Stress induced by the socially evaluated cold-pressor test cause equivalent deficiencies of sensory gating in male subjects with schizophrenia and healthy controls

Article *in* Psychiatry Research · June 2015

DOI: 10.1016/j.psychres.2015.05.097 · Source: PubMed

CITATION
1

READS
127

10 authors, including:

Gabriel Rubio
Complutense University of Madrid
326 PUBLICATIONS **3,321** CITATIONS

SEE PROFILE

Francisco López-Muñoz
Universidad Camilo José Cela
263 PUBLICATIONS **2,214** CITATIONS

SEE PROFILE

Rosa Jurado Barba
Hospital 12 de Octubre
61 PUBLICATIONS **126** CITATIONS

SEE PROFILE

Isabel Martínez-Gras
Complutense University of Madrid
48 PUBLICATIONS **546** CITATIONS

SEE PROFILE

Psychiatry Research ■ (■■■■) ■■■–■■■

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Stress induced by the socially evaluated cold-pressor test cause equivalent deficiencies of sensory gating in male subjects with schizophrenia and healthy controls

Gabriel Rubio [a,b,c,d], Francisco López-Muñoz [b,e,f,*], Rosa Jurado-Barba [a,b,g], Isabel Martínez-Gras [a,b,c,d], Roberto Rodríguez-Jiménez [a,b,c,d], Regina Espinosa [g], Miguel Ángel Pérez-Nieto [g], Stephan Moratti [h,i], Miguel Ángel Jiménez-Arriero [a,b,c,d], Juan Carlos Leza [b,h,j]

[a] Department of Psychiatry, 12 de Octubre University Hospital, Madrid, Spain
[b] "Hospital 12 de Octubre" Research Institute, Madrid, Spain
[c] Department of Psychiatry, Complutense University, Madrid, Spain
[d] Networks for Cooperative Research in Health (RETICS-Addictive Disorder Network), Institute of Health Carlos III (ISCIII), MICINN and FEDER, Madrid, Spain
[e] Genomic Medicine and Faculty of Health Sciences, Camilo José Cela University, Madrid, Spain
[f] Department of Biomedical Sciences (Pharmacology Area), Faculty of Medicine and Health Sciences, University of Alcalá, Madrid, Spain
[g] Department of Psychology, Faculty of Health Sciences, Camilo José Cela University, Madrid, Spain
[h] Biomedical Research Center Network for Mental Health (CIBERSAM), Madrid, Spain
[i] Center for Biomedical Technology, Polytechnic University, Madrid, Spain
[j] Department of Pharmacology, Complutense University, Madrid, Spain

ARTICLE INFO

Article history:
Received 26 July 2014
Received in revised form
28 May 2015
Accepted 31 May 2015

Keywords:
Schizophrenia
Prepulse inhibition
Psychopathology
Cortisol
Stress
Socially evaluated cold-pressor test

ABSTRACT

It is known that patients with schizophrenia show a deficiency in the prepulse inhibition reflex (PPI). These patients display abnormalities in autonomic nervous system and hypothalamic–pituitary–adrenal function and may have an altered sensitivity to stress. To date, no studies have been carried out to determine the effect of acute stress on the PPI. We investigated whether there was a differential response in reactivity to acute stress caused by the socially evaluated cold-pressor test (SECPT) in a sample of 58 chronic male patients with schizophrenia and 28 healthy control subjects. PPI, salivary cortisol and heart rate (HR) were measured. The patients were evaluated in two sessions (with and without the SECPT) 72 h apart and basal measurements were carried out and 30 min post-startle probe. We found an increase in salivary cortisol levels and the HR with SECPT condition in both groups and a significantly lower PPI% in patients with schizophrenia. The most relevant findings of this study are that the impairment of the PPI is increased by stress. Stress-induced increase in cortisol in both groups, mainly in healthy control group which allows us to hypothesize that at least such deterioration may be due to the hypercortisolemia caused by the SECPT.

1. Introduction

The pathophysiology of schizophrenia is not totally known. In the last few decades there has been a particular focus on the malfunctioning of the sensory–motor system gating mechanisms that rely on the prefrontal cortex of those patients. The gating of information flow within the limbic system and the pathophysiology of schizophrenia has been assumed (Grace, 2000) and social deficits of schizophrenia (emotional processing, social perception, emotion recognition, etc.) could be linked to it. Thus, higher stress levels could affect sensory input. It has come to be considered that these deficiencies could be an endophenotype of schizophrenia (Braff, 2010). This deficit has been linked with weak dopamine regulation by the frontal cortex (Arnsten, 2013). Although several paradigms of startle reflex have been used (Hasenkamp et al., 2011; Dominelli et al., 2014), one of the most classic for studying this deficient sensory gating in schizophrenia is the prepulse inhibition of the startle reflex (PPI) (Hasenkamp et al., 2010).

