmoker, (IV) normal weight, (V) absence of hearing impairments, (VI) no history of mental or neurological illness (e.g. schizophrenia-spectrum disorder, epilepsy or mood disorder) in the participant himself or a first-degree relative, (VII) absence of internal or endocrine diseases (e.g. liver dysfunction or diabetes), (VIII) no long term pharmacological treatment and (IX) no actual or former abuse of drugs and psychoactive substances (including illegal drugs as well as coffee, alcohol and cigarette smoking). For their participation in the recruiting session all participants received a monetary remuneration in the amount of 10 Euros. Subjects who met all the requirements and showed sufficient startle response – hence were not considered non-responders[1] – were invited to participate in the main experiment. To minimize the effects of caffeine on PPI and startle (Braff et al., 2001), subjects were asked to omit caffeinated beverages one hour before the start of the test sessions, as well as medication intake and alcohol consumption within 24 hours before testing. Furthermore, they were asked to be well rested and not to wear contact lenses on the days of testing. Prior to the measurements the study procedure was fully explained and all study participants provided written informed consent. For participation in the main measurements they received an expense allowance in the amount of 70 Euros.

Thirty two subjects (mean age = 25.3 ± 2.8 [SD] years) participated in the main study. Two subjects were excluded from data analysis. In one subject data from one recording session were missing due to a technical problem in the data acquisition. The other subject was excluded as outlier since his PPI values deviated strongly from the rest of the sample. Therefore, the final sample for the analysis included 30 participants. The initial

[1] Subjects were classified non-responders when spontaneous and voluntary blinks were clearly apparent during EMG recording, but startle responses at EMG-frequencies of 100μV were not distinguishable throughout the session.

test sessions were carried out between May 2013 and February 2014 and the main data collection lasted from March to April 2014.

2.3 Procedure

All measurements were conducted in the Laboratory of Cognitive Neuroscience at the Institute of Normal and Pathological Physiology (INPP), Slovak Academy of Sciences, Bratislava, Slovakia, and were in accordance with the Declaration of Helsinki and approved by the Ethical Committee of the INPP. Participants were invited to the laboratory at three different days: one day initial test session (see following section) and two days of main measurements (see section 2.3.2). On all days, the recordings of the startle reflex (see section 2.6) were carried out in an electrophysiological laboratory. All other procedures, i.e. interviews, administration of questionnaires, gel application etc. were carried out in a separate room next to the laboratory.

2.3.1 Initial test session

Upon arrival at the laboratory participants received thorough instructions about the experiment and gave written informed consent. Thereafter, a standardized interview served to clarify the participants' use (frequency, recency etc.) of psychoactive substances, including caffeine, alcohol, nicotine, cannabinoids, methamphetamine, MDMA (ecstasy), cocaine, amphetamines, opiates, hallucinogens, organic intoxicants and psychotropic drugs. In addition to this self-report, all subjects received a urine toxicological screening for cotinine (i.e. nicotine consumption; Diagnostik Nord, Schwerin, Germany), cannabis, amphetamines, methamphetamine, MDMA, cocaine, barbiturates, benzodiazepines, LSD and opiates (BIOGEMA, Košice, Slovak Republic) and were excluded on the basis of any positive result. Furthermore, vague and conspicuous responses in the online survey (see section 2.2) were discussed to clarify and ensure the participants' physiological and mental health. As Eisenegger et al. (2013) suggest to collect pharmacokinetic data in subjects with similar anthropometric characteristics, the participants' height and weight were measured and the body mass index (BMI[2]) calculated. Subjects then underwent a PPI test session (cf. sections 2.6 and 2.7) in order for them to become familiar with the task and for the experimenters to discover possible non-responders (see section 2.2). To verify good hearing ability white noise was presented at increasing intensities (25, 35, 45 and 55 dB)

[2] The body mass index provides an indicator for body fat and is defined as the individual's body mass divided by the square of their height (BMI=kg/m²).

and all subjects confirmed to hear at least 35 dB. At the end of the initial session subjects completed the Schizotypal Personality Questionnaire (SPQ; Raine, 1991) translated into Slovak and the Slovak version of the NEO Five Factor Inventory (NEO-FFI; Ruisel & Halama, 2007; Costa & McCrae, 1992). The total length of the initial session was approximately two hours.

2.3.2 Main test sessions

On their arrival subjects were welcomed and asked to provide the first urine sample for the multiple toxicological drug screening (cf. sections 2.3.1 and 2.5). Then the first saliva sample was collected (see section 2.5) in order to determine the hormonal baseline levels. After that, either the estradiol or the placebo gel was administered respectively as described in the following section. Subsequent changes in the hormonal concentration were monitored by collecting five further saliva samples hourly after gel administration as well as two further urine samples. The PPI measurement was carried out two hours after the gel was applied, as the maximum blood estradiol concentration was expected to be at that point of time (Eisenegger et al., 2013). The waiting time before and after the PPI measurement subjects spent reading or using the computer, with social interaction kept at a minimum. On the second test day participants completed the BIS BAS questionnaire (Carver & White, 1994; Slovak translation) and their palms of both hands were scanned in order to determine the second-to-fourth digit ratio (2D:4D; ratio of the lengths of the index finger, 2D, and the ring finger, 4D; see section 2.9). On both days of measurement subjects spent approximately 5.5 hours at the INPP in order to complete the data collection.

2.4 Gel application

Subjects self-applied either gel to their bare chest, upper arms and shoulders. They were then instructed not to wash hands or redress within ten minutes after the administration as to ensure total absorption.

