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Behavioral Inhibition System activity is associated with increased amygdala and hippocampal gray matter volume: A voxel-based morphometry study

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Recent research has examined anxiety and hyperactivity in the amygdala and the anterior hippocampus while processing aversive stimuli. In order to determine whether these functional differences have a structural basis, optimized voxel-based morphometry was used to study the relationship between gray matter concentration in the brain and scores on a Behavioral Inhibition System measure (the Sensitivity to Punishment scale) in a sample of 63 male undergraduates. Results showed a positive correlation between Sensitivity to Punishment scores and gray matter volume in the amygdala and the hippocampal formation, that is, in areas that Gray, J.A., and McNaughton, N.J. (2000). The neuropsychology of anxiety. Oxford: Oxford Medical Publications. associated with the Behavioral Inhibition System.

Keywords: Behavioral Inhibition System; Sensitivity to Punishment; Gray's model; Amygdala; Septo-hippocampal system

Relying on data from behavioral and psychopharmacological experiments, Gray (1982) described the Behavioral Inhibition System (BIS), a hypothetical construct which mediates anxiety in animals and humans. The BIS is activated by warnings of punishment or non-reward, novel stimuli and innate fear stimuli, its outputs being the inhibition of ongoing motor behavior, an increased level of arousal and increased attention. In the initial model, the fact that the similarities between the behavioral effects of anxiolytic drugs and hippocampal lesions were the basis on which the septo-hippocampal system was proposed as the neural substrate for the BIS. However, since 1982 it has become well accepted that the amygdala is involved in the control of both fear and anxiety (LeDoux, 1994). In particular, anxiolytic drugs act directly on the amygdala to reduce the arousal associated with anxiety (Davis, 2000), and this arousal is not mediated by the septo-hippocampal system. In a recent review of the model, Gray and McNaughton (2000, McNaughton and Corr, 2004) granted the amygdala a central role in anxiety due to its participation both in the processing of warnings of punishment (a function dependent on the Flight–Fight system; FFS) and in promoting the arousal reaction of the BIS.

Gray (1982) also proposed that the BIS mediates individual differences in trait anxiety. Anxious individuals and patients with generalized anxiety disorder would have an overactive BIS (Gray, 1982), whereas low anxiety subjects and primary psychopaths would be characterized by an underactive BIS (Fowles, 1980). The BIS construct is then related to a dimension that comprises inhibitory as well as disinhibitory disorders. One of the most widely used scales to detect and measure individual differences in the functioning of the BIS is the Sensitivity to Punishment (SP) scale of the Sensitivity to Reward and Punishment Questionnaire (SPSRQ; Torrubia et al., 2001). The SP is a 24-item scale that assesses individual differences in BIS functioning, including behavioral inhibition in response to novelty or punishment cues (*Are you often afraid of new or unexpected situations?*) and cognitive worry in response to failure or punishment cues (*Do you often refrain from doing something you like in order not to be rejected or disapproved of by others?*). This measure was strongly correlated with the other well-known BIS-related measures (Caseras et al., 2003; Smillie and Jackson, 2005) and was related to behavioral and cognitive symptoms of anxiety (Torrubia et al., 2001). High scores on the SP scale have been found in patients with obsessive-compulsive disorder (Fullana et al., 2004), in patients with current major depression (Pinto-Meza et al., 2006) and with Cluster C personality disorders (Caseras et al., 2001), whereas low scores have been found in primary psychopaths (Newman et al., 2005). Results of behavioral studies have been an evident source of support for Gray's model as they demonstrate that individuals with higher scores on the SP scale have better passive

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avoidance learning (Ávila, 2001; Ávila et al., 1999; Ávila and Torrubia, 2006; Torrubia et al., 1995) and extinction learning (Ávila et al., 2000), in addition to a greater tendency to focus their attention on threatening stimuli (Ávila and Parcet, 2002). In summary, the SP scale has received some support from research (see Corr, 2004; Torrubia et al., 2006).

Despite the significance of Gray's model in the understanding of human anxiety, little evidence exists in humans of the relationship between BIS self-report measures and the involvement of brain areas proposed as being associated with the BIS. Structural MRI studies using voxel-based morphometry (VBM) have not found any correlation between gray matter volume and a measure related to the BIS, such as the Harm Avoidance scale of the TCI (Pezawas et al., 2005). Functional neuroimaging studies, in contrast, have found that BIS-related measures are associated with a greater responsivity of the BIS (right amygdala or hippocampus) to fearful faces (Bishop et al., 2004; Cools et al., 2005; Etkin et al., 2004) and aversive pictures (Mathews et al., 2004; Most et al., 2006).