The PPI is the inability to effectively attenuate the startle

* Correspondence to: Faculty of Health Sciences, Camilo José Cela University, C/ Castillo de Alarcón, 49, Urb. Villafranca del Castillo, 28692 Villanueva de la Cañada, Madrid, Spain. Fax: +34 91 860 9343.
E-mail addresses: flopez@ucjc.edu, francisco.lopez.munoz@gmail.com (F. López-Muñoz).

http://dx.doi.org/10.1016/j.psychres.2015.05.097
0165-1781/

response when it is preceded by a weak prepulse stimulus (Braff and Geyer, 1990). In a recent review on PPI in patients with schizophrenia, the existence of impaired inhibition of the PPI was confirmed in those patients (García-Sánchez et al., 2011). These alterations may be modulated by drug use; improve due to treatment with antipsychotics, especially atypical antipsychotics; be present in the initial stages of the illness; seem to be stable throughout the evolution of the disorder; and have been linked with positive or negative symptoms, or with the general psychopathology (Martínez-Gras et al., 2009; Jurado-Barba et al., 2011). Together with that the loss of sensory gating seems independent from a psychotic state, it may be suggested that it reflects a trait rather than a state phenomenon (Baker et al., 1987). Thus, in schizophrenia, a loss of sensory gating may result in an overflow in the brain of irrelevant stimuli and may therefore alter perception of the environment (see Mazza et al., 2013; Ebisch et al., 2014). This may have repercussions on the way that a stress stimulus could be interpreted.

Another area of investigation connected to schizophrenia is its relationship with stress. According to the vulnerability-stress model, schizophrenia is described as the result of a complex interaction between biological and psychosocial factors, the former being genetically determined, the latter being predominantly developed during life, which both contribute to the individual's vulnerability to develop a psychosis under stressful circumstances (Nuechterlein et al., 1994).

Although data on the impairment of the PPI in schizophrenia and the model of vulnerability to stress date back to the end of the 70s (Zubin and Spring, 1977; Braff et al., 1978), no studies have been carried out to determine the impact of acute stress on the PPI. For this reason, we conducted this study, which aimed to investigate whether there was a differential response in reactivity to acute stress caused by the socially evaluated cold-pressor test (SECPT) among a sample of subjects with schizophrenia and healthy controls. Our main hypothesis was that the subjects with schizophrenia, after being exposed to the SECPT would have a worse inhibition response in the PPI than the healthy controls. Bearing in mind the results of previous studies (Brenner et al., 2009), we also hypothesized that cortisol response would be blunted, while that of heart rate would be increased.

2. Methods and materials

2.1. Subjects

Fifty-eight male patients (age range: 25–56 years; mean age: 36.3 years, SD: 6.4) with schizophrenia diagnosed using the structured clinical interview for DSM-IV (SCID-P) (First et al., 1995) were recruited through the Brief Hospitalization Unit at the Mental Health Services of 12 de Octubre University Hospital (Madrid, Spain). The study sample was limited to male subjects because of previous reports of gender differences in PPI (Kumari et al., 2004). Subjects were excluded if they had any other Axis I psychiatric disorder, significant active medical illness, mental retardation, history of any neurological condition, head trauma or loss of consciousness, substance abuse within the past year, or any history of substance dependence (excluding nicotine and caffeine). Subjects who regularly used caffeine or smoked cigarettes maintained their usual pattern on the days of testing. No first-episode patients were included. All patients had been treated with haloperidol (mean dose 7.9 ± 0.9 mg) for 5–8 days, being hospitalised.

Twenty-eight healthy subjects (all males, age range: 29–53 years; mean age: 36.6 years, SD: 6.2) were recruited from the community and among the staff of the Mental Health Services. Before being included as participants, they were screened using a semi-structured interview for exclusion criteria: thyroid dysfunction, heart disease, hypo- or hypertension, regular medical prescriptions, a history of mental illness, rapid mood changes, drug (ascertained by urine toxicology screen) and alcohol abuse, and psychosis in first-degree relatives. All subjects included in the study were also screened to ensure intact auditory abilities (using an AudioScope 3, Welch Allyn WA® audiometer) and to exclude those who could not detect 40 dB tones at 1000 Hz.

2.2. Saliva sampling, cortisol analysis and cardiovascular data

Saliva was collected by the subjects themselves using standard Eppendorf tubes (1.5 ml, Eppendorf, Hamburg, Germany), stored at room temperature until completion of the session, and then kept at −20 °C until analysis. After thawing for biochemical analysis, the fraction of free cortisol in saliva (salivary cortisol) was determined using a RIA with *Salivettes* (Sarstedt Inc., Texas). Inter- and intra-assay coefficients of variance were below 9%. Heart rate (HR) was measured with a wrist cuff monitor (beats/minute).

2.3. Measurement of PPI

A commercial human startle response monitoring system (CIBERTEC, S.A.) was used to generate and deliver the startle stimuli and to record and score electromyographic (EMG) activity (STARTLEH software, a WNS 220 electronic module, an ADInstrument Bio Amp, and a PowerLab data unit). Startle stimuli were presented to subjects binaurally through headphones. EMG recordings were taken with subjects sitting comfortably in a moderately lit, soundproof room. The eye blink component of the startle response was indexed by recording EMG activity of the orbicularis oculi muscle directly beneath the right eye, with two, miniature silver/silver chloride electrodes filled with Dracard electrolyte paste. The startle system recorded EMG activity for 250 ms (sample interval 1 ms) from the onset of the startle stimulus. Recorded EMG activity was band-pass filtered, as recommended by the SR-LAB™ Startle Response System. A 50 Hz filter was used to eliminate 50 Hz interference. EMG data were scored off-line by the system's analytic program for response amplitude (in arbitrary analogue-to-digital units), and latencies to response onset and peak (in ms).

The methodology used in the startle session was consistent with previous studies (Braff et al., 1992; Martínez-Gras et al., 2009), starting with a 5min acclimatisation period of 70 dB white noise, followed by four blocks. The first and last blocks consisted of five pulse-alone trials of 40 ms, 115 dB startle stimuli. Blocks two and three consisted of pulse-alone and prepulse–pulse trials presented in pseudorandom order. The 20 prepulse stimuli preceded the startle stimulus by 30, 60 or 120 ms, and were 15 dB above the 70 db background noise.

