“Change the mind and you change the brain”: effects of cognitive-behavioral therapy on the neural correlates of spider phobia

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Abstract

Questions pertaining to the neurobiological effects of psychotherapy are now considered among the most topical in psychiatry. With respect to this issue, positron emission tomography (PET) findings indicate that cognitive and behavioral modifications, occurring in a psychotherapeutic context, can lead to regional brain metabolic changes in patients with major depression or obsessive-compulsive disorder. The goal of the present functional magnetic resonance imaging (fMRI) study, which constitutes the first neuroimaging investigation of the effects of cognitive-behavioral therapy (CBT) using an emotional activation paradigm, was to probe the effects of CBT on the neural correlates of spider phobia. In order to do so, fMRI was used in subjects suffering from spider phobia (n = 12) to measure, before and after effective CBT, regional brain activity during the viewing of film excerpts depicting spiders. Normal control subjects were also scanned (once) while they were exposed to the same film excerpts. Results showed that, in phobic subjects before CBT, the transient state of fear triggered, during the viewing of the phobogenic stimuli, was correlated with significant activation of the right dorsolateral prefrontal cortex (Brodmann area—BA 10), the parahippocampal gyrus, and the visual associative cortical areas, bilaterally. For normal control subjects (n = 13), only the left middle occipital gyrus and the right inferior temporal gyrus were significantly activated. In phobic subjects before CBT, the activation of the dorsolateral prefrontal cortex (BA 10) may reflect the use of metacognitive strategies aimed at self-regulating the fear triggered by the spider film excerpts, whereas the parahippocampal activation might be related to an automatic reactivation of the contextual fear memory that led to the development of avoidance behavior and the maintenance of spider phobia. After successful completion of CBT, no significant activation was found in the dorsolateral prefrontal cortex (BA 10) or the parahippocampal gyrus. These findings suggest that a psychotherapeutic approach, such as CBT, has the potential to modify the dysfunctional neural circuitry associated with anxiety disorders. They further indicate that the changes made at the mind level, within a psychotherapeutic context, are able to functionally “rewire” the brain.

Introduction

Specific phobias are the most common psychiatric disorders, with an estimated lifetime prevalence of 11.3% in the United States (Magee et al., 1996). Spider phobia (SP) is one of the most widespread forms of specific phobia (Bourdon et al., 1988). People with SP experience persistent and intense fear when confronted with spiders and develop avoidance behavior of all contexts related to this animal (APA, 1994).

To date, a few functional brain imaging studies have been carried out to map the neural substrate of SP. In the first two of this series of studies, subjects were scanned with positron emission tomography (PET) while they were viewing a color videotape of a spider (Fredrikson et al., 1993,
With respect to this issue, recent PET in psychiatry (Kandel, 1999; Gabbard, 2000; Thase, 2001).

Questions pertaining to the neurobiological effects of psychotherapy are now considered among the most topical in psychiatry (Kandel, 1999; Gabbard, 2000; Thase, 2001). With respect to this issue, recent PET findings indicate that psychotherapy can lead to regional brain metabolic changes in patients with major depression (Brody et al., 2001; Martin et al., 2001). Along the same lines, a few PET studies have demonstrated that successful cognitive-behavioral therapy (CBT) of obsessive-compulsive disorder is associated with significant changes in glucose metabolic rates within various brain regions (Baxter et al., 1992; Schwartz et al., 1996). In all these PET studies, metabolic changes were measured during resting state.

CBT is an effective psychotherapeutic approach for reducing the symptoms of specific phobias (Ost, 1989, 1996; Anthony and Swinson, 2000). This form of therapy consists of exposure-based treatment to the phobic stimuli (e.g., spiders) combined with education for changing negative cognitive misattributions related to these stimuli. Although several psychological models have been proposed to explain the therapeutic effects of CBT, little is known regarding the neurobiological mechanisms underlying this form of psychotherapy.

