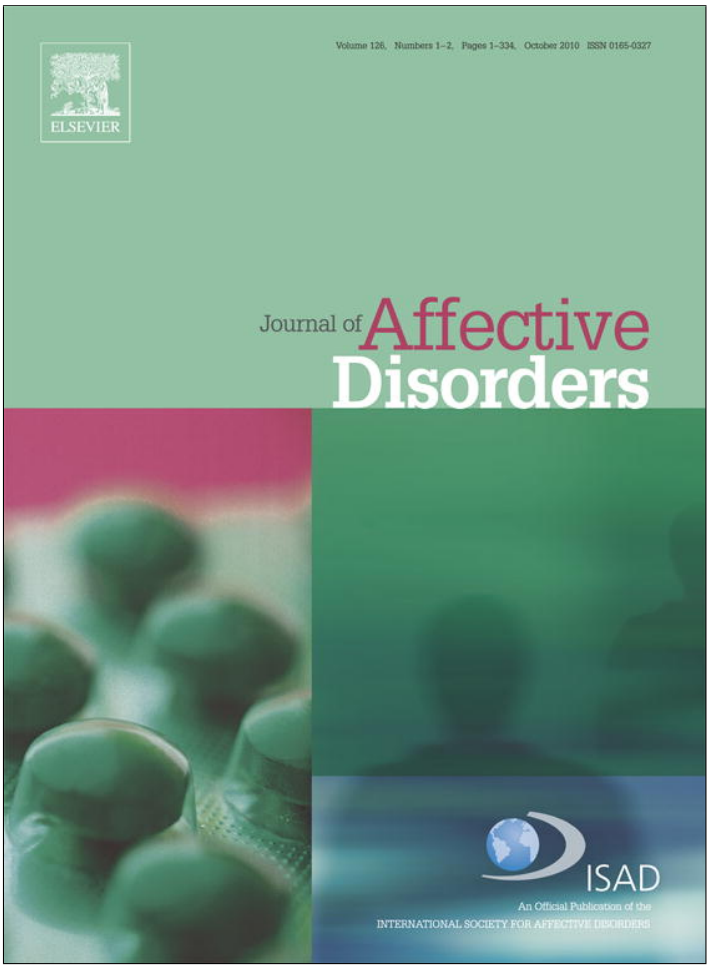

Journal of Affective Disorders 126 (2010) 321–325

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Brief report

An fMRI study on mental pain and suicidal behavior

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ARTICLE INFO

Article history:
Received 10 January 2010
Received in revised form 5 March 2010
Accepted 6 March 2010

Keywords:
Suicide
Attempted suicide
Mental pain
Suicide action
Suicidal mode
Dissociation
Neuroimaging

ABSTRACT

Background: Suicide is a poorly understood phenomenon. A clinical model of suicide conceptualizes suicidal behavior as a solution to an unbearable state of mind, experienced as mental pain.
Methods: In order to investigate the neural correlates of suicidal behavior, we used fMRI during presentation of autobiographical scripts extracted from personal narratives reactivating patients' memories of a recent episode of attempted suicide. Brain activation was measured during three recalled conditions: mental pain, suicide action, and neutral activity.
Results: Recall of suicidal episodes, that is, mental pain plus suicide action, compared to neutral activity, was associated with deactivation in the prefrontal cortex (BA 6, 10, and 46). Recall of suicide action, however, compared to mental pain, was associated with increased activity in the medial prefrontal cortex, the anterior cingulate cortex, and the hippocampus.
Limitations: This is a pilot study with eight female subjects.
Conclusions: Clinical and fMRI data suggest that mental pain triggering suicidal behavior may have the quality of traumatic stress, associated with decreased prefrontal activity. Planning and acting out suicidal impulses in response to mental pain, however, is associated with increased activity in the frontal cortex, suggesting that goal-directed suicidal behavior is associated with a reduction of mental pain.

1. Introduction

The neural basis of suicide is poorly understood. Biological models favor a stress-diathesis model (Mann et al., 1999), while psychological models focus on an individual's emotional, cognitive and behavioral experience, encompassing concepts such as mental pain (Orbach et al., 2003a), escape from self (Baumeister, 1990), and deficits in problem-solving (Pollock and Williams, 2001). Behavior therapists have introduced the concept of the "suicidal mode", a cognitive–emotional–behavioral pattern that is "switched on" immediately when triggered (Rudd, 2000). Most neuroimaging studies with suicidal individuals have focused on neurotransmitter receptor function of suicide victims, which do not allow insight into state-dependent brain activity related to suicidal behavior. Exceptions are the studies by Oquendo et al. (2003) and by Jollant et al. (2008), the former comparing the prefrontal cortex (PFC) serotonergic response of high-lethality with low-lethality suicide attempters, and the latter investigating the neural correlates of rejection sensitivity in suicidal individuals. Here, we used script-driven recall during fMRI (Lanius et al., 2001) to reactivate the suicidal mode in patients with a recent history of attempted suicide. We hypothesized that negative emotions experienced as mental pain would show similarities with traumatic stress and would therefore be associated with a decreased neural activity in the

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doi:10.1016/j.jad.2010.03.005

frontal cortex (e.g. Bremner et al., 1999). We further hypothesized that patients' narratives about planning and acting out suicidal impulses would represent a form of goal-directed behavior, which would be associated with increased activity in the medial prefrontal cortex (Matsumoto and Tanaka, 2004).