The inter-trial interval averaged 15 s (range: 8–22 s). Settings were adjusted so that the program excluded spontaneous and voluntary eye blinks. Criteria for excluding a stimulus were a difference between the onset and peak latencies greater than 95 ms, or a baseline shift exceeding 90 digital units.

Subjects were regarded as PPI non-responders if the mean pulse-alone magnitude in the first block was less than 10 digital units. Data from subjects who showed extreme inconsistency in PPI within the same session (mean PPI change from block 2 to block $3 \geq 1.5$ standard deviations in at least one interstimulus interval) were also excluded from the analyses (see Martínez-Gras et al., 2009). Three control subjects and 8 patients were excluded based on this criterion. Thus the final sample consisted of 50 patients with schizophrenia and 25 healthy control subjects.

The prepulse inhibition was calculated as the percentage decrement in startle amplitude in the presence vs. in the absence of the prepulse, i.e. $100 - [\text{prepulse amplitude}/\text{pulse amplitude}] \times 100$ (Braff et al., 1992; Martínez-Gras et al., 2009).

2.4. The socially evaluated cold-pressor test (SECPT)

We followed this procedure as a stressor stimulus (Schwabe et al., 2008). Subjects were informed that they would be videotaped and that these video recordings would be analysed for facial expression. After participants provided written consent for the video recordings to be used for scientific purposes, they were asked to immerse their right hand up to and including the wrist into ice water (0–2C). Subjects were instructed to look into the camera and keep their hand in the water for as long as possible. Those participants who kept their hand in the water for 4 min were instructed at that point to remove their hand. Then, they responded to a questionnaire (Likert visual analogue scale 0–10) on the stimulus aversiveness through three subscales (unpleasant/painful/unexpected).

The research protocol for this study was approved by the Research Ethics Board of the 12 de Octubre University Hospital and all participants signed an informed consent form on the day of their participation. All experimentation sessions began at 13:00 h and were completed by 15:30 h, to capitalize on the slow descent in cortisol levels at this time of day (Smyth et al., 1997), permitting changes in salivary cortisol following the SECPT to be observed without extensive correction. The experimentation sessions were 72 h apart (the first part on Monday or Tuesday and the second on Thursday or Friday).The procedure used in this protocol is presented graphically in Fig. 1.

Upon arrival at the psychophysiology lab room, participants were asked to refrain from drinking beverages, eating, smoking, exercising and brushing their teeth for the duration of the 2 h protocol. Water was available for all participants to drink.

2.4.1. Experimentation session without the SECPT

First, participants completed the various questionnaires. A trained research assistant was present to help complete them as needed. Participants were then

Please cite this article as: Rubio, G., et al., Stress induced by the socially evaluated cold-pressor test cause equivalent deficiencies of sensory gating in male.... Psychiatry Research (2015), http://dx.doi.org/10.1016/j.psychres.2015.05.097

given magazines and asked to sit comfortably in this same room for about 30 min until the research assistant returned to continue with the other parts of the protocol. This waiting period at the lab was a means of ensuring that all participants refrained from performing prohibited activities during the 40 min before the experimentation session.

Before starting with the actual session, while at rest, two buffer samples of saliva and two buffer cardiac measurements were taken in order to eliminate novelty effects in the baseline measurements. These buffer measurements were taken 10 min apart; 10 and 20 min before the baseline measurements. Baseline measurements were taken at Time 1 (T1). Then the startle probe began. Once the electrodes and headphones had been put on, the participants spent 5 min getting used to listening to white noise and then came the blocks of alternating pulse and prepulse trials. After finishing the startle probe, samples of saliva were taken again as well as cardiovascular variables. Another measurements were taken 30 min post-startle probe; Time 2 (T2).

2.4.2. Session with the SECPT

The procedure was similar to the previous one (see Fig. 1) but 4 min before the startle probe the patients underwent the SECPT. Also here, after the startle probe, salivary cortisol samples were taken as well as cardiovascular variables. At the end of the session, the patients completed a visual analogue test on the aversiveness of the session. Due to the randomisation of the SECPT, in 50% the first session was without the SECPT and in the other 50%, with the SECPT.

2.5. Statistical analysis

Continuous demographic variables were evaluated using one-way analysis of variance (ANOVA). When the variances of the dependent variables were not equal across groups, we used the Welch test as a more robust and conservative alternative to the usual *F*-test. We used a 3-way ANOVAs repeated measures dependent variables (i.e. PPI, salivary cortisol and HR), incorporating group (patients with schizophrenia and control subjects) × condition (with the SECPT and without SECPT) × time (T1 and T2). Significant main and interaction effects were further analysed by post-hoc comparisons with Bonferroni adjusted alpha level. All statistical analyses were performed using the SPSS package (SPSS, version 20.0).

3. Results

The demographic and clinical characteristics of the sample of patients with schizophrenia and the healthy control subjects are shown in Table 1. In SECPT, all subjects took the hands of ice water before 4 minutes. The score on the subjective pain scale was 6.28 ± 1.36 in patients with schizophrenia and 6.40 ± 1.34 in control subjects; $F=0.015$, $p=0.903$.