2.5 Saliva and urine sampling

A total of six saliva samples were collected at hourly intervals (at hours 0, 1, 2, 3, 4 and 5 in relation to gel application). Participants were asked not to eat or drink 10 min before sampling. For each sample they obtained a new pair of disposable gloves and then passed saliva through a plastic straw into a plastic container (SalicaCap Tubes, IBL

international). Following Granger, Shirtcliff, Booth, Kivlighan, and Schwartz's (2004) recommendation, the samples were frozen and stored at -80°C.

In addition, three urine samples were collected: the first one upon arrival (also serving the drug screening), and then three and five hours after the gel administration. Similar to saliva sampling, subjects received disposable gloves and provided the sample into a plastic container. The samples were again frozen and stored at -80°C.

2.6 EMG recording

Approximately 1.5 hours after gel application subjects were asked to remove all metal objects (e.g. keys and jewelry) and turn off their mobile phones and were guided into the sound-attenuated and electrically shielded laboratory. In preparation of the EMG recording, the skin area below the eyes and at the central forehead was cleansed with a cotton swab saturated with ethyl alcohol and then scarified with a sterile needle. To record EMG, two sintered Ag/AgCl ring electrodes (EASYCAP, Herrsching, Germany) were fixed beneath every eye over the left and right orbicularis oculi muscle. Following Blumenthal et al. (2005) one electrode was placed below the lower eyelid in line with the pupil in forward gaze and the second one was placed 2 cm lateral to the first. The ground electrode was attached to the center of the forehead. All electrodes were fixed using electrode adaptors and double-sided adhesive collars and were filled with a high conductivity electrode gel (Adagel; Neuris, Pieštany, Slovak Republic). Electrode impedances were measured and kept below 3 kΩ. Electrodes were connected to NeXus-10 DC-amplifier (Mind Media B.V., 2005) and signal was registered with a sampling rate of 2048 Hz. To minimize eye movements, a white linen cloth was placed approximately 10-15 cm in front of the participants' faces and they were instructed to sit still, keep their eyes open, look straight ahead and avoid unnecessary blinking.

2.7 Auditory stimulation

Auditory stimuli were delivered via audiometric headphones ER-2 (tubephone insert earphones with 13 mm foam eartips; Etymotic Research, Groove Village, USA). The experimental session began with a 3-minute acclimation period to 55 dB white noise that continued as background noise throughout the session in order to mask eventual environmental noises. In the subsequent PPI/PPF paradigm pulse stimuli (white noise, 105 dB, 40 ms; with instantaneous rise/fall) were either presented alone or following a prepulse

(white noise, 75 dB, 20 ms). There was a range of interstimulus intervals (ISI; prepulse onset to pulse onset) to elicit either PPI (30, 60 and 120 ms) or PPF (4500 ms). At a whole, the session consisted of 53 trials in three blocks. Inter-trial interval (ITI) was randomized within an interval ranging from 10 to 20 s. Block 1 consisted of 3 successive pulse alone (PA) trials. In block 2 eight PA trials, eight prepulse alone (PPA) trials and eight trials of each ISI (PP30, PP60, PP120, and PP4500) were presented in random order. Block 3 consisted of 2 PA trials. Stimuli were presented using E-Prime 2.0 (Psychology Software Tools, Inc., Sharpsburg, PA, USA). Overall duration of the PPI session was approximately 20 min.

2.8 EMG processing and analysis

Prior to data analysis EMG data was processed using the MATLAB-based software toolbox EEGLAB (Delorme & Makeig, 2004). EMG was digitally filtered in the range 28-800 Hz and a 48-52 Hz notch filter was used to eliminate 50 Hz interference. Epochs from -100 to 400 ms with respect to startle stimulus onset were selected, visually inspected and trials containing artifacts were removed. The magnitude of the startle response was determined as the peak value of the rectified EMG within a time window ranging from 21 to 150 ms after stimulus onset. Mean blink amplitudes were calculated for each subject, session (treatment), condition (i.e. trial type: PA, PP30, PP60, PP120, PP4500) and eye (i.e. channel, right: EMG-R; left: EMG-L).

The following startle response measures were examined:

(I) Startle prepulse modulation (**prepulse inhibition** and **prepulse facilitation**), calculated according to the formula (1-PP/PA)*100%, where PP and PA denote startle amplitude in prepulse-pulse and pulse alone trials (recorded in block 2) respectively. Thus, large values indicate strong PPI, small values indicate weak PPI, and values lower than 0 indicate an augmentation of the startle response (i.e. PPF). Prepulse modulation was calculated separately for each ISI, yielding conditions termed ISI30, ISI60, ISI120, and ISI4500.

(II) **Initial startle reactivity** (ISR), the blink amplitude in the very first PA trial (i.e. 1st trial of block 1);

(III) **Habituation** of the startle response (HAB) over the session, computed as (1-PA1/PA3)*100%, where PA1 and PA3 denote mean startle response within block 1 and 3 respectively.

2.9 Measurement of 2D:4D digit ratio

For the second-to-fourth digit ratio assessment the palmar surface of both hands was scanned – fingers in a "stretched" position – with a digital image scanner (Canon, CanoScan 4400F). As suggested by Kemper and Schwerdtfeger (2009) the AutoMetric 2.2 software (DeBruine, 2008) was used to determine the lengths of the second and fourth digits as the distance of the fingertip to the ventral proximal crease of each digit. For both hands, digit ratios were calculated by dividing the length of the index finger (2D) by the length of the same hand ring finger (4D). For further analysis the values of the left and right hand were averaged.

