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Is there a hypersensitive visual alarm system in panic disorder?

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ABSTRACT

Agoraphobia in panic disorder (PD) has been related to abnormal balance system function. Vision influences balance and behavioural adaptations; peripheral vision influences orienting and fast defensive reactions whereas central vision analyzes details of objects. We have hypothesized that the abnormal balance function in PD could be mainly related to peripheral vision as part of a defensive alarm system in the brain. In 25 patients with PD and agoraphobia and 31 healthy controls we assessed, by posturography, balance system reactivity to video-films projected in peripheral and central visual fields (randomized sequence). Length, velocity and surface of body sway were calculated. Patients increased their body sway during peripheral stimulation, whereas controls did not; the two groups showed a similar increase of body sway during central stimulation. Anxiety levels during peripheral stimulation significantly influenced the postural response in the group of patients. These preliminary results suggest that the higher visual sensitivity to peripheral stimulation in patients with PD and agoraphobia may be linked to a more active "visual alarm system" involving visual, vestibular and limbic areas that might influence the development of agoraphobia in situations where environmental stimuli are uncertain.

1. Introduction

Hypersensitive alarm systems have been postulated in panic disorder (PD). Klein's suffocation false alarm theory postulates that panic attacks occur when a suffocation alarm system is erroneously triggered (Klein, 1993); Gorman's neuroanatomical model postulates panic attacks as conditioned fear responses mediated by an overly sensitive fear network (Gorman et al., 2000); the three-alarms (true, false, learned) theory postulates panic attacks as the results of both spontaneous firing of fear system and conditioning processes to internal or external cues (Bouton et al., 2001). Although these theories do not completely overlap, they share the idea that hypersensitivity in alarm systems triggered by stimuli plays a key role in the pathogenesis of PD and related phobic conditions.

Patients with PD and agoraphobia often show a high sensitivity to complex sensorial environments (shopping malls, traffic, crowds) where they experience dizziness and discomfort (Jacob et al., 1993; Asmundson et al., 1998). Most studies showed that these patients do not have specific vestibular diseases but have subclinical abnormalities of the balance system and that their balance control relies mainly on non-vestibular cues, propioceptive or mostly visual (visual dependence) (Jacob et al., 1995, 1997; Asmundson et al., 1998; Perna et al., 2001; Staab, 2006).

Overall, vision provides important information for balance adaptations and behavioural responses to surrounding stimuli; visual information from central visual fields and that from peripheral visual fields have complementary roles with specific functions and might have different effects on postural control (Berencsi et al., 2005). Keeping in mind that there are partial overlap and significant cross-talk among the areas comprising the two visual streams, preferred pathways have been proposed. Central vision involves mainly parvocellular cells and the ventral stream visual areas (V1-V2-V4, inferior occipital-temporal cortex) and analyzes details of objects near the focus of attention (Kandell, 1991; Stephen et al., 2002; Palmer and Rosa, 2006). Peripheral vision involves mainly magnocellular retinal cells, lateral geniculate nucleus and the dorsal stream visual areas (occipital -V1-V2-V3-V5/MT- and parietal cortices); this is a fast pathway, with shorter latency and more sustained activation than the central vision pathway, and has connections with areas of limbic cortex; thus, peripheral vision scans surroundings for changing conditions and is involved in fast orienting and postural adaptations and in defensive reactions to potentially dangerous stimuli.

On this basis, we hypothesized that the patients with PD who develop agoraphobia might be hypersensitive to the influence on

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balance of moving visual stimuli, resembling the everyday-life environment, localized in the peripheral visual field.

2. Methods

2.1. Subjects

Twenty-five outpatients with PD and agoraphobia and 31 healthy subjects were included. Patients were recruited among those consecutively referred to the Anxiety Disorders Clinical and Research Unit of San Raffaele Turro Hospital in Milan, over a year. Healthy controls (free of lifetime psychiatric disorders) were recruited by advertisements placed around the University.