3.1. Startle measurements in experimentation sessions with and without the SECPT

The 3-way ANOVAs repeated measures analyses with one between-subjects variable of group (patients with schizophrenia *vs.* control subjects), and two within-subject variables condition (with the SECPT *vs.* without the SECPT) and prepulse-pulse interval (T1–T2–T3; 30, 60 and 120 ms) indicated that there was not a significant interaction between groups × condition × prepulse-pulse interval T1–T2–T3 (Wilk's $\lambda=0.96$; $F=1.58$; $p=0.21$; Eta^2 Partial$=0.03$; see Table 2). However, there was a significant interaction between groups × prepulse-pulse interval (Wilk's $\lambda=0.91$; $F=4.04$; $p=0.02$; Eta^2 Partial$=0.08$) showing that the group with schizophrenia presented a lower PPI% at 30, 60 and 120 ms than control subjects (see Table 2). Finally, our results showed a significant interaction between condition × prepulse-pulse interval (Wilk's $\lambda=0.39$; $F=64.64$; $p=0.0001$; Eta^2 Partial$=0.60$). All of the PPI% (30, 60 and 120 ms) were lower in the with SECPT conditions than in without the SECPT (see Table 2).

3.2. Cortisol response and heart rate in experimentation sessions with and without the SECPT

A $2 \times 2 \times 2$ mixed design ANCOVA was carried out with one between-subjects variable of group (schizophrenia *vs.* control subjects), and two within-subject variables: condition (with the SECPT *vs.* without the SECPT) and salivary cortisol time (T1 *vs.* T2) (Fig. 2). BMI and number of cigarettes smoked were introduced as co-variables, in order to control the potential effect of such variables. The results, after controlling for BMI and number of cigarettes smoked showed that the cortisol response at T2 was higher than T1 (Wilk's $\lambda=0.91$, $F=7.56$; $p=0.007$; Eta^2 Partial$=0.08$). Also, there was a significant interaction between group and time

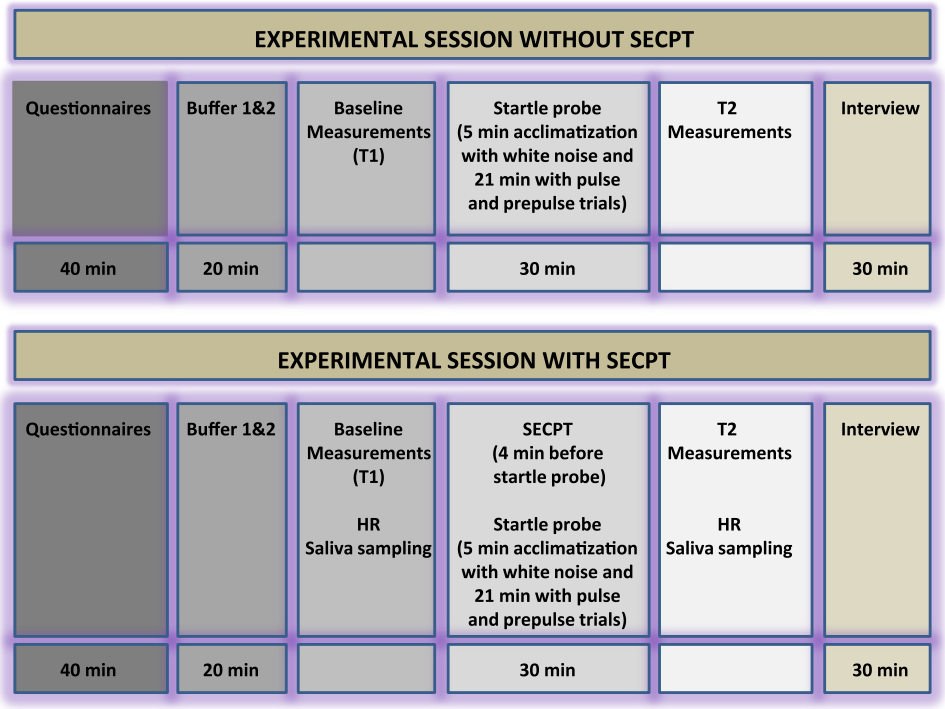

Fig. 1. Protocol procedure. HR: Heart rate. B1&2: Buffer 1 and 2. T1 and T2: Time 1 (baseline) and Time 2 (30 min post-startle probe). SECPT: socially evaluated cold-pressor test.

(T1–T2), both groups showed significantly higher levels of cortisol at the point of the T2 measurements of cortisol (Wilk's $\lambda=0.92$, $F=6.63$; $p=0.01$; Eta^2 Partial$=0.07$).

There was a significant interaction between group and condition showing an increase in the cortisol response of the groups during the SECPT condition (Wilk's $\lambda=0.93$; $F=5.50$; $p<0.05$; Eta^2 Partial$=0.06$). Finally, there was a significant main effect of three way interaction (Wilk's $\lambda=0.92$; $F=6.73$; $p=0.01$; Eta^2 Partial$=0.07$); the increase of cortisol at the point of the T2 measurement, with the SECPT condition, was significantly higher in the control group than in the schizophrenia group.

A second $2\times2\times2$ mixed design ANCOVA was carried out to examine the impact of the SECPT on heart ratio (HR) (Fig. 3). Our analyses had one between-subjects variable of group (patients with schizophrenia *vs.* control subjects), and two within-subject variables: the SECPT condition (with the SECPT *vs.* without the SECPT) and HR time (T1 and T2). Also, BMI and number of cigarettes smoked were introduced as co-variables. First, the results indicated a group effect, patients with schizophrenia had higher HR than control subjects ($F=123.6$; $p=0.001$). Second, the results showed significant higher levels the HR of T2 of participants (Wilk's $\lambda=0.91$; $F=7.25$; $p=0.009$; Eta^2 Partial$=0.08$). Third, there was a significant interaction between group and condition; group with schizophrenia had significantly higher levels of HR than the control subjects group and there was a significant increase in HR in the with SECPT condition for both groups (Wilk's $\lambda=0.93$, $F=5.93$; $p=0.01$; Eta^2 Partial$=0.06$). However, there was not a significant main effect of three-way interaction (Wilk's $\lambda=0.96$; $F=2.63$; $p=0.10$; Eta^2 Partial$=0.03$).