The main goal of the present functional magnetic resonance imaging (fMRI) study, which constitutes the first neuroimaging investigation of the effects of CBT using an emotional activation paradigm, was to probe the effects of CBT on the neural correlates of SP. A more general objective of this study was to investigate how changes made at the mind level, within a psychotherapeutic context, are transduced at the neurobiological level. Subjects suffering from this specific form of phobia were scanned, before and after CBT, while they were viewing film excerpts showing either living spiders (activation task) or living butterflies (reference task). We predicted a priori that successful completion of CBT would be accompanied by a marked reduction of activity in the brain regions (prefrontal cortex, hippocampal/parahippocampal region, visual associative cortex) associated with SP.

Methods

Phobic subjects

Twelve females (mean age = 24.8 years; SD = 4.5), medication free at the time of the scan, were included in this study. They were selected from a group of 60 respondents to an advertisement in a local newspaper. After a first phone selection that permitted the screening of potential subjects, and the exclusion of individuals with psychiatric or neurological brain disorder, a behavioral interview was scheduled. SP was defined based on: (1) DSM-IV (APA, 1994) criteria of specific phobias, (2) a house questionnaire about arachnophobia, according to the Spider Phobia Questionnaire (Watts and Sharrock, 1984) and the Fear of Spider Questionnaire (Szymanski and O’Donohue, 1995), (3) the spider’s item of the Fear questionnaire (Marks and Mathews, 1979) and of the Fear Survey Schedule-II (Geer, 1965), and (4) the responsiveness of phobic subjects to confrontation with spiders. This latter procedure consisted of viewing film excerpts of spiders in a homemade MRI scanner simulator. Subjects were selected if the film excerpts showing living spiders evoked an experience of fear that was judged intense but tolerable by them. All subjects completed the written informed consent approved by the local Ethics Committee of Notre-Dame Hospital.

Normal control subjects

Thirteen healthy females (X = 28.6; SD = 7.8) with no history of neurological or psychiatric illness were recruited. To ascertain the nonphobic status of these subjects, they were selected based on their absence of responsiveness to the film excerpts of spiders that were presented during the actual experiment. As in the case of phobic subjects, this selection procedure was carried out 1 week before scanning. Normal control subjects did not receive any psychological treatment and were scanned only once. The decision to scan...
normal control subjects one time only was taken because the
main objective of this study was to measure the effects of
CBT on the neural correlates of SP.

Cognitive-behavioral therapy

This therapy consisted of gradual exposure-based treat-
ment to spiders (Öst, 1996) using guided mastery (Bandura,
1997) and education for correcting misbeliefs about this
animal. This approach was chosen considering the evidence
suggesting that short intensive exposure sessions should be
considered the method of choice for specific phobias (Öst,
1989, 1996; Antony and Swinson, 2000). The 12 phobic
subjects were divided into two groups (each group compris-
ing 6 subjects). The procedure used was standardized for
both groups of subjects. During 4 consecutive weeks, pho-ic subjects met once a week with their therapists (V.P. and
J.L.) for a 3-h intensive group session. During the first
session, phobic subjects were gradually exposed to an ex-
ercise book containing 50 color pictures of spiders. During
the second session, they were gradually exposed to films
excerpts of living spiders (excerpts that were also used in
this study). All subjects had the same exercise book and
the same videotape. Self-exposure homework, with the exercise
book and the videotape, was given between each session
and was reviewed with the therapists at the next meeting. In
the third session, subjects were exposed to real spiders
(spiders were the same for all phobic subjects). Finally,
during the fourth and last session, subjects were asked to
touch a tarantula. All phobic subjects responded success-
fully to CBT and, therefore, were scanned for a second time
1 week after the last group session. Responders to CBT
were defined a priori as subjects who were able to touch,
without reporting fear reactions (behaviorally and cogni-
tively), the entire series of pictures depicting spiders, the TV
screen showing living spiders, and the real spiders.