The aim of the present study was to investigate the relationship between scores on the SP scale and gray matter volume in the whole brain using voxel-based morphometry. Our interest was to test the possibility of finding limbic structural differences associated with trait anxiety scores measured with the SP scale. In other words, we wished to find out whether well-reported BIS-mediated differences in passive avoidance, sensitivity to punishment and amygdala/hippocampus activity had a structural basis.

Methods

Participants

Sixty-three male undergraduates (mean age = 22.43; range 18–34) were studied. All participants completed the SP scale of the SPSRQ (Torrubia et al., 2001), with a mean score of 9.88 (SD = 5.55) and a Cronbach's alpha of 0.81.

MRI acquisition and VBM

Images were acquired with a 1.5-T Siemens Sonata scanner. Contiguous 1-mm sagittal images across the entire brain were acquired with a T1-weighted fast field echo sequence (TE = 4.2 ms, TR = 11.3 ms, flip angle = 90°; FOV = 24 cm; matrix = 256 × 224 × 176).

Voxel-based morphometry was performed with the SPM2 package (Wellcome Department of Imaging Neuroscience, London, United Kingdom). A standard template set was created specifically for the study, consisting of a mean T1-weighted image and a priori gray matter, white matter and CSF templates, based on the images of all participants.

Subsequently, the processing of the original images from all participants was carried out, beginning by image segmentation with the study-specific, a priori gray matter, white matter and CSF templates. Extracted gray and white matter images were then spatially normalized to the customized gray and white matter templates with 12-parameter linear and nonlinear (7 × 9 × 7 basis functions) transformations. The parameters resulting from this spatial normalization step were then reapplied to the original structural images. These fully normalized images were then resliced with trilinear interpolation to a final voxel size of $1 \times 1 \times 1$ mm^3 and segmented into gray matter, white matter and CSF partitions. Voxel values were modulated by the Jacobian determinants derived from the spatial normalization, thus allowing brain structures that had their volumes reduced after spatial normalization to have their total counts decreased by an amount that was proportional to the degree of volume shrinkage (Good et al., 2001). Finally, images were smoothed with a 12-mm Gaussian kernel.

Statistical analysis

Voxel-by-voxel regression analysis of gray matter volume was performed by taking total brain volume as confound and scores on the SP scale as a covariate of interest, within the framework of the general linear model in SPM2. Resulting statistics at each voxel were transformed to Z scores and displayed as SPMs within standard space. Parameters to determine regions of significant differences were set conservatively. These include a P value of 0.05 (corrected for multiple comparisons), height threshold $t = 4.86$ and the extent threshold with a value of 80 voxels.

Results

Optimized VBM whole-brain analysis ($p < 0.05$, corrected for multiple comparisons) detected two clusters of gray matter in the right parahippocampus, amygdala and hippocampus and in the left anterior parahippocampus that correlated positively with SP scores (see Fig. 1). The Talairach local maxima for the right cluster ($k = 2619$) were located at the amygdala ($x = 24$, $y = -3$, $z = -18$) and the anterior parahippocampus ($x = 24$, $y = -10$, $z = -30$), whereas the local maximum for the left cluster ($k = 94$) was located at the anterior parahippocampus ($x = -21$, $y = -4$, $z = -27$). No significant clusters were obtained when the negative correlation between SP scores and the gray matter volume was calculated.

Discussion

The main result of the present study is that BIS scores in males correlated with an increased volume of the bilateral amygdala and the hippocampal formation (Fig. 1). All these brain areas corresponded to some of the structures proposed as parts of the BIS and FFS system (Gray and McNaughton, 2000). In other words, SP scores were associated with increased volume of the brain involved in the two systems that process warnings of punishment or non-reward (i.e. the FFS) and promote response to them (i.e. the BIS). Therefore, the present study offers a structural basis for the individual differences in sensitivity to punishment consistent with Gray's neuropsychological model.

Gray matter correlation was circumscribed to ventral parts of the hippocampal formation and the amygdala. Previous reports have specifically associated the ventral part of the hippocampal formation with the BIS and anxiety (Bannerman et al., 2004). In contrast, the ventral part of the amygdala, which corresponded to the basolateral nuclei (Somerville et al., 2004), has been proposed as a critical structure in the acquisition of fear responses (Davis, 2000; LeDoux, 1994). Overall, data suggest that SP scores were positively related to increased gray matter volume in structures related to both anxiety and fear.

A previous study on personality research employed a different personality scale, which was not designed to measure BIS activity (i.e. the Harm Avoidance scale of the TPQ) and did not find any relationship to amygdala/hippocampus volume (Pezawas et al., 2005). Harm avoidance is a measure that is correlated with the SP scale ($r = 0.63$), but which has slight differences with it, such as a stronger negative correlation with extraversion and BAS measures