4. Discussion

In our knowledge, this is the first study in which the PPI response in patients with schizophrenia treated with haloperidol has been compared with healthy subjects when they are subjected to an acute stressful situation as is the case with the SECPT. The most relevant findings of this research are that the stress caused by the SECPT worsens the PPI response both in subjects with schizophrenia and healthy subjects and that this dysfunction seems to be associated with an increase in the cortisol response. Contrary to our initial hypothesis, the patients did not have significantly worse performance in the PPI than the healthy subjects after the stress test. Nonetheless, it is true that the patients began with some basal values in which there was impairment of the PPI, which together with the impairment induced by the stress made the sensory gating capacity more deteriorated in patients that in controls. On the other hand, the subjects with schizophrenia, after being exposed to the SECPT, had lower levels of salivary cortisol, but a faster heart rate than the healthy subjects.

Table 1
Demographic and clinical characteristics.

	Patients with schizophrenia ($n=58$)		**Control subjects** ($n=28$)			
	Mean	*SD*	Mean	*SD*	*F/W*	*p*
Age (years)	36.3	6.4	36.6	6.3	0.04	0.83
Age when academic studies ended (years)	17.9	3.4	18.4	2.1	0.46	0.49
Number of cigarettes smoked	15.6	11.7	5.1	6.6	29.4	0.001*
BMI	25.4	3.3	22.8	2.4	18.9	0.001*
Age when schizophrenia was diagnosed	20.0	2.59				
Number of psychotic episodes	4.7	2.4				
Number of times hospitalised	3.7	2.2				
Haloperidol dose	7.99	0.93				
PANSS subscale for positive symptoms	16.98	1.98				
PANSS subscale for negative symptoms	19.71	2.51				
PANSS subscale for general psychopathology symptoms	53.71	5.76				

BMI: Body mass index.
* $p<0.001$

It is known that cigarette smoking can alter the PPI and that BMI may alter the response to stress. For these reasons these variables have been considered, as in other papers (Brenner et al., 2009). Regarding the PPI and cigarette smoking, it is true that influence (Jurado-Barba et al., 2011), both withdrawal and nicotine consumption. In our experimental design smoking was allowed all subjects before the PPI. This was done to avoid the influence of nicotine withdrawal on the PPI syndrome (Jurado-Barba et al. 2011; Morales-Muñoz et al. 2014).

4.1. Why does the stress of the SECPT cause alteration of the cognitive process?

Other studies also show the effect of the cold pressor test (CPT) on cognitive processing. That of Fulbright et al. (2001), using magnetic resonance, demonstrated that the cold task activated the left middle frontal gyrus and the adjacent superior frontal sulcus, right inferior frontal gyrus and left postcentral gyrus. Also by means of magnetic resonance, Frankenstein et al. (2001) showed that the changes in the activation of the anterior cingulate cortex caused by the cold were very similar to those induced by a verbal attention task. Chang et al. (2002), using electroencephalography (EEG), demonstrated that the CPT caused a reduction in alpha brain waves, which could explain the deficient information processing. In this sense, our results support the hypothesis that the stress caused by cold generates an increase in activity in areas of the frontal cortex, hindering attention tasks and information processing in preattentive stages.

With regard to the stress caused by the SECPT, the results of other studies that have used this test indicate that acute SECPT stress could impair the goal-directedness of behaviour and promoted habitual performance. It has been assumed that the SECPT-induced increase in habitual performance is at least partly due to detrimental effects of the SECPT on cognitive control, in particular response inhibition (Schwabe et al., 2008).

Recently, Arnsten's group suggested that acute stress, through its action on brain dopamine and adrenergic receptors (β_1) could alter the functional connectivity of the prefrontal cortex and therefore of the working memory, especially in subjects with schizophrenia (Arnsten and Jin, 2012). On the other hand, the chronic stress would produce a loss of neuronal spines in these same areas (Arnsten, 2011). This view is in line with the assumption that the SECPT affected primarily subjects' ability to inhibit learned responses since the PFC is also of central importance for cognitive control and response inhibition (Aron et al., 2004; Li et al., 2006).

4.2. The effect of the SECPT on cortisol and the cardiovascular parameters

We found an increase in salivary cortisol levels and the HR in the SECPT condition in the two groups. However, the results indicated that the effect of the SECPT on cortisol levels was higher in the non-clinical group than in the schizophrenia group. In relation to HR, the two groups showed a similar increased pattern in the

Please cite this article as: Rubio, G., et al., Stress induced by the socially evaluated cold-pressor test cause equivalent deficiencies of sensory gating in male.... Psychiatry Research (2015), http://dx.doi.org/10.1016/j.psychres.2015.05.097

Table 2
Means of groups (patients with schizophrenia *vs.* control subjects) in PPI% (30, 60 and 120 min), before and during a cold-pressor test condition (Pre-Post), and 3-way ANOVAs repeated measures results.