Experimental design

A block design paradigm was used. Within a single run,
subjects were exposed to five blocks of film excerpts of
living spiders in captivity (activation task), alternating with
five blocks of emotionally neutral film excerpts displaying
butterflies in nature (reference task). Each block lasted 30 s.
Blocks were separated by resting periods of 15 s during
which a blue screen was presented. The order of presenta-
tion of the blocks was counterbalanced across subjects. The
film excerpts showing the two categories of stimuli (spiders,
butterflies) were matched in terms of color, speed, camera
angle, and focus. Subjects were asked to watch attentively
both categories of film excerpts. These film excerpts were
displayed soundless through goggles connected to an MR-
compatible video system (Resonance Technology, Inc., Van
Nuys, CA).

Subjective ratings

Subjective ratings of the fear experienced during the
viewing of the film excerpts showing spiders were recorded
immediately after the scanning session on an 8-point Anx-
ity Analog Scale (AAS), with 0 representing absence of
fear reaction and 8 representing a fear as intense as if real
spiders were touching phobic subjects’ bodies.

MRI

Echoplanar images (EPI) were acquired on a 1.5 T sys-
tem (Magnetom Vision, Siemens Electric, Erlangen, Ger-
many). Twenty-eight slices (5 mm thick) were acquired
every 3 s in an inclined axial plane, aligned with the AC-PC
axis. These T2*-weighted functional images were acquired
using an EPI pulse sequence (TR = 0.8 ms, TE = 44 ms,
flip angle = 90°, FOV = 215 mm, matrix = 64 × 64, voxel
size = 3.36 × 3.36 × 5 mm). Following functional scan-
ing, high-resolution anatomical data were acquired via a
T1-weighted 3D volume acquisition obtained using a gra-
dient echo pulse sequence (TR = 9.7 ms, TE = 4 ms, flip
angle = 12°, FOV = 250 mm, matrix = 256 × 256, voxel
size = 0.94 mm3).

Data analysis

Data were analyzed using Statistical Parametric Mapping
software (SPM99, Wellcome Department of Cognitive Neu-
rology, London, UK). Images for all subjects were realigned
to correct for artifacts due to small head movements and
spatially normalized into an MRI stereotactic space (the
MNI template in SPM99). Images were then convolved in
space with a three-dimensional isotropic gaussian kernel (12
mm FWHM) to improve the signal-to-noise ratio and to
accommodate residual variations in functional neuroanat-
omy that usually persist between subjects after spatial nor-
amization. The time-series images were scaled to circum-
vent global nuisance effects. For statistical analyses, effects
at each and every voxel were estimated using the general
linear model. Voxel values for this contrast yielded a sta-
tistical parametric map of the t statistic (SPM t), subse-
quently transformed to the unit normal distribution (SPM
Z). For both normal control and phobic subjects, a “fixed-
effects model” was implemented to contrast the brain ac-
tivity associated with the viewing of the film excerpts show-
ing spiders and that associated with the viewing of the film
excerpts depicting butterflies (Spiders minus Butterflies
contrast). This fixed-effects model produced individual con-
trast images, which were used as raw data for the imple-
mentation of a random-effects model (Friston and Fracko-
wiak, 1997). Within such random-effects model, and using
After CBT—normal control subjects.

For the phobic subjects, an a priori search strategy was used. This a priori search strategy was carried out in the prefrontal (orbitofrontal, dorsolateral, anterior cingulate) cortex, and the visual associative cortex. The search volume corresponding to the brain regions of interest was defined a priori by tracing the neuroanatomical boundaries of these regions on the MR reference image (MNI templates), using SVC and box volume function in SPM99.

For this a priori search, a probability threshold of \( P < 0.05 \), corrected for multiple comparisons, was used to identify the significant loci of activation. Subsequently, the activated ROIs were corrected for volume of interest. For the normal control subjects, a whole-brain post hoc analysis was carried out, and a corrected probability threshold of \( P < 0.01 \), corrected for multiple comparisons, was utilized. Only clusters showing a spatial extent of at least 5 contiguous voxels were kept for image analysis.