2. Method

2.1. Procedures

Narrative interviews (Michel et al., 2004) with patients who had recently attempted suicide were conducted. In a second exploratory session, the video-recorded interviews were played back to the patient in order to gain further information on the suicidal process. Mental pain sequences, suicide action sequences and neutral sequences were identified and classified independently by two coders (TR and KM), followed by consensus classification. Mental pain sequences were defined as subjectively unbearable states of mind related to the suicide attempt. Suicide action sequences were defined as narratives of pre-attempt preparation behaviors (e.g. gathering drugs and writing farewell letters) and the actual suicide attempt. In the neutral control sequences patients described everyday activities such as getting up in the morning, making coffee, etc. Three scripts of each condition (mental pain, suicide action, and neutral) were condensed and, in a third session, presented to the patient to assure correctness of details, and, if necessary, adapted.

2.2. Participants

Ten individuals who had attempted suicide one to four weeks prior to the interview were included. After the scanning procedure two patients were excluded from data analysis due to claustrophobia or active avoidance to concentrate on the scripts during fMRI procedure. The mean age of the eight remaining subjects was 38.5 years (SD 13.1 years). The mean time period between suicide attempt and fMRI was 51 days (SD 17.4 days). Subjects were female and right-handed. All had used overdosing for attempting suicide. Seven patients were prescribed antidepressants at the time of scanning. The study was approved by the local ethics committee, and written informed consent was obtained from each patient.

Subjects had a mean score of 26.75 (SD 11.49) on the Beck Depression Inventory (Beck et al., 1961) indicating depression in the same range as in other studies of attempted suicide (Oquendo et al., 2004). Furthermore, they had, consistent with Orbach's original sample of suicidal patients (Orbach et al., 2003a), a mean item score of 3.37 (SD 1.03) in the Orbach and Mikulincer Mental Pain Scale (Orbach et al., 2003b), a 44-item self-rating questionnaire, developed to quantify the subjective experience of mental pain, high levels of mental pain before and during the suicide attempt. Dissociative symptoms were assessed using the Peritraumatic Dissociation Index (PDI; Griffin et al., 1997). Items were rated for the time periods (a) *before* initiating the suicide attempt (=mental pain) and (b) *during* the suicide attempt. The mean PDI item score was 1.55 (SD 0.57) for the mental pain phase, and 1.73 (SD 0.61) for the suicide action phase, with no statistically significant difference between the two conditions.

2.3. Image acquisition

During scanning, the subjects heard the auditory stimuli via MRI-compatible headphones. Each script (read in first person by the interviewer) lasted 25 s (script modality) and was followed by an imagination phase (imagination modality) of the same duration. Three different scripts (for mental pain, suicide action and neutral conditions) were presented in an alternating order, three times (total: 27 blocks). Scanning was carried out on a 1.5 T Scanner (Siemens, Erlangen, Germany) using a standard 8 channel head coil. For fMRI (30 slices, 724 volumes, slice thickness of 4 mm with no gap and inter-slice time of 110 ms, matrix 64×64, field of view 230×230 mm, echo time (TE) 50 ms, repetition time (TR) 3318 ms), an echoplanar sequence emitting a quasi-continuous noise gradient switch pattern was used (Seifritz et al., 2006). Anatomical T1-weighted volumes were obtained with a three-dimensional magnetization-prepared rapid acquisition gradient echo sequence (MPRAGE) at a voxel size of 1 mm3 (TR 2000 ms, TE 3.42 ms).

2.4. fMRI data analysis

Functional image time-series were motion-corrected using the scanner's manufacturer software (MRIP) and the first 25 s were discarded to allow complete magnetization saturation. Volume series were corrected for the different slice acquisition times and for linear and non-linear trends, registered to anatomical scans, warped into Talairach space, resampled into 3 mm isotropic voxels and spatially smoothed with a 6 mm full-width-at-half-maximum Gaussian kernel. Each voxel time-course was scaled to percent signal change and linearly regressed to six "box-car" functions modelling the script and imagination phases in the three different conditions convolved with the double-gamma function (Friston et al., 1995, 1998). A fit–refit procedure was used for estimating this general linear model (GLM) while correcting the error term serial correlation according to a first-order autoregressive model (Bullmore et al., 1996). The GLM estimates were entered into a second-level (random-effects) analysis of variance (ANOVA) and two statistical *F*-maps were generated expressing the main effects of both suicide-related conditions in comparison to the neutral condition. The *F*-maps were displayed in color overlaid to the average Talairach-normalized anatomical scans after thresholding at 5% (cluster-level corrected for multiple comparisons, Forman et al., 1995; Etkin et al., 2004; Riecke et al., 2007). A region of interest (ROI) was defined to compare the amount of BOLD percent-signal-change within and between phases and conditions. Image data preparation and preprocessing, voxel- and ROI-level statistical analyses and display were performed with the software BrainVoyager QX® (Brain Innovation, Maastricht, The Netherlands).