Groups	PPI% 30 ms without the SECPT	PPI% 30 ms with the SECPT	PPI% 60 ms without the SECPT	PPI% 60 ms with the SECPT	%PPI 120 ms without the SECPT	PPI% 120 ms with the SECPT
Schizophrenia	5.55 ± 3.18	3.12 ± 5.10	15.24 ± 4.78	9.72 ± 7.62	24.26 ± 7.90	18.38 ± 8.71
Control	16.93 ± 6.37	15.36 ± 6.61	30.12 ± 8.30	25.81 ± 10.9	42.64 ± 10.1	36.50 ± 10.1
Group: $F_{(1,\ 84)}=181.21$; $p=0.001$**						
Condition: $F_{(1,\ 84)}=556.51$; $p=0.001$**						
T1–T2–T3: $F_{(2,\ 83)}=151.04$; $p=0.001$**						
Group × condition: $F_{(1,\ 84)}=2.77$; $p=0.10$						
Group × T1–T2–T3: $F_{(2,\ 83)}=4.04$; $p=0.02$*						
Condition × T1–T2: $F_{(2,\ 83)}=64{,}64$; $p=0.001$**						
Group × Condition × T1–T2–T3: $F_{(2,\ 83)}=1.58$; $p=0.21$						

Mean ± standard deviation
* $p<0.05$
** $p<0.001$

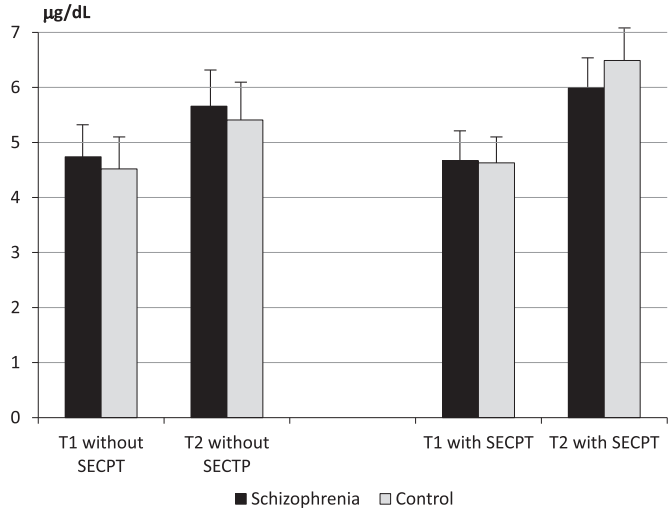

Fig. 2. Means of groups (patients with schizophrenia *vs.* control subjects) in salivary cortisol time T1 and T2, with and without the SECPT, and 3-way ANCOVAs repeated measures results. Group: $F_{(1,\ 82)}=0.31$; $p=0.57$ Condition: $F_{(1,\ 82)}=0.57$; $p=0.45$ Time (T1–T2): $F_{(1,\ 82)}=7.56$; $p=0.007$** Group × condition: $F_{(1,\ 82)}=5.50$; $p=0.02$* Group × time (T1–T2): $F_{(1,\ 82)}=6.73$; $p=0.01$* Condition × time (T1–T2): $F_{(1,\ 82)}=0.07$; $p=0.78$ Group × condition × time (T1–T2): $F_{(1,\ 82)}=6.73$; $p=0.01$* Mean ± standard deviation SECPT: socially evaluated cold-pressor test. *$p<0.05$ **$p<0.01$.

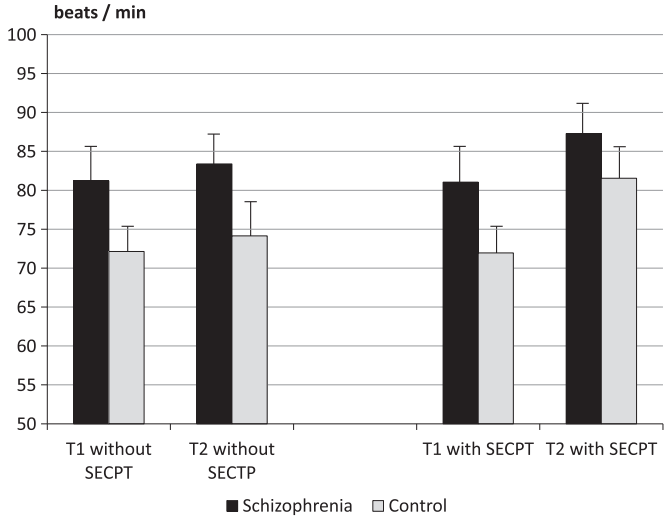

Fig. 3. Means of groups (patients with schizophrenia *vs.* control subjects) in heart rate (HR) baseline levels and levels 30 min later, before and during a cold-pressor test, and 3-way ANCOVAs repeated measures results. Group: $F_{(1,\ 82)}=123.6$; $p=0.001$*** Condition: $F_{(1,\ 82)}=0.00$; $p=0.99$ Time (T1–T2): $F_{(1,\ 82)}=7.25$; $p=0.009$** Group × condition: $F_{(1,\ 82)}=5.93$; $p=0.01$* Group × time (T1–T2): $F_{(1,\ 82)}=2.15$; $p=0.14$ Condition × time (T1–T2): $F_{(1,\ 82)}=0.33$; $p=0.56$ Group × condition × time (T1–T2): $F_{(1,\ 82)}=2.63$; $p=0.10$ Mean ± standard deviation. SECPT: socially evaluated cold-pressor test.*$p<0.05$ **$p<0.01$ ***$p<0.001$.