All subjects underwent the MINI International Neuropsychiatric Interview for DSM IV-Plus (Sheehan et al., 1994), neuro-otological examination and medical history collection (Day 1, 7±2 days after recruitment). Exclusion criteria were: lifetime therapies with ototoxic drugs, chemotherapy; lifetime neurological and orthopaedic diseases, migraine, polyneuropathies; lifetime diagnoses of vestibular disorders or episodes of rotational vertigo with nausea; pregnancy; concurrent psychiatric disorders for patients with PD.

The clinical symptomatology was quantified by the Panic Associated Symptoms Scale (PASS) (Argyle et al., 1991). All subjects were assessed by the State-Trait Anxiety Inventory for trait anxiety (STAI-II) (Spielberger et al., 1970), the 25-item Dizziness Handicap Inventory scale (DHI, total score, range 0-100), evaluating the self-perceived handicap associated with dizziness (Jacobson and Newman, 1990), and the Visual Analogue Scales for Dizziness (VAS-D) describing, on a continuum from 0 (no dizziness) to 100 (the worst dizziness imaginable), the severity of dizziness in their everyday life over the 2 months before recruitment.

Patients were free of psychotropic medications for at least 2 weeks before posturography; all subjects had to refrain from alcohol and any kind of medication for at least 2 days, xanthines for at least 8 hours and food or smoking for at least 2 hours before posturography (Gagey and Weber, 1999). Posturography was performed within 2 days after the clinical examination (Day 2).

This study was in accordance with the Declaration of Helsinki and approved by the Ethical Committee ASL "City of Milan"; all participants provided their written informed consents after the procedure had been fully explained.

2.2. Procedure

Each subject underwent posturography in two different conditions: 1) with visual stimulation in peripheral visual field and 2) with visual stimulation in central visual field. The two testing conditions were carried out in a randomized sequence according to a computer-generated list. After each posturography, the subjects had a 5-min rest break. The subjects were told that posturography is a safe test assessing the individual strategy in maintaining posture in different conditions, that they should act on the instructions given by the examiner and could stop the session whenever they wanted. We did not mention moving visual stimuli in order to minimize the influence of expectation and high level readjustment processes on postural responses (Guerraz et al., 2001).

2.3. Posturography

Posturography gives information on the ability to integrate multiple inputs in the control of posture (Gagey, 1991). We used a force platform (Amplaid SveP, 10 Hz-signal acquisition), conforming to the standards of the International Society of Posturology (Bizzo et al., 1985). Vertical force transducers recorded changes in successive positions of the Centre-of-Pressure (COP), obtaining the total sway path of the COP. Posturography was carried out by otolaryngologists blind to the diagnosis of the subjects, according to a standardized procedure (Gagey and Weber, 1999), in a quiet room between 4 p.m. and 6 p.m.

The following variables were evaluated (Gagey and Weber, 1999; Yasuda et al., 1999; Gagey, 1991):

Length of body sway (mm), that is, the sum of the distances between the sequential sampled positions of COP. Length is considered the main posturographic variable.
Velocity of body sway (mm/s), which represents the energy spent by the system in maintaining posture.
Surface of the body sway (mm^2), that is, the confidence ellipse containing 90% of the sampled positions of the COP and indicating the precision of the postural system.

Each posturography with visual stimulation comprised three sequential conditions:

1. Open-Eyes pre-visual stimulation; 2. Visual stimulation; 3. Open-Eyes post-visual stimulation.

The recording in each condition took 30 s. During the Open-Eyes conditions, the subjects stared at a white vertical line (20 cm long by 4 cm wide) on a black background projected on a 17-in. display in front of them.

Visual stimulation in peripheral visual field was produced by a video-film (32 times-accelerated), showing people moving in various contexts, projected on a lateral (right side) 150-cm square screen, forming a 30° angle with the line connecting the head of the subjects and the central display and covering an angle from 10° to 50° of the visual field. The subjects were instructed to stare at a white vertical line on a black background projected on the display in front of them, without moving head and gaze during the whole visual stimulation.

Visual stimulation in the central visual field was produced by a video-film showing moving images of a tree in a square with buildings, resembling an optokinetic stimulus with slow phase velocity of 30°/s without any spatially fixed reference points (Jacob et al., 1995); moving images were projected on the display in front of the subjects, adjusted in height to eye level, at a distance of 130 cm, covering a visual field of 12°. The subjects were instructed to stare at the display without moving head and gaze during the whole visual stimulation.

The moving scenes were selected in order to resemble everyday life contexts not related to agoraphobic situations. The room was in dim illumination during the visual stimulations and in full-light during all the other conditions.

Visual Analogue Scales for Anxiety (VAS-A) and Dizziness (VAS-D) (continuum from 0, no anxiety / dizziness, to 100, the worst anxiety / dizziness imaginable) were administered immediately before and after posturography; the VASs-after were referred to the visual stimulation and to the moment immediately after posturography.

2.4. Statistical analyses

Continuously distributed variables are described as mean and standard deviation (SD) (standard deviations are reported in parentheses); the significance of any difference between groups was evaluated by *t*-test for independent samples and analysis of variance (ANOVA) for repeated measures. Post-hoc comparisons were performed using the Tukey HSD test. Since anxiety and dizziness measures and posturographic variables showed standard deviations proportional to the means, a logarithmic transformation was applied to the data in order to meet requirements for performing ANOVA. When ANOVA for repeated measures was performed with covariates, we carried out pairwise comparisons between adjusted means for covariate effects, applying Sidak *p*-value correction, since the post-hoc tests on observed means do not take in account the confounding factors related to the use of the covariates in the model. Nominal data were compared by chi-square test.

3. Results

Table 1 reports demographic and clinical features of patients with PD and agoraphobia and controls. Patients with PD and agoraphobia showed higher STAI-Trait, Dizziness Handicap Inventory and VAS-D scores than controls.

3.1. Anxiety and dizziness during posturography

3.1.1. Anxiety and dizziness during visual stimulation in peripheral visual field

Mean VAS-A scores before, during and after peripheral stimulation in patients with PD and agoraphobia were reported in Table 2. ANOVA

Table 1
Demographic and clinical features of the two groups.

	Patients with PD and Ago ($n=25$)	Healthy subject ($n=31$)	t	$p^{\dagger}$
Age (years)	34.9 (11.3)	32.0 (10.4)	0.99	0.32
Female	17 (68%)	15 (48.4%)	-	0.14
BMI (kg/m^2)	22.7 (3.9)	22.0 (2.9)	0.73	0.46
Sport activity				
Subjects*	7 (28%)	15 (48.8%)	-	0.12
Hours/weeks	2.8 (1.3)	2.9 (1.8)	0.09	0.92
STAI-II	48.1 (11.1)	36.1 (8.0)	4.62	<0.001
DHI	26.6 (20.1)	3.8 (7.8)	5.19	<0.001
VAS-D	38.1 (31.6)	1.8(5.4)	5.65	<0.001
Age of onset of PD (years)	27.2 (9.6)	-	-	-
Illness duration (years)	8.5 (11.3)	-	-	-
PASS				
Total score	5.1 (1.8)	-	-	-
Panic attacks	1.6 (1.6)	-	-	-
Anticipatory anxiety	2.1 (0.6)	-	-	-
Agoraphobia	1.4 (0.6)	-	-	-

Values are expressed as mean (SD) or number of subjects (%).
BMI = Body Mass Index; Ago = Agoraphobia; * Subjects practising sports for at least 6 months before recruitment.
STAI-ii = State-Trait Anxiety Inventory-Trait; DHI = Dizziness Handicap Inventory; PASS = Panic Attack Scale.
VAS-D = Visual Analogue Scale for DIzziness.
† Significance of between-group difference by *t*-test for independent sample or chi-square test.