Results

Subjective data

Before CBT

Phenomenologically, viewing the film excerpts depicting spiders induced a transient state of fear in all phobic subjects (mean rating of fear = \( 6.3/8; SD = 1.2 \)). While they experienced fear, phobic subjects reported having attempted to control the magnitude of the fearful feeling by volitionally acting on their respiration. No fear reaction was reported in normal control subjects (mean rating of fear = \( 0.4/8; SD = 0.7 \)). A significant difference was observed between the average ratings of fear measured in the two groups (\( P < 0.001 \)).

After CBT

All phobic subjects were judged responders to CBT. Accordingly, the post-CBT scanning session for treated subjects was marked by a dramatic reduction of the fear experienced during the exposure to the film excerpts showing spiders (mean rating of fear = \( 0.1/8; SD = 0.3 \)). The
After CBT. In treated subjects, the Spiders minus Butterflies contrast produced significant loci of activation, bilaterally, in the middle occipital gyrus (BA 18 and 19) and the superior parietal lobule (BA 7). Significant peaks of activation were also seen in the left inferior occipital gyrus (BA 18), left fusiform gyrus (BA 37), and right inferior temporal gyrus (BA 44) (see Table 1). The post- minus pretreatment comparison (using two-sample t test) confirmed that these regions were significantly activated after but not before CBT. In addition, the pre- minus posttreatment comparison (using two-sample t test) demonstrated that the right dorsolateral prefrontal cortex (BA 10; coordinates: −42, −65, −14, Z-score = 3.12) and the right parahippocampal gyrus (BA 36; coordinates: 30, −27, −19, Z-score = 2.72) were significantly activated before CBT but not after CBT (P < 0.05 for corrected volume).

Normal control subjects

In normal control subjects, the random-effects model indicated that the Spiders minus Butterflies contrast was associated with significant peaks of BOLD signal increases in the left middle occipital gyrus (BA 19) (x = −45, y = −72, z = 2, Z-score = 5.59) and right inferior temporal gyrus (BA 37) (x = 50, y = −53, z = −18, Z-score = 4.48). Direct comparison of the Control group with the pretreatment group (using a two-sample t test) revealed that the dorsolateral prefrontal cortex (BA 10) and the parahippocampal gyrus (BA 36) were significantly activated in phobic subjects, before CBT, but not in the control group (P < 0.05 for corrected volume).

Discussion

Before CBT

Exposure to the film excerpts showing spiders produced, in phobic subjects before CBT, significant bilateral activation of the parahippocampal gyrus (BA 36) and associative visual cortex (BA 19, 20, 37), as well as activation of the right dorsolateral prefrontal cortex (inferior frontal gyrus—BA 10). Taken together, these results are fairly consistent with most of the previous PET studies that have investigated the neural substrate of SP (Fredrikson et al., 1995; Johanson et al., 1998).

Regarding the prefrontal activation before CBT, a fMRI study recently carried out by our group (Beauregard et al., 2001) has confirmed the hypothesis that the dorsolateral prefrontal cortex (BA 10) is a key brain structure implicated in voluntary self-regulation of emotion (Davidson et al., 2000). This finding accords with the view that this heteromodal (higher order) association isocortex (Mesulam, 2000) plays a crucial role in metacognitive/executive top-down processes, which refer to the ability to monitor and control the information processing necessary to produce voluntary action (Flavell, 1979). There is an interesting parallel to draw between the prefrontal activation seen in this study, when phobic subjects were volitionally attempting to control the magnitude of their fear associated with viewing the spider film excerpts, and that previously reported in frightened phobic subjects when they were exposed to spiders (Johanson et al., 1998). According to Johanson and coworkers (1998), the frontal rCBF increase seen in their PET study was correlated with the use of cognitive strategies to cope with the phobic situation. In this context, we surmise that the dorsolateral prefrontal activity noted here relates to the use of proactive metacognitive strategies aimed at self-regulating the fear and anxiety evoked by the phobogenic stimuli. In keeping with the conclusions raised by Fredrikson and colleagues (1993, 1995), it is possible that the prefrontal rCBF decreases noted in their PET studies, when spider phobics were viewing a color videotape of a spider, reflected a different psychological response to the phobogenic stimuli than that experienced by the phobic subjects examined in the present study, namely, reduced conscious cognitive processing associated with a defense reaction against those stimuli. Alternatively, it is plausible that, in keeping with Davidson’s model, the right prefrontal cortical activation seen here reflected a withdrawal response linked to a negative affect such as fear (Davidson et al., 1990; Tomarken et al., 1992; Wheeler et al., 1993).

Functional brain imaging studies have shown that the parahippocampal region is involved in panic attacks in individuals suffering from panic disorder (Reiman et al., 1984, 1986; Nordahl et al., 1990). Behaviorally, both phobic and panic disorders are characterized by phobic avoidance, which arises from an association of panic attacks or intense fear reaction with the context in which the fear response originally occurred. Phobic avoidance represents a type of contextual learning analogous to that seen in fear conditioning in animals (Phillips and LeDoux, 1992). Indeed, animals that have undergone a fear-conditioning experience also become conditioned to the context in which the negative conditioning experience occurred. This learn-
ing phenomenon has its neural basis mostly in the memory systems of the hippocampal formation and the medial temporal lobe. In humans, the contextual fear memory through which the fear conditioning is established also appears to involve the hippocampal formation (Bechara et al., 1995). Given that the majority of phobic subjects examined in this study developed SP following an early experience perceived in a traumatic manner, we propose that the parahippocampal activation seen here might be related to an involuntary reactivation of the contextual fear memory that led to the development of avoidance behavior and the maintenance of SP.

Activation of the ventral stream of the visual system (including the inferotemporal cortex) is consistent with the results of recent functional neuroimaging studies showing that, when compared with neutral visual stimuli, emotionally laden visual stimuli elicit increased activation in this cortical region (Lang et al., 1998; Lane et al., 1999; Karama et al., 2002). In light of the various lines of evidence indicating that attention to visual stimuli can modulate neural activity in the visual associative cortex (Corbetta et al., 1991; Treue and Maunsell, 1996; Lane et al., 1997; O’Craven et al., 1997; Büchel et al., 1998; Chawla et al., 1999), it seems conceivable that, in the Spiders minus Butterflies contrast, activation in this cortical region may reflect enhanced visual attention to the phobic stimuli presented (e.g., spiders). As already suggested, such a modulatory action may support vigilance functions in anxiety (Fredrikson et al., 1993, 1995).

As in the case of the Fredrikson et al. (1993, 1995) and Johanson et al. (1998) studies, and contrary to the Rauch et al. (1995) study, no significant locus of activation was noted in the anterior cingulate cortex and the insula. With respect to this issue, a recent metaanalysis of emotion activation studies in PET and fMRI (Phan et al., 2002) reveals that these two brain structures are mainly associated with the cognitive/internal generation of emotional state by evoking visual imagery or memories, rather than with the external visual induction of emotion (using, for instance, pictures or film clips). Such a conclusion is consistent with the fact that, in our study and those of Fredrikson et al. (1993, 1995) and Johanson et al. (1998), subjects had their eyes open and were asked to focus their attention on the phobic stimuli that were presented visually, whereas in the Rauch et al. (1995) study, subjects were requested to close their eyes and to allow their thoughts to focus on their individualized phobic stimulus.