SECPT condition.The subjective ratings of the degree of pain, stress and discomfort experienced as a result of the SECPT did not discriminate between the two groups.

The results of our study indicate that there is less reactivity to cortisol in patients than in controls, which suggests a dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis (Marcelis et al., 2004; Brenner et al., 2009). It is impossible for us to conclude that subjects with schizophrenia have a generally blunted cortisol response on the basis of significant group differences at only one point in time. Previous studies, however, found the cortisol response in schizophrenia patients to be blunted at several points in time, whether during a psychosocial stress task (Jansen et al., 1998; Brenner et al., 2009), or during a mixture of psychosocial and physical stress tasks (Albus et al., 1982). Another study found that the blunted reaction applied specifically to psychosocial stress and not to physical stress (Jansen et al., 2000). In our case, which was a mixed physical and psychological stress, the results should be interpreted as suggesting that in these patients are more vulnerable to the acute stress effects.

In summary, our results showed that the impairment of the PPI correlated with the increase in cortisol in both subject groups, which enabled us to hypothesize that at least such deterioration may be due to the increase in the response to cortisol caused by the SECPT. This finding supports the role of stress, hypercortisolemia and glucocorticoids in the deterioration of sensory gating found in schizophrenia (Walker et al., 2008; Braff, 2010; Arnsten, 2013).

4.3. Limitations

The stress used is basically physical (pain), which is not very common in real life, and the observation time was too short to make long-term predictions. The minimum exposure to Cold-Pressor was 1 min and nobody surpassed the 4 min. Still, superior control of exposure time would be desirable in future research. Several issues need to be addressed using other study designs. For example, longitudinal studies may answer the question of whether improvement of PPI performance precedes the improvement of clinical symptoms or vice versa, i.e. whether PPI performance can be used to assess the clinical potential of a specific medication in a given patient. Finally, repeated measure designs such as that used

Please cite this article as: Rubio, G., et al., Stress induced by the socially evaluated cold-pressor test cause equivalent deficiencies of sensory gating in male.... Psychiatry Research (2015), http://dx.doi.org/10.1016/j.psychres.2015.05.097

in the present study may help clarify whether the changes induced in PPI performance can be disentangled from more stable PPI impairments that could be linked to specific risk factors for schizophrenia.

Funding

This research was supported by Janssen-Cilag (grant number 03-2010).

Contributors

GR, IM-G, RJ-B and FL-M designed the study and wrote the protocol. MAJ-A, RR-J, JCL and SM managed the literature searches and analyses. GR, IM-G, RR-J, and RJ-B selected the sample and evaluated patients. RE, MAP-N, GR and FL-M undertook the statistical analysis. GR and FL-M wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

