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Brief report

Acoustic startle response in panic disorder

Elisa Favaron [a,*], Laura Bellodi [a], Sara Biffi [a], Giovanna Vanni [a], Claudia Zorzi [a], Laura Liperi [a], Giampaolo Perna [a,b]

[a] Anxiety Disorder Clinical and Research Unit, Vita-Salute S.Raffaele University, Milan, Italy
[b] Department of Psychiatry and Neuropsychology, Faculty of Health, Medicine and Life Sciences, University of Maastricht, The Netherlands

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ABSTRACT

The amygdala and the limbic system are important in inducing a fear reaction; if this "fear network" is involved in panic disorder, panic patients might be more sensitive to fear stimuli than healthy subjects. We compared the startle response with an aversive stimulus in a sample of 29 patients with panic disorder and a sample of 29 healthy controls. The intensity of the startle response, induced by a series of aversive loud (100 dB) sounds, was measured by skin conductance recording in each subject. No statistically significant differences between the two groups were found in either the baseline level of skin conductance or in the response to the stimuli. Nonetheless, panic patients reported significantly higher levels of baseline anxiety measured by the State-Trait Anxiety Inventory. In conclusion, our data do not support the hypothesis that patients with panic disorder are characterised by a hyperreactivity, as measured by the skin conductance response, to fearful sudden stimuli or, at least, to those delivered to the auditory system.

1. Introduction

One of main theories on the etiopathogenesis of panic disorder (PD) posits the existence of a hypersensitive fear network that involves prefrontal cortex, hippocampus, amygdala and brain stem structures (Sinha et al., 2000), suggesting that panic resembles fear (Gorman et al., 2000). Other authors have hypothesized that this circuit, although important, is not exclusively involved in the phenomenon, stressing a specific role of the respiratory mechanisms (Klein, 1993; Caldirola et al., 2004).

If patients with PD have a hypersensitive fear system, we would expect an abnormally increased response, a sort of "hyperreactivity," to a variety of aversive stimuli.

In laboratory settings, the acoustic startle response (ASR) is widely used as an index of the physiological response to an intense and sudden auditory stimulation; the ASR has two components, referred as the startle reflex and the autonomic reaction. The brainstem circuit that mediates the primary acoustic startle response consists of three sets of synapses: those made by spiral ganglion cells within the cochlea onto cochlear root neurons, those made by cochlear root neurons onto neurons within the nucleus reticularis pontis caudalis (PnC), and those made by PnC neurons onto spinal motor neurons (Davis et al., 1982). Since Rosen et al. (1991) identified pathway connecting the central nucleus of the amygdala with the PnC, several studies have clarified the neuro-anatomical substrates of the modulation of the startle pathway, including the afferents from the locus coeruleus and the amygdala (Walker and Davis, 2002; Davis, 1990).

The mechanism of fear-potentiated-startle, defined as the increase in startle amplitude in the presence versus absence of the conditioned fear stimulus, is mediated by the activation of the amygdala (Walker and Davis, 2002; Frankland et al., 1997). Given this correlation between the amygdala and the modulation of the startle response, we have studied the startle reflex in a sample of patient with PD.

2. Materials and method

2.1. Subjects

Twenty-nine outpatients with PD with agoraphobia agreed to participate in the study. They were among those referred to the outpatients facility of the Anxiety Disorders Clinical and Research Unit of the Department of Neuropsychiatric Sciences, S. Raffaele Hospital, Milan over a period of 6 months.

They were matched for sex with 29 healthy controls. Consensus diagnoses according to DSM-IV criteria were obtained by two senior psychiatrists who independently assessed patients and controls by a clinical interview and the MINI International Neuropsychiatric Interview-Plus (Sheehan et al., 1994). Exclusion criteria for all subjects were psychiatric disorders other than PD with agoraphobia, major medical diseases and neurological syndromes according to direct physical examination and to a careful review of their medical histories and their use of any psychotropic drugs. All participants gave written informed consent to the study after a detailed explanation of the entire procedure, which is in compliance with APA ethical standards. Table 1 lists the demographic and clinical characteristics of the subjects.