No significant amygdaloid activation was found in phobic subjects during the viewing of the film excerpts depicting spiders. This absence of amygdaloid activation is in line with the results of all previous functional neuroimaging studies of specific phobia (Fredrikson et al., 1993, 1995; Rauch et al., 1995; Johanson et al., 1998). This suggests that the amygdala may not be related to the phobic expression and/or experience. However, it seems conceivable that this brain region may be involved in the pathogenesis of specific phobia, given the pivotal role played by the amygdala in fear conditioning (LeDoux, 1993).

After CBT

The fact that all phobic subjects after CBT were able to touch, without reporting fear reaction, the entire series of pictures depicting spiders, the TV screen showing living spiders, and the real spiders; moreover, the fact that, after CBT, the absence of behavioral (fear) manifestation correlated well with the anxiety analog scale (AAS); taken together, these findings rule out the likelihood that the self-reported patient data reflected demand effects.

Exposure to the film excerpts depicting spiders was associated, in treated subjects, with activation of the associative visual cortex (BA 18, 19, 37) and superior parietal lobule (BA 7), bilaterally. Significant activation was also noted in the right inferior frontal gyrus (BA 44). Interestingly, no significant activation was seen in the dorsolateral prefrontal cortex (BA 10) and the parahippocampal gyrus (BA 36). The brain activation pattern found in phobic subjects, after effective CBT, displayed some similarity with that noted in normal control subjects; that is, in controls, no frontal or hippocampal activity was detected during the viewing of the spider film excerpts. The activation of the middle temporal gyrus, in normal control subjects, is consistent with the findings of a recent PET study (Kosslyn et al., 1996) showing that emotionally laden negative stimuli can modulate activity in this cortical brain area.

The absence of activation in the dorsolateral prefrontal cortex (BA 10) and parahippocampal gyrus, after CBT, provides strong support to the view that CBT reduces phobic avoidance by deconditioning contextual fear learned at the level of the hippocampal/parahippocampal region, and by decreasing cognitive misattributions and catastrophic thinking at the level of the prefrontal cortex (Gorman et al., 2000). This deconditioning process would prevent the reactivation of the traumatic memories by allowing the phobic subjects to modify their perception of the fear-evoking stimuli. Once this perception has been reframed, the phobic stimuli would not constitute a threat anymore. Such cognitive restructuring would render obsolete the activation of the brain regions previously associated with the phobic reaction.

The superior parietal lobule (BA 7) was seen activated, bilaterally, after CBT. This cortical region—which is a component of the dorsal stream of the visual cortex—is known to be involved in vigilance (Pardo et al., 1991) and in sustained visual attention for emotionally neutral stimuli (Posner and Raichle, 1994; Shibata and Ioannides, 2001). In view of the neuroanatomical data showing that this parietal area (BA 7) sends extensive projections to BA 44 of the inferior frontal gyrus (Kaufman and Lewis, 1999), and of the clinical neuropsychological data showing that the dorsal portion of the right inferior frontal gyrus (BA 44) may be involved in the guidance of attention in visual space (Husain, 1991; Treue and Maunsell, 1996; Lane et al., 1997; O’Craven et al., 1997; Büchel et al., 1998; Chawla et al., 1999), it seems conceivable that attention to visual stimuli can modulate neural activity in this cortical region.
and Kennard, 1996), we propose that the activations seen here in the superior parietal lobule and the right inferior frontal gyrus may be related to a state of “visual vigilance” devoid of emotion.

In conclusion, the present findings suggest that a psychotherapeutic approach, such as CBT, has the potential to modify the dysfunctional neural circuitry associated with anxiety disorders. These findings support the conclusions of previous PET studies showing that psychotherapy can lead to adaptive regional brain metabolic changes in patients suffering from major depression (Brody et al., 2001; Martin et al., 2001) and obsessive-compulsive disorder (Baxter et al., 1992; Schwartz et al., 1996). These findings further indicate that the changes made at the mind level, in a psychotherapeutic context, are able to functionally “rewire” the brain. In other words, “change the mind and you change the brain.”

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