3. Results

Because the shortest script had a duration of 15 s, we standardized the analysis of the fMRI scans to the first 15 s of each script. Suicidal episodes (mental pain plus suicide action), compared with the neutral condition, were associated with reduced activation in the left dorso-lateral prefrontal cortex (BA 46; $p=0.0023$, Fig. 1A), in the right anterior prefrontal cortex (BA 10; $p=0.0003$), and the left medial prefrontal

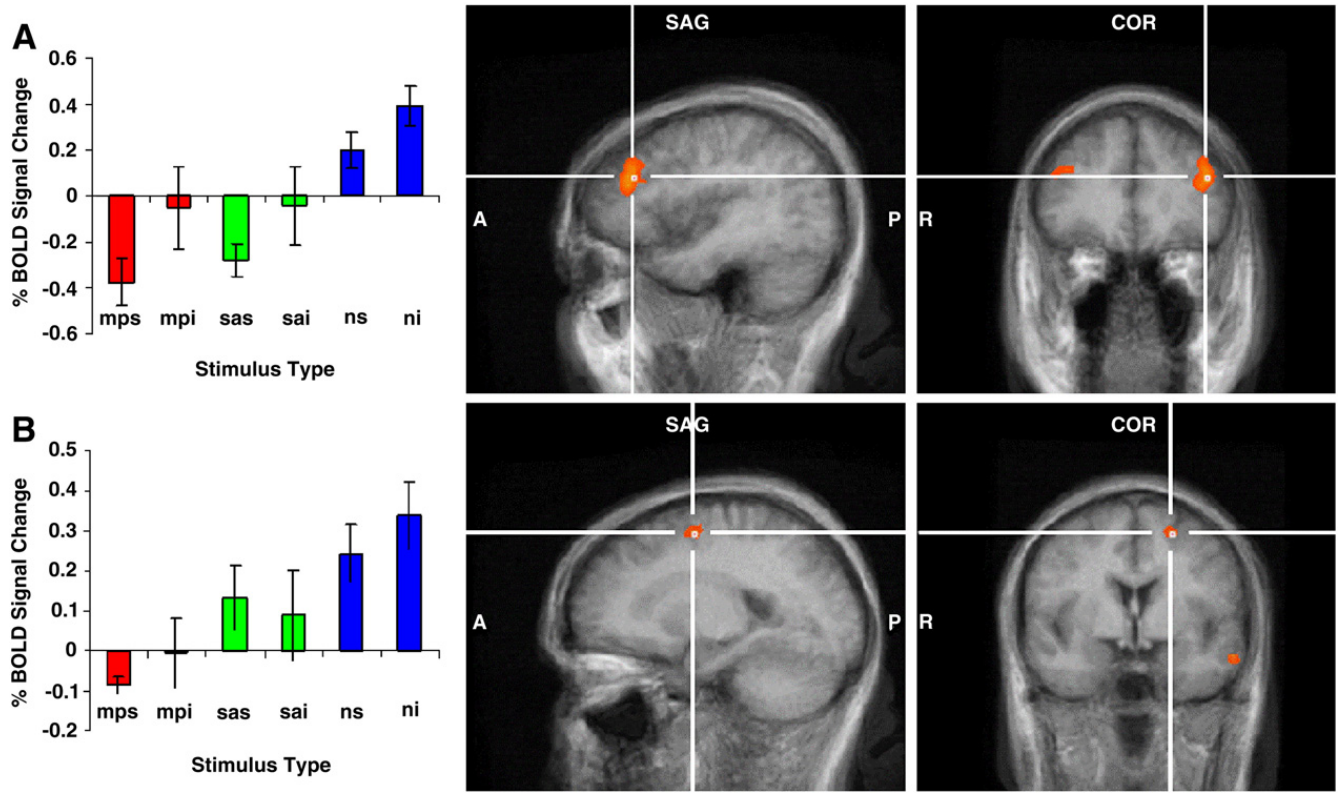

Fig. 1. (A) Reduced neural activation in the left middle frontal gyrus (BA 46) during recall of the suicidal episode vs neutral activity (random-effects ANOVA *F*-map, $p = 0.05$ corrected for multiple comparisons). ROI–GLM contrast: Ns + ni > ms + mi + sas + si; peak: $t = 4.675$, $p = 0.0023$. (B) Increased neural activation in the left medial PFC (BA 6) during recall of the suicide action vs mental pain (random-effects map ANOVA *F*-map, $p = 0.05$ corrected for multiple comparisons). ROI–GLM contrasts: sas > mps, peak: $t = 2.573$, $p = 0.0368$; mps + mpi < ns + ni, peak: $t = 3.583$, $p = 0.0089$; sas + sai < ns + ni, peak: $t = 2.777$, $p = 0.0274$; mps = mental pain script, mpi = mental pain imagination; sas = suicide action script, sai = suicide action imagination; ns = neutral script, ni = neutral imagination.

cortex (BA 6; $p = 0.0090$). This pattern was consