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Nonhomogeneous results in place learning among panic disorder patients with agoraphobia

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A B S T R A C T

Patients affected by panic disorder with agoraphobia (PDA) often suffer from visuo-spatial disturbances. In the present study, we tested the place-learning abilities in a sample of 31 PDA patients compared to 31 healthy controls (CTR) using the computer-generated arena (C-G Arena), a desktop-based computer program developed at the University of Arizona (Jacobs et al 1997, for further detail about the program, see http://web.arizona.edu/~arg/data.html). Subjects were asked to search the computer-generated space, over several trials, for the location of a hidden target. Results showed that control subjects rapidly learned to locate the invisible target and consistently returned to it, while PDA patients were divided in two subgroups: some of them (PDA-A) were as good as controls in place learning, while some others (PDA-B) were unable to learn the correct strategies to find the target. Further analyses revealed that PDA-A patients were significantly younger and affected by panic disorder from less time than PDA-B, indicating that age and duration of illness can be critical factors that influence the place-learning abilities. The existence of two different subgroups of PDA patients who differ in their spatial orientation abilities could provide new insight into the mechanisms of panic and open new perspectives in the cognitive–behavioral treatment of this diffuse and disabling disorder.

1. Introduction

Anxiety disorders are often characterized by automatic attentional biases for selective processing of information or stimulation related to cues perceived as threatening in the anxious people's environment (Keogh and French, 1999; Wittchen and Hoyer, 2001). In particular, visuo-spatial cognition biases are common in patients affected by panic disorder with agoraphobia (PDA), who are often so worried about their own physical reactions that they become unable to be attentive to changes occurring in the surrounding environment (Kallai et al., 1995). These observations are supported by different experimental studies showing that patients with PDA have scarce abilities in orientating in a maze and in performing blind orientation tasks as compared with patients affected by other anxiety disorders and healthy controls (Kallai et al., 1995, 1996). Recent data obtained by Kallai et al. (2007a) have also shown a correlation between altered physiological parameters and the PDA patients' inability to detect the navigation signals indicating the right route to exit from a labyrinth.

Disorders of visuo-spatial attention have been found in PDA patients during a computerized visual target discrimination task (Dupont et al., 2000) and in a distance estimation task, indicating the presence of a possible distortion in the patients' representational mechanisms of the extrapersonal space (Iavarone et al., 2005). PDA patients also present deficit in spatial memory and learning, as shown by Boldrini et al. (2005). Moreover, the positive effects of attentional fixation training in reducing panic-related symptoms (Kallai et al., 1999) strengthen the hypothesis that spatial disturbances are often associated with PDA.

Besides these experimental data supporting the hypothesis that PDA should at least partially depend on the ways in which the cognitive structures interact with the situational variables (Taylor et al., 1986), there are a series of neuropsychological studies that have failed to find any spatial deficit in PDA patients compared to control subjects (Gladsjo et al., 1998; Purcell et al., 1998). These discordant results make the role of visuo-spatial abilities in PDA still unclear. However, as shown by Kallai et al. (1999), understanding the role of orientation abilities in PDA is crucial to gain new insight into the mechanisms of panic disorder and to find an efficient therapeutic approach.

In the present study, we propose to test spatial orientation and place-learning abilities in a sample of severe PDA patients using the computer-generated arena (C-G Arena), a desktop-based computer program

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developed at the University of Arizona ((Jacobs et al., 1997, 1998); for further detail about the program, see http://web.arizona.edu/~arg/data.html) representing a virtual adaptation of the original water maze task (Morris, 1981). The main advantage of using a virtual space instead of a real one is the possibility to test patients in a safe and controlled environment reducing the risk, usually associated with *in vivo* exposure, of inducing panic-related symptoms and altering their physiological, emotional, and cognitive functioning during the experimental session. Moreover, compared to the traditional neuropsychological tests, a virtual space has the advantage of enhancing the ecological validity of the test, increasing predictions about the patient's functioning in the real world (Parsons et al., 2008). Up to date, several researches using such technology have been conducted (Gillner and Mallot, 1998; Jacobs et al., 1997, 1998; May et al., 1995; Nadel et al., 1998; Ruddle et al., 1997). The main findings emerged from these studies are that (a) subjects can make accurate judgments about metrics in real space after learning in a virtual environment (Péruch et al., 1995), (b) there is good transfer of spatial information from virtual to real environments (Wilson et al., 1997), (c) different spatial performances in the virtual spaces are predicted by different search strategies that reproduce the strategies used in real spaces (Kallai et al., 2005, 2007b), (d) virtual environments are suitable to explore the neural substrate of place learning and spatial navigation in humans (Thomas et al., 2001), and (e) virtual environments, and virtual reality technology, in general, show promise in aiding neuropsychological evaluation and rehabilitation (Rizzo et al., 1998; Rose et al., 1996; Thomas et al., 2001). Additionally, thanks to their programmable flexibility, data-handling capabilities, and their psychometric properties, virtual environments reproducing classical navigation tasks have been also used to explore the issue of gender (Astur et al., 1998, 2004) and age-related (Thomas et al., 1999) differences showing robust sex differences in virtual place learning, as well as the presence of age-related changes in the human cognitive mapping system.

The C-G Arena consists in a computer-generated three-dimensional virtual space in which subjects are asked to find a hidden platform using a number of distal cues on the walls. This kind of place-learning task requires distal spatial orientation abilities (Morris, 1981): to complete it, subjects use only localized distal cues coming from fixed places at some distance from the target objects, learning and remembering location of the target relative to them. In order to successfully perform the task, organisms use a spatial map consisting of information about specific objects and relations among them, formed when they enter and observe a new environment for the first time (Jacobs et al., 1997). As demonstrated by Jacobs et al. (1998), the place learning in C-G space is comparable to both rat and human place learning in real space.

Using the C-G Arena we wanted to investigate if place learning based on distal cues occurs in PDA patients as it occurs in healthy subjects and if it generalizes from familiar to novel start locations. To answer these questions, we used a version of the C-G Arena in which only distal cues existed and trained participants to find an invisible target entering in the virtual space from different start locations. Our hypothesis is that the ecological characteristics of the C-G Arena could be useful to discriminate the spatial abilities of subjects, eventually indicating difference between PDA patients and healthy controls, or within the PDA group itself, allowing the therapist to decide to integrate the traditional therapeutic approach with spatial orientation training.

2. Methods

2.1. Subjects

Thirty-one patients with PDA (seven males and 24 females; mean age: 35.52 years, S.D. = 14.30; years of education: 16.54, S.D. = 3.32) who applied for the cognitive-behavioral therapy (CBT) program at the Academic Anxiety Center (AAC) in Maastricht, NL, were included in the study. The mean duration of PDA was 8.77 years, S.D. = 8.28 years. Fifteen out of 31 patients who took psychotropic medications were asked to suspend them at least one week before their participation to the study (two weeks in case of antidepressant treatments). Psychiatric diagnosis was made according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, third revision (DSM-IV-TR) criteria by two experienced psychiatrists working at the AAC and not directly involved in the study. The Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) was administered to support the diagnosis. Patients who received a different primary psychiatric diagnosis or affected by neurological illnesses that would interfere with completing the computer-based spatial task were excluded from the study. PDA was also investigated using the Panic and Agoraphobia Scale (P & A) (Bandelow, 1995) (mean value = 25.87, S.D. = 4.42) and the Agoraphobic Cognitions Questionnaire (ACQ) (Chambless et al., 1984) (mean value = 21.48, S.D. = 13.45).

In addition, 31 healthy volunteers (CTR), matched with patients on gender, age, and educational level (12 males and 19 females; mean age: 30.23 years, S.D. = 12.02; years of education: 14.13, S.D. = 4.87) and recruited by advertisement in local newspapers, were included in the study. They were also evaluated with the MINI in order to exclude any current or past psychiatric illness.

Participants meeting the inclusion criteria and having agreed in signing the informed consent were informed in advance about the aims and procedures of the experiment and recruited for the study.

In order to anticipate a possible distortion coming from individual differences of computer game playing practice (Waller, 2000) participants were pre-selected, during recruitment, on the basis of a questionnaire about their computer-using habits. Only those subjects whose computer game playing did not exceed half an hour per week were eligible for the study. Following the administration of this questionnaire, three healthy controls were excluded from the study.

2.2. The C-G Arena software

The Water Maze Task (Morris, 1981), a place-learning test originally developed by Morris to investigate the spatial abilities in rats, served as a model for developing the C-G Arena, a desktop-based computer-generated virtual space created to investigate the place learning abilities in humans (Jacobs et al., 1997). The C-G Arena is a three-dimensional circular virtual environment housed within a large experimental room (arena). The subjects' task is to explore it using a joystick, in order to find a platform (target) hidden on the floor. The experimental room consists of a computer-generated display of a 1500 × 1500 × 475 unit room (10 units corresponds to 1 virtual meter). The ceiling of the room is a light gray and the floor a dark gray. The walls of the room, programmed to appear at some distance from the arena wall, are arbitrarily designated the North, East, South, and West walls. The North wall is gray and displays a door flanked by two windows; the East wall displays six and one half arches; the South wall is gray and displays three centered windows; and the West wall displays red bricks. A featureless purple wall, 460 units in radius and 30 units high, encloses the central portion of the floor of the experimental room, defining the arena (see Fig. 1). The actual viewpoint of the participants is a first-person perspective, so they look at the scene as though standing on the floor of the arena.

The hidden target is a 142 × 142-unit square located on the floor of the experimental room. Its color is identical to the surrounding arena floor, but becomes red when subjects reach it and stand on it. Finally, a beep sounds each time the subject moves on it. The target is level with the arena floor.

Another room of the same shape and size of the experimental room, but without any texture on the walls serves as training room (also called waiting room) and is located immediately before the entrance of the experimental room. No target is contained in it.

The arena is divided into four imaginary quadrants. Moving clockwise, the first is named Northwest (NW), the second is named Northeast (NE), the third is named Southeast (SE), and the fourth is named Southwest (SW). Lines delineating the quadrants are not visible. The invisible target is located in the NE quadrant for the entire duration of the experiment.

2.3. Procedure

Participants were seated in front of a standard PC with a 17 in. SVGA screen, equipped with stereo speakers and a joystick. Each experimental session started in the waiting room, in which subjects became familiar with the virtual space and practiced virtual locomotion using the joystick. They could stay in this room all the time they needed. When ready, they were asked to press the space bar on the computer keyboard to be moved ("teleported") to the experimental room. At each trial subjects entered in the experimental room from a different starting position (randomly determined by the computer) facing and within 2 units of the arena wall, and were asked to turn around, search for, find, and stand on the hidden platform located on the arena floor under the shortest time possible. The invisible target was centered in the NE quadrant, approximately 234 units from the closest part of the arena wall, in each acquisition trial. Once subjects found and stood on it, the target became visible and they had as much time as they wanted to stay on it trying to remember its position, using the distal cues on the walls. The position of the distal cues and the target remained the same during all the trials.

Subjects had a maximum of 4 min to find the platform and complete each trial. If they failed, the trial terminated and they were automatically teleported in the waiting room.