2.10 Statistical analysis

All analyses were carried out using Statistical Package for the Social Sciences (SPSS, version 17.0) with an α-level for statistical significance set at 0.05 unless otherwise specified. Descriptive statistics, histograms and boxplots were used to explore data and identify outlying values (thereupon two cases were excluded; see section 2.2). To further reduce the effect of outliers in the startle parameters, the startle measures were winsorized within groups before inferential statistical data analysis. Values lower/higher than the $25^{th}/75^{th}$ percentile minus/plus 1.5 times the interquartile range of the group were replaced with the minimum/maximum value within the respective interval (replaced values ISR: 5.8%; HAB: 2.5%; PPI: 3.1%; PPF: 0.8%). To identify possible covariates, Pearson correlation coefficient was calculated between PPI/PPF values on the one hand and the scores on NEO-FFI subscales of Neuroticism and Extraversion, the 2D:4D digit ratio, the SPQ total score and the four BIS/BAS domains on the other hand.

As previously implemented in other studies investigating PPI/PPF (e.g. Aasen et al., 2005; Kumari et al., 2008, 2010) the effects of the experimental manipulation on either PPI or PPF were examined with separate mixed-design analyses of variance (ANOVA) and covariance (ANCOVA), with the within-subject factors *ISI* (PPI: 30, 60, 120 ms; PPF: 4500 ms), *Channel* (EMG-R, EMG-L) and *Substance* (placebo, estradiol) and the between-subject factor *Order* (placebo first; estradiol first). The effects of Order were only analyzed in interactions with Substance. In case the assumption of data sphericity was violated (tested with Mauchly's test), Greenhouse-Geisser correction for degrees of freedom was used. Significant interactions and main effects were followed up by repeated contrasts. To

test the experimental effects on the initial startle reactivity and on habituation, 2 x 2 x 2 (Substance x Channel x Order) mixed-design ANOVAs were calculated.

3 Results

Two-tailed Pearson correlations between startle parameters on the one hand and the 2D:4D digit ratio, SPQ total score, NEO-FFI subscales Extraversion and Neuroticism and the BIS/BAS subscales are presented in Table 3. A significant negative correlation was found between ISI4500 and Extraversion at EMG-R, $r = .38$, $p = .045$, but not at EMG-L, $r = .23$, $p = .226$ (note that more negative values of relative startle modulation indicate stronger PPF). Furthermore, there was a significant positive correlation between ISI4500 and the BIS score at EMG-L, $r = -.39$, $p = .034$, and a trend for negative association between ISI60/ISI120 and the SPQ total score.

The experimental effects on PPI were analyzed using 3 x 2 x 2 x 2 (ISI x Channel x Substance x Order) mixed-design ANCOVA (covariate: SPQ total score). This analysis revealed significant main effects of ISI, $F(1.29, 34.85) = 9.25$, $p = .002$, $\eta^2 = .255$, Channel, $F(1, 27) = 6.16$, $p < .020$, $\eta^2 = .186$, but not Substance, $F(1, 27) = 1.46$, $p = .238$ (Table 5). Pairwise comparisons revealed that ISI30 was significantly smaller than both ISI60, $F(1, 27) = 13.25$, $p = .001$, $r = .57$, and ISI120, $F(1, 27) = 7.32$, $p = .012$, $r = .46$. ISI60 and ISI120 did not differ significantly, $F(1, 27) = 1.88$, $p = .182$, $r = .26$. The significant main effect of Channel reflected overall weaker PPI at EMG-L than EMG-R. Furthermore, we found a marginally significant ISI x Substance interaction, $F(2, 54) = 2.74$, $p = .073$, but a significant interaction between ISI, Substance and Order, $F(2, 54) = 8.19$, $p = .001$, $\eta^2 = .233$ (see Figure 3). An analysis of simple effects showed that the Substance x Order interaction was significant only for ISI30, $F(1, 13) = 7.56$, $p = .017$, but not ISI60, $F(1, 13) = .60$, $p = .452$, and ISI120, $F(1, 13) = .05$, $p = .830$. Furthermore, a paired t-test showed a marginally significant difference, $t(15) = -1.71$, p(one-tailed) = .055, in the scores of the estradiol ($M = 72.24$, $SD = 17.63$) and placebo ($M = 65.56$, $SD = 19.53$) conditions at ISI30 in subjects who received estradiol on the second day (Figure 3A). This indicates that estradiol increased PPI at ISI30, but only when administered at the second day of testing. Furthermore, the interaction between ISI and SPQ total score was significant, $F(1.29, 34.85) = 4.06$, $p = .045$, $\eta^2 = .131$. Hence, the influence of self-reported schizotypy on PPI varied in respect of the interstimulus interval. As depicted in Figure 4,

the association between the Schizotypal Personality Questionnaire and PPI was highest at ISI120 but lowest at ISI30.

Figure 2 shows that, on average, the ISI of 4500 ms did not result in an augmentation of the startle reaction relatively to the PA trials (note that PPF would be indicated by negative values; cf. section 2.8). For the analysis of this condition extraversion and the BIS score were used as covariates. The 2 x 2 x 2 (Channel x Substance x Order) ANCOVA revealed no significant main and interaction effects (Table 6).

Startle response habituation was analyzed using a 2 x 2 x 2 (Channel x Substance x Order) mixed-design ANOVA (Table 7). This analysis revealed no significant main and interaction effects. The interaction Substance x Order was marginally significant, $F(1, 28) = 3.14$, $p = .087$. Figure 5 indicates that habituation was approximately the same in both experimental conditions when estradiol was administered on the second day of measurement. But habituation was stronger after estradiol application when administered on the first day of testing. Furthermore, on the first day of measurement habituation was lower in subjects who received estradiol, while on the second day of testing habituation was higher in subjects who received estradiol.

To analyze initial startle reactivity a 2 x 2 x 2 (Channel x Substance x Order) mixed-design ANOVA was calculated. This analysis revealed no significant effects. A trend significance was found for the interaction Channel x Substance, $F(1, 28) = 3.89$, $p = .059$, (Table 8): estradiol administration tended to decrease startle reactivity at EMG-L and to increase ISR at EMG-R (Figure 6).

4 Discussion

This study examined the effects of estradiol administration on several measures of startle response modulation in men, including PPI, PPF and habituation, as well as initial startle reactivity. The study replicated earlier findings that PPI varies with the interstimulus interval (c.f. Braff et al., 2001) and is weaker for a prepulse lead interval of 30 ms than ISIs of 60 and 120 ms. However, in contrast to previous reports (Graham, 1975; Braff et al., 1978; Kumari et al., 2008) the prepulse lead interval of 4500 ms did not result in an augmentation of the startle reflex (cf. Figure 2).

In contrast to our expectations, this study suggests that a single dose of 3 mg transdermal estradiol has no overall influence on PPI and other measures of the startle response. For PPI, we only found a tendency towards stronger gating at ISI30, but only

when estradiol was administered at the second testing day. It is unclear how such an effect could be explained. In general, our findings resemble those of Gogos et al. (2005) who found that oral administration of 2 mg of 17 β-estradiol compensated a buspirone-induced PPI disruption but did not induce any changes in PPI or startle if administered alone. They therefore concluded that the reversal of the buspirone-induced disruption of PPI was not due to a direct effect of estradiol on PPI, but due to estradiol's modulation of 5-HT_{1A} receptor signaling. However, as the used doses of estradiol in this (cf. Eisenegger et al., 2013) as well as Gogos et al.'s (2005) study were expected to raise serum concentrations to levels found in normally cycling women during the luteal phase, these results are at odds with reports of reduced levels of PPI in the luteal compared to the follicular phase (Swerdlow et al., 1997; Jovanovic et al., 2004; Kumari et al., 2010). It can be speculated that such discrepancy may result from different types of estrogen stimulation, with naturally produced vs. externally delivered estradiol (cf. Gogos et al., 2005). Moreover, the menstrual cycle phase effects on PPI might not result from estradiol level variations only. For instance, Kumari et al. (2010) found no relation between PPI and estradiol, but reported that from the follicular to the luteal phase larger increases of progesterone were associated with smaller decreases in PPI – a finding that is also supported by animal research (Gogos & van den Buuse, 2004). On the other hand, it has been suggested that besides female sex hormones, PPI and PPF might also be sensitive to male sex hormones, particularly testosterone (Kumari et al., 2008). Another explanation could be that the relationship between estrogen and PPI is not linear but follows an inverted U-shaped curve, with both very high and very low levels being associated with low PPI (Kumari, 2011). Furthermore, it has been argued that estrogen may reduce stimulated dopamine release in the striatum at high doses or with a prolonged exposure, but enhance it when administered at low doses (for review see Markham, 2012). This is partly underpinned by recent findings in mice that revealed a significant increase of PPI after chronic 17-β estradiol administration (Charitidi, Meltser, & Canlon, 2012). We can thus speculate that the single dose of estradiol in our study (3 mg) was too high to induce PPI reduction or too low to induce PPI enhancement. However, to follow up possible non-linear relationships in more detail, the data on estradiol concentration would be helpful, but the results of the saliva and urine analyses have not been available at the time of completing this thesis.

The observation that startle reactivity and habituation were not considerably modulated by estradiol seems in line with reports of no sex differences in these parameters (Swerdlow et al., 1993; Ludewig et al., 2003; Kumari et al., 2010) and is also in

accordance with findings obtained from animal research (Charitidi et al., 2012). Nonetheless, we observed a trend for estradiol administration on the first day of measurement to result in smaller habituation on the second day (i.e. after placebo administration). This might be caused by estradiol's influence on learning and memory (cf. Brann et al., 2007; Gervais, Jacob, Brake, & Mumby, 2014). However, such effects cannot explain why PPI at ISI30 was increased after estradiol administration on the second but not the first day of measurement.

In the present study substantial differences between left and right EMG recording sites were apparent in the PPI – but not PPF – conditions, especially when controlled for schizotypal traits. The greater PPI on the right compared to the left side EMG in this study corresponds with the normal lateralization in EMG startle response that has been reported previously (Swerdlow et al., 2000; Braff et al., 2001). Interestingly, initial startle reactivity was stronger on the right side only in the estradiol, but not the placebo, condition. For this finding, we have no explanation.