* Corresponding author. University of Oxford, Dept. of Psychiatry, Psychopharmacology Research Unit, Neurosciences Building, Warneford Hospital, OX3 7JX Oxford, UK.
E-mail address: elisa.favaron@psych.ox.ac.uk (E. Favaron).

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Table 1
Clinical and demographic characteristics of the sample.

	Patients	Healthy controls
Age (years)	34.7 ± 9.7	32.3 ± 8.4
Gender (M/F)	12/17	12/17
Educational level (years)	15.1 ± 3.5	15.5 ± 2.9

2.2. Clinical assessment

The clinical symptomatology was measured by the Panic Associated Symptoms Scale (PASS), which assesses panic attacks, anticipatory anxiety and agoraphobia (Argyle et al., 1991); the Fear Questionnaire (FQ), which assesses agoraphobia, blood-injury phobia and social phobia (Marks and Mathews, 1979); and the Mobility Inventory for Agoraphobia (MIA) (Chambless et al., 1985), which measures self-reported agoraphobic avoidance. Before recording began, each subject filled in the State Trait Anxiety Inventory for state anxiety (STAI) (Spielberger, 1983).

2.3. Skin conductance response recording

All of the subjects underwent skin conductance response (SCR) recording. Subjects had to have been off all psychotropic medications for at least 2 weeks before the tests. None of the patients took fluoxetine in the 2 months before. Because many substances can affect SCR (Lyvers and Miyata, 1993; Zahn and Rapoport, 1987), subjects were asked to refrain from alcohol for at least 36 h, from beverages or food containing xanthines for at least 8 h, or from smoking for at least 2 h before the recording.

Electrodes were attached to the 2nd and 3rd finger of the non-dominant hand after the subjects were seated in a comfortable chair at 45 cm in front of a computer screen. They were asked to relax, to remain silent and still, and to pay attention to a screen showing emotionally neutral images (a random series of colors) for 3 min. After this rest period, the first startling loud sound (a 100 dB, 1 s, 250 Hz tone) was delivered. The other three noise stimuli were delivered at a time interval ranging from 40 to 90 s. Throughout the experiment, SCR activity was continuously acquired via an MP100 WS system (Biopac Systems) and the data were recorded on a PC and analyzed by AcqKnowledge 3.7.2 software.

2.4. Data quantification and analysis

Quantification of the SCR, performed according to the method described by Bechara et al. (1995), entails the following steps:

- Elimination of the downdrift in the SCR wave, using a mathematical transformation function called "Difference." This function measures the difference (in amplitude) of two sample points separated by 10 samples. The difference is then divided by the time interval between the first and the last selected sample.
- Measurement of the "area under the curve" in the 10-s time window after the onset of the loud sound. The "area under the curve" (AUC) measurement is similar to the function of an "integral," except that instead of using zero as a baseline for integration, a straight line is drawn between the endpoints of the selected area to function as the baseline. The area is expressed in amplitude units (microSiemens = μS) per time interval (s).

A different analysis was performed according to Hamann et al. (2002) using a peak-to-peak measurement defining an SCR as the largest increase in skin conductance level with its onset occurring within a window of 0.5 and 4.5 s after the onset of the stimulus. Like Hamann et al., we used a cut-off of adequate response to the loud sound: subjects who failed to show a minimum mean SCR of 0.25 μS across the four stimuli were not included in further data analysis.

Since the scores in our sample were not normally distributed — according to the Shapiro–Wilk test of normality — we decided to use non-parametric testing. Statistical analyses were performed with the Statistica package, version 5.

3. Results

We did not find any significant difference between the two groups regarding age, scholarship or sex distribution. Patients with PD had the following scores on the psychometric scales: PASS: 8.5 ± 3.7; FQ: 39.5 ± 28.2; MIA alone: 1.9 ± 0.7; MIA accompanied: 2.3 ± 0.8.

There was a significant difference between patients (50.6 ± 9) and controls (32.3 ± 9.5) in the baseline levels of anxiety measured by STAI ($Z = 2.9$, $P < 0.02$).

Two patients and two healthy controls reported an SCR score to the four noise stimuli lower than the established cut-off and were excluded from the analysis.

Table 2 shows the mean values of the skin conductance parameters measured in the two groups.

Baseline levels of skin conductance (SCL) measured using the AUC were not statistically different in the two groups ($Z = -0.55$; $P < 0.58$). The Mann–Whitney test did not show any significant difference between patients and healthy controls as regards the response to the first stimulus measured, regardless of whether the AUC method ($Z = 0.14$; $P < 0.88$) nr with the peak-to-peak method ($Z = -1.10$; $P < 0.28$) was used. Also, no differences were found for the other three subsequent stimuli. There was a significant decrease of the magnitude of SCR across the four startling sounds delivered both among patients ($\chi^2 = 40.6$, df = 3, $P < 0.001$) and among controls ($\chi^2 = 35.7$, df = 3, $P < 0.001$), but no differences were found in comparisons of the delta score (SCR of the first sound minus the SCR of the fourth sound) between patients and controls.

4. Discussion

Our results show that patients with PD exhibit similar tonic levels and responses to acoustic startling stimuli, measured by skin conductance, compared with healthy controls. A similar decrease of the startle response was observed in patients and controls.

This is partially in line with a previous study of Roth et al. showing significant differences in baseline SCL between a similar number of agoraphobic and control subjects, but not significantly different levels in the measure of the reactivity to aversive auditory stimuli (Roth et al., 1998). Another study by Grillon et al. failed to find a significant difference in the response to loud sounds in a sample of 34 PD patients and 49 healthy controls (Grillon et al., 1994).

Taken together, these data are not in line with the "hypersensitive fear network" hypothesis of PD patients as suggested by Gorman et al. (2000). We can argue that patients with PD could be more sensitive only to specific stimuli related to internal body state, such as interoceptive sensations like heart pounding, tachycardia or shortness of breath. It would be of interest to administer other types of stimuli more specific for panic patients, such as carbon dioxide inhalation, to evaluate their effect on the autonomic nervous system beside the well-known action on the respiratory system.

Furthermore we can observe that in the baseline phase, while physiological measurements between the two groups are not significantly different, PD subjects report levels of anxiety before testing that are significantly higher than those in healthy controls. This can indicate a mismatch between the subjective feelings and the objective measurement.

In conclusion, our data suggest that the reaction of patients with PD to a noxious loud sound is not different from that of healthy subject's suggesting that PD is not characterized by a specifically stronger reactivity to non-specific threatening stimuli. However, since skin conductance response measures only some aspects of the startle response, it might be useful to use other parameters, such as the eye-blink reflex or heart rate, to have a complete picture of startle reflex in PD. In addition, there might be possible differences in the latency and in the recovery time of the startle response and also differences in spontaneous fluctuations of skin conductance.

Table 2
Skin conductance parameters measured.

	Patients	Healthy controls
SCL baseline [AUC] (μS/s)	0.17 ± 0.198	0.17 ± 0.231
1st stimulus [AUC] (μS/s)	2.23 ± 2.82	1.74 ± 1.93
1st stimulus [p-p] (μS)	2.54 ± 2.35	3.06 ± 2.72
2nd stimulus [p-p] (μS)	1.52 ± 1.31	2.03 ± 1.50
3rd stimulus [p-p] (μS)	1.36 ± 1.55	1.52 ± 1.10
4th stimulus [p-p] (μS)	1.05 ± 1.12	1.40 ± 0.96
Mean 1–4 stimuli [p-p] (μS)	1.65 ± 1.36	2.00 ± 1.42

AUC = area under the curve method; p-p = peak-to-peak method.