References

Albus, M., Ackennheil, M., Engel, R.R., Muller, F., 1982. Situational reactivity of autonomic functions in schizophrenic patients. Psychiatry Res. 6, 361–370.
Arnsten, A.F., 2011. Catecholamine influences on dorsolateral prefrontal cortical networks. Biol. Psychiatry 69, e89–e99.
Arnsten, A.F., 2013. The neurobiology of thought: the groundbreaking discoveries of Patricia Goldman-Rakic 1937–2003. Cereb. Cortex 23, 2269–2281.
Arnsten, A.F., Jin, L.E., 2012. Guanfacine for the treatment of cognitive disorders: a century of discoveries at Yale. Yale J. Biol. Med. 85, 45–58.
Aron, A.R., Robbins, T.W., Poldrack, R.A., 2004. Inhibition and the right inferior frontal cortex. Trends Cogn. Sci. 8, 170–177.
Baker, N., Adler, L.E., Franks, R.D., Waldo, M., Berry, S., Nagamoto, H., Muckle, A., Freedman, R., 1987. Neurophysiological assessment of sensory gating in psychiatric inpatients: comparison between schizophrenia and other diagnoses. Biol. Psychiatry 22, 603–617.
Braff, D.L., 2010. Prepulse inhibition of the startle reflex: a window on the brain in schizophrenia. Curr. Top. Behav. Neurosci. 4, 349–371.
Braff, D.L., Geyer, M.A., 1990. Sensorimotor gating and schizophrenia. Human and animal model studies. Arch. Gen. Psychiatry 47, 181–188.
Braff, D., Stone, C., Callaway, E., Geyer, M., Glick, I., Bali, L., 1978. Prestimulus effects on human startle reflex in normals and schizophrenics. Psychophysiology 15, 339–343.
Braff, D.L., Grillon, C., Geyer, M.A., 1992. Gating and habituation of the startle reflex in schizophrenic patients. Arch. Gen. Psychiatry 49, 206–215.
Brenner, K., Liu, A., Laplante, D.P., Lupien, S., Pruessner, J.C., Ciampi, A., Joober, R., King, S., 2009. Cortisol response to a psychosocial stressor in schizophrenia: blunted, delayed, or normal? Psychoneuroendocrinology 34, 859–868.
Chang, P.F., Arendt-Nielsen, L., Chen, A.C., 2002. Dynamic changes and spatial correlation of EEG activity during cold pressor test in man. Brain Res. Bull. 57, 667–675.
Dominelli, R.M., Boggs, J.M., Bolbecker, A.R., O'Donnell, B.F., Hetrick, W.P., Brenner, C.A., 2014. Affect modulated startle in schizophrenia: subjective experience matters. Psychiatry Res. 220, 44–50.
Ebisch, S.J.H., Mantini, D., Northoff, G., Salone, A., De Berardis, D., Ferri, F., Ferro, F. M., Di Giannantonio, M., Romani, G.L., Gallese, V., 2014. Altered brain long-range functional interactions underlying the link between aberrant self-experience and self-other relationship in first-episode schizophrenia. Schizophr. Bull. 40, 1072–1082.
First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1995. Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-P). State Psychiatric Institute, Biometrics Research, New York.
Frankenstein, U.N., Richter, W., McIntyre, M.C., Remy, F., 2001. Distraction modulates anterior cingulate gyrus activations during the cold pressor test. Neuroimage 14, 827–836.
Fulbright, R.K., Troche, C.J., Skudlarski, P., Gore, J.C., Wexler, B.E., 2001. Functional MR imaging of regional brain activation associated with the affective experience of pain. Am. J. Roentgenol. 177, 1205–1210.
García-Sánchez, F., Martínez-Gras, I., Rodríguez-Jiménez, R., Rubio, G., 2011. Prepulse-inhibition of the startle response/reflex in neuropsychiatric disorders. Rev. Neurol. 53, 422–432.
Grace, A.A., 2000. Gating of information flow within the limbic system and the pathophysiology of schizophrenia. Brain Res. Rev. 31, 330–341.
Hasenkamp, W., Epstein, M.P., Green, A., Wilcox, L., Boshoven, W., Lewison, B., Duncan, E., 2010. Heritability of acoustic startle magnitude, prepulse inhibition, and startle latency in schizophrenia and control families. Psychiatry Res. 178, 236–243.
Hasenkamp, W., Kelley, M., Egan, G., Green, A., Wilcox, L., Boshoven, W., Lewison, B., Duncan, E., 2011. Lack of relationship between acoustic startle and cognitive variables in schizophrenia and control subjects. Psychiatry Res. 187, 324–328.
Jansen, L.M., Gispende Wied, C.C., Gademan, P.J., De Jonge, R.C., van der Linden, J.A., Kahn, R.S., 1998. Blunted cortisol response to a psychosocial stressor in schizophrenia. Schizophr. Res. 33, 87–94.
Jansen, L.M., Gispende Wied, C.C., Khan, R.S., 2000. Selective impairments in the stress response in scchizoprenic patients. Psychopharmacology (Berlin) 149, 319–325.
Jurado-Barba, R., Morales-Muñoz, I., Del Manzano, B.A., Fernández-Guinea, S., Caballero, M., Martínez-Gras, I., Rubio, G., 2011. Relationship between measures of inhibitory processes in patients with schizophrenia: role of substance abuse disorders. Psychiatry Res. 190, 187–192.
Kumari, V., Aasen, I., Sharma, T., 2004. Sex differences in prepulse inhibition deficits in chronic schizophrenia. Schizophr. Res. 69, 219–235.
Li, C.R., Huang, C., Constable, R.T., Sinha, R., 2006. Imaging response inhibition in a stop-signal task: neural correlates independent of signal monitoring and post-response processing. J. Neurosci. 26, 186–192.
Marcelis, M., Cavalier, E., Gielen, J., Delespaul, P., Van Os, J., 2004. Abnormal response to metabolic stress in schizophrenia: marker of vulnerability or acquired sensitization? Psychol. Med. 34, 1103–1111.
Martínez-Gras, I., Rubio, G., Álvarez del Manzano, B., Rodríguez-Jiménez, R., García-Sánchez, F., Bagney, A., Leza, J.C., Borrell, J., 2009. The relationship between prepulse inhibition and general psychopathology in patients with schizophrenia treated with long-acting risperidone. Schizophr. Res. 115, 215–221.
Mazza, M., Tripaldi, S., Pino, M.C., Stama, R., Valchera, A., Serroni, N., De Berardis, D., 2013. Assessment of attention network efficiency in schizophrenic patients with positive and negative symptoms. Riv. Psichiatr. 48, 252–260.
Morales-Muñoz, I., Jurado-Barba, R., Ponce, G., Martínez-Gras, I., Jiménez-Arriero, M.A., Moratti, S., Rubio, G., 2014. Characterizing cannabis-induced psychosis: a study with prepulse inhibition of the startle reflex. Psychiatry Res. 220, 535–540.
Nuechterlein, K.H., Dawson, M.E., Ventura, J., Gitlin, M., Subotnik, K.L., Snyder, K.S., Mintz, J., Bartzokis, G., 1994. The vulnerability stress model of schizophrenic relapse: a longitudinal study. Acta Psychiatr. Scand. 89, 58–64.
Schwabe, L., Haddad, L., Schachinger, H., 2008. HPA axis activation by a socially evaluated cold pressor test. Psychoneuroendocrinology 33, 890–895.
Smyth, J.M., Ockenfels, M.C., Gorin, A.A., Catley, D., Porter, L.S., Kirschbaum, C., Hellhammer, D.H., Stone, A.A., 1997. Individual differences in the diurnal cycle of cortisol. Psychoneuroendocrinology 22, 65–128.
Walker, E., Mittal, V., Tessner, K., 2008. Stress and the hypothalamic pituitary adrenal axis in the developmental course of schizophrenia. Annu. Rev. Clin. Psychol. 4, 189–216.
Zubin, J., Spring, B., 1977. Vulnerability: a new view of schizophrenia. J. Abnormal Psychol. 86, 103–112.

Please cite this article as: Rubio, G., et al., Stress induced by the socially evaluated cold-pressor test cause equivalent deficiencies of sensory gating in male.... Psychiatry Research (2015), http://dx.doi.org/10.1016/j.psychres.2015.05.097