Also in accordance with previous research is the interaction between PPI at different ISIs and schizotypy. As mentioned above, PPI is deficient in schizophrenia patients (cf. section 1.2), their unaffected relatives (Cadenhead et al., 2000; Kumari et al., 2005; Takahashi et al., 2010) and in patients with schizotypal personality disorder (Cadenhead et al., 1993, 2000). Moreover, there have also been reports about an inverse relationship between schizotypal traits and PPI in the general (healthy) population (Swerdlow, Filion, Geyer, & Braff, 1995; Abel, Jolley, Hemsley, & Geyer, 2004; Takahashi et al., 2010; see Giakoumaki, 2012 for review). In this study, we did not find statistical evidence for healthy subjects high in schizotypy to show generally lower PPI. However, we found that the association between schizotypy and PPI depends on the prepulse-pulse interstimulus interval, i.e. it was lowest at ISI30 and highest at ISI120 (Figure 4). In contrast to our study, the previously mentioned studies examined the schizotypy–PPI relationship only at a single prepulse lead interval, i.e. at either 60 ms ISI (Swerdlow et al., 1995) or 120 ms ISI (Abel et al., 2004; Takahashi et al., 2010). However, our results seem to be related to findings in schizophrenia patients who show greater PPI deficits at ISI60 (Braff & Geyer, 1990; Swerdlow et al., 2006) and ISI120 (Braff & Geyer, 1990) than at ISI30.

In our search for covariates of startle modulation we assessed several psychological and biological trait measures. Analyses of associations between these variables revealed a strong positive correlation of BIS scores with the NEO-FFI neuroticism scores, which has

already been reported by Heubeck, Wilkinson, and Cologon (1998). We also found a negative correlation between 2D:4D and neuroticism, i.e. higher (more feminine) 2D:4D ratio (Gooding, Johnson, & Peterman, 2010) was associated with lower neuroticism scores. This contradicts previous findings in female and combined sex samples, in which either no relation was found (Lippa, 2006; Burton, Guterman, & Baum, 2013) or an association in the opposite direction was revealed (Austin, Manning, McInroy, & Mathews, 2002; Fink, Manning, & Neave, 2004). The relationship between 2D:4D digit ratio and personality traits thus remains a subject for further investigations and future research.

5 Conclusion

The present study found no considerable influence of a single dose of 3 mg transdermally administered estradiol on prepulse modulation, habituation and initial magnitude of the acoustic startle response in men.

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Figures

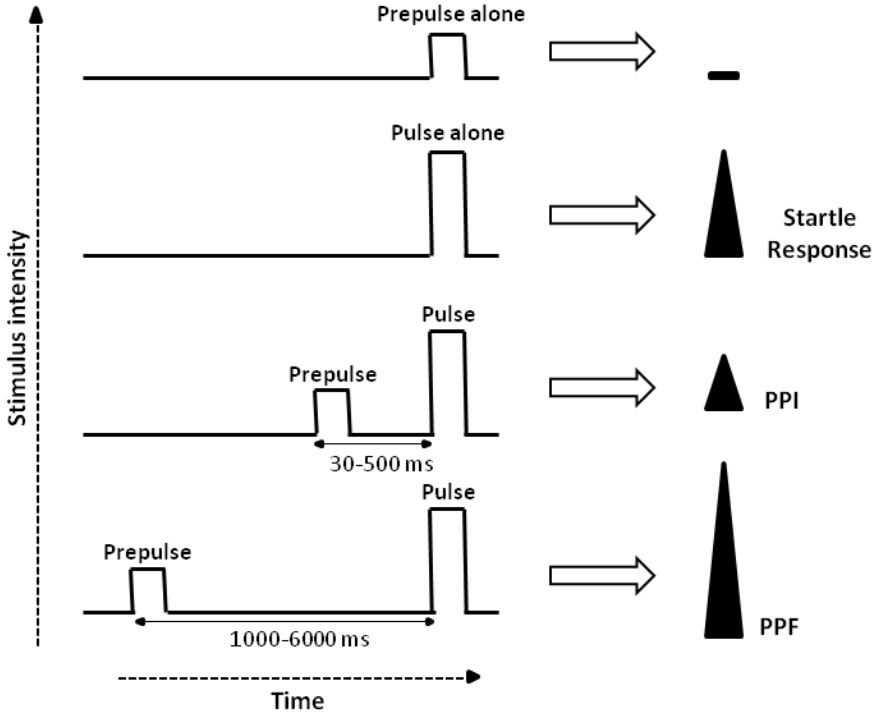

Figure 1 Graphic Representation of Prepulse Inhibition (PPI) and Prepulse Facilitation (PPF) (modified from Kumari, 2011, p.3)

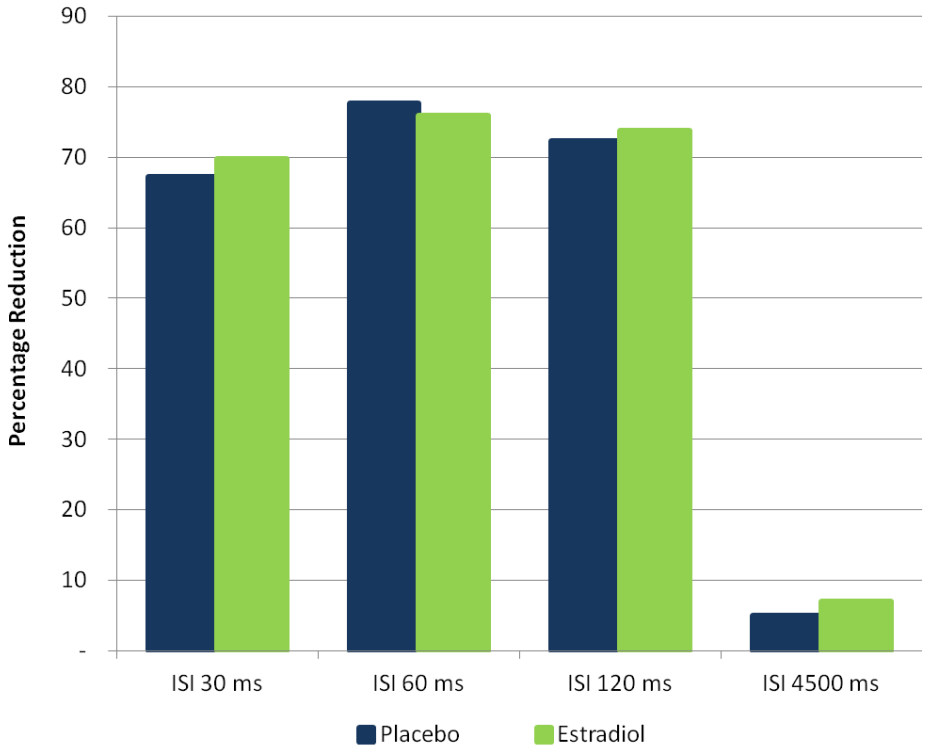

Figure 2 Mean values of percentage reduction in startle amplitude at different ISIs, displayed separately for Placebo and Estradiol.

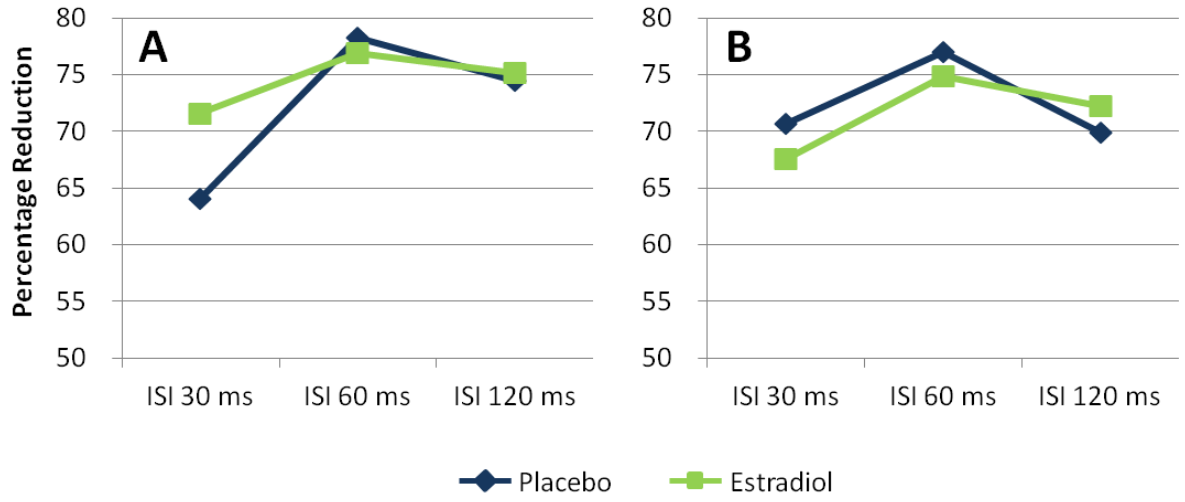

Figure 3 Prepulse inhibition at different ISIs and under different Substance conditions (Placebo: blue lines; Estradiol: green lines) in consideration of the application order.

A: Placebo first (i.e., placebo on 1st day of measurement; estradiol on 2nd day of measurement)

B: Estradiol first (i.e., 1st day estradiol; 2nd day placebo)

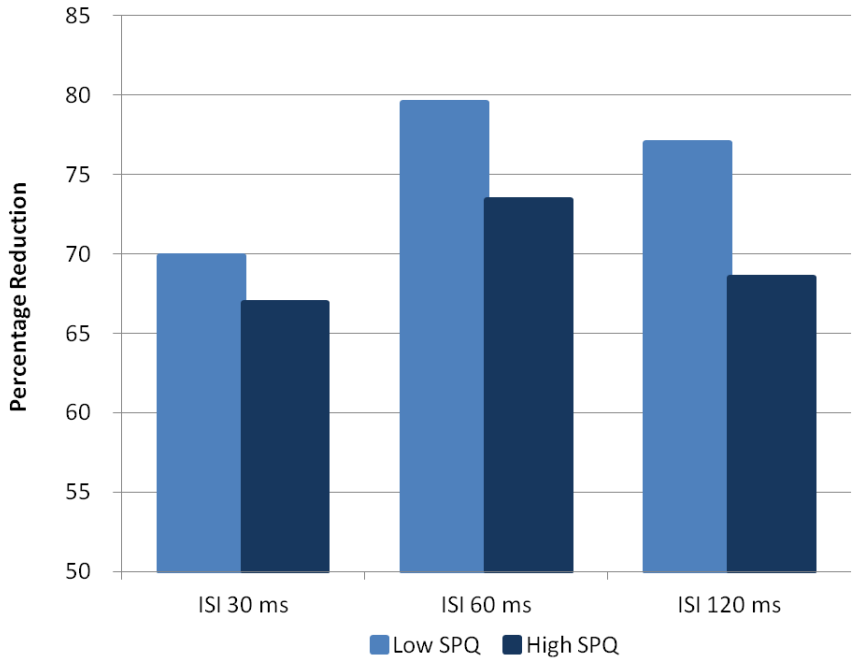

Figure 4 Prepulse inhibition at different ISIs for low SPQ (SPQ total score < median) and high SPQ (SPQ total score > median).

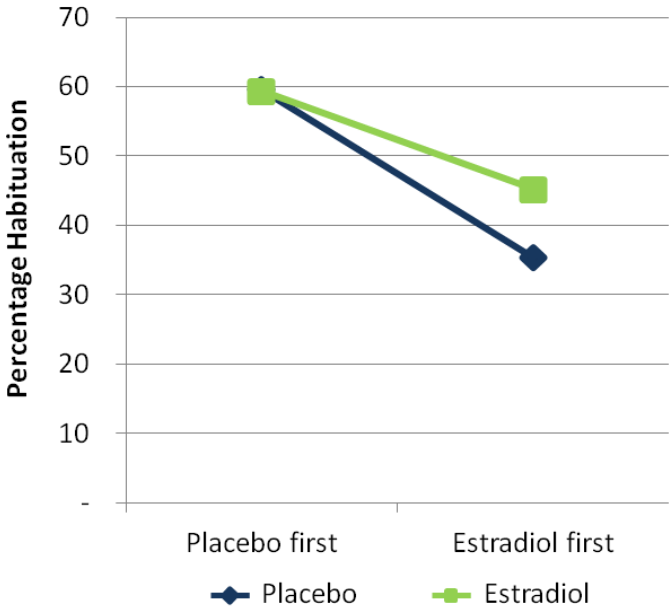

Figure 5 Startle habituation after placebo/ estradiol application and with respect to application order (Placebo first vs. Estradiol first).

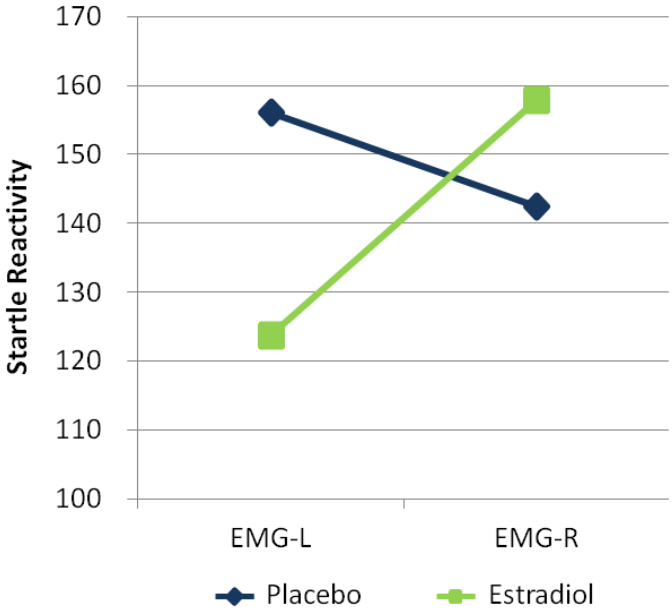

Figure 6 Initial startle reactivity at EMG-L/ EMG-R displayed for the placebo and estradiol condition.

Tables

Table 1

Descriptive Statistics of Trait Variables

	Mean	*SD*	*Min*	*Max*
Age	25.30	2.81	21.90	33.20
BMI	22.91	1.85	19.10	26.50
GHQ	1.50	2.35	0	9
2D:4D	.96	.03	.91	1.02
SPQ	14.77	9.92	1	39
Neuroticism	14.41	6.12	4	26
Extraversion	30.62	6.40	16	40
BAS Drive	12.47	1.85	8	16
Fun Seeking	12.67	2.25	6	16
Reward Responsibility	17.53	1.87	13	20
BIS	26.67	3.72	18	35

Table 2

Descriptive Statistics of Prepulse Inhibition (PPI), Prepulse Facilitation (PPF) and Habituation for EMG-L and EMG-R for Placebo and Estradiol

	Placebo		Estradiol	
Condition	*M*	*SD*	*M*	*SD*
EMG-L				
PPI30	63.64	22.62	67.52	20.37
PPI60	77.47	16.25	73.91	18.19
PPI120	72.22	19.54	74.39	16.10
PPF	1.83	35.29	6.19	35.96
Habituation	51.29	30.55	48.95	31.73
EMG-R				
PPI30	70.76	16.41	71.94	18.93
PPI60	77.94	16.34	77.97	17.05
PPI120	72.48	19.69	73.20	21.12
PPF	7.98	28.65	7.73	30.38
Habituation	45.36	35.96	56.57	27.09

Table 3

Pearson correlation coefficients between Startle Parameters and Second-to-Fourth Digit Ratio, SPQ Total Score, NEO-PI-R Domains Neuroticism and Extraversion and the BIS/BAS Scales for EMG-L and EMG-R

Condition	DR	SPQ	N	E	BAS DR	BAS FS	BAS RR	BIS
EMG-L								
PPI30	-.09	.13	-.19	.07	.03	-.16	-.02	-.26
PPI60	-.10	-.04	-.12	.12	-.12	-.25	-.04	-.18
PPI120	-.07	.01	-.02	-.02	-.07	-.06	-.04	-.08
PPF	-.03	-.18	-.06	.23	.15	.04	.03	-.39*
Habituation	.07	.03	.09	-.09	.22	.26	-.01	.05
Reactivity	.09	.20	-.16	-.03	-.11	-.03	-.09	-.24
EMG-R								
PPI30	-.19	.03	-.07	.00	-.09	-.03	-.01	-.08
PPI60	-.25	-.26	-.04	.27	-.12	-.16	.16	.02
PPI120	-.09	-.21	-.21	.16	.07	.06	.14	-.12
PPF	-.08	.01	.12	.38*	.31	.02	.29	-.12
Habituation	-.01	.15	.09	-.19	.03	-.09	-.02	.32
Reactivity	-.03	.19	-.05	-.18	-.15	-.15	-.25	-.02

Note. DR = 2D:4D Digit Ratio, SPQ = Schizotypal Personality Questionnaire, N = NEO-FFI Neuroticism, E = NEO-FFI Extraversion, BAS DR = BIS/BAS BAS Drive, BAS FS = BIS/BAS Fun Seeking, BAS RR = BIS/BAS Reward Responsibility, BIS = BIS/BAS Behavioral Inhibition System.
*p < .05, two-tailed

Table 4

Pearson correlation coefficients between 2D:4D Digit Ratio, SPQ Total Score, NEO-FFI Domains Neuroticism and Extraversion and the BIS/BAS Scales

	DR	SPQ	N	E	BAS DR	BAS FS	BAS RR	BIS
DR	1	.14	-.45*	-.26	-.10	.25	-.05	-.28
SPQ	.14	1	.33	-.34	.15	-.01	-.19	.19
Neuroticism	-.45*	.33	1	-.06	.15	-.10	-.08	.65**
Extraversion	-.26	-.34	-.06	1	.20	.40*	.66**	-.30
BAS Drive	-.10	.15	.15	.20	1	.19	.30	.15
BAS Fun Seeking	.25	-.01	-.10	.40*	.19	1	.46*	-.32
BAS Reward Resp.	-.05	-.19	-.08	.66**	.30	.46*	1	.04
BIS	-.28	.19	.65**	-.30	.15	-.32	.04	1

Note. DR = 2D:4D Digit Ratio, SPQ = Schizotypal Personality Questionnaire, N = NEO-FFI Neuroticism, E = NEO-FFI Extraversion, BAS DR = BIS/BAS BAS Drive, BAS FS = BIS/BAS Fun Seeking, BAS RR = BIS/BAS Reward Responsibility, BIS = BIS/BAS Behavioral Inhibition System.
*p < .05, **p < .01, two-tailed

Table 5

Statistical analysis of experimental effect on PPI (3 x 2 x 2 x 2 repeated measures ANCOVA)

	df_1	df_2	*F*	*p*
ISI	1.29	34.85	9.25	.002[1]
Channel	1	27	6.16	.020[2]
Substance	1	27	1.46	.238
SPQ	1	27	.89	.353
ISI x SPQ	1.29	34.85	4.06	.042[3]
ISI x Channel	1.46	39.35	.02	.943
ISI x Substance	2	54	2.74	.073
Channel x SPQ	1	27	2.84	.103
Channel x Substance	1	27	2.15	.154
Substance x Order	1	27	1.05	.315
Substance x SPQ	1	27	1.62	.214
ISI x Channel x SPQ	1.46	39.35	1.15	.313
ISI x Channel x Substance	2	54	1.56	.219
ISI x Substance x Order	2	54	8.19	.001[4]
Substance x $Order_{ISI30}$	1	13	7.56	.017[5]
Substance x $Order_{ISI60}$	1	13	.60	.452
Substance x $Order_{ISI120}$	1	13	.05	.830
ISI x Substance x SPQ	2	54	.619	.542
Channel x Substance x Order	1	27	.88	.357
Channel x Substance x SPQ	1	27	2.85	.103
ISI x Channel x Substance x Order	2	54	1.86	.165
ISI x Channel x Substance x SPQ	2	54	.72	.490

Note.

[1] $\eta^2 = .255$

[2] $\eta^2 = .186$

[3] $\eta^2 = .131$

[4] $\eta^2 = .233$

[5] $\eta^2 = .368$

Table 6

Statistical analysis of experimental effect on PPF (ISI4500) (2 x 2 x 2 repeated measures ANCOVA)

	df_1	df_2	*F*	*p*
Channel	1	25	1.30	.265
Substance	1	25	.01	.909
Extraversion	1	25	.40	.534
BIS	1	25	.21	.652
Channel x Extraversion	1	25	.75	.396
Substance x Extraversion	1	25	1.64	.212
Channel x BIS	1	25	1.35	.256
Substance x BIS	1	25	1.14	.296
Substance x Order	1	25	.04	.847
Channel x Substance	1	25	2.19	.152
Channel x Substance x Extraversion	1	25	.39	.539
Channel x Substance x BIS	1	25	2.70	.113
Channel x Substance x Order	1	25	.07	.796

Table 7

Statistical analysis of experimental effect on the Startle Habituation (2 x 2 x 2 repeated measures ANOVA)

	df_1	df_2	*F*	*p*
Channel	1	28	.21	.650
Substance	1	28	2.84	.103
Substance x Order	1	28	3.14	.087
Channel x Substance	1	28	2.53	.123
Channel x Substance x Order	1	28	.72	.403

Table 8

Statistical analysis of experimental effect on Startle Reactivity (2 x 2 x 2 repeated measures ANOVA)

	df_1	df_2	*F*	*p*
Channel	1	28	.60	.445
Substance	1	28	.25	.620
Substance x Order	1	28	.43	.519
Channel x Substance	1	28	3.89	.059
Channel x Substance x Order	1	28	.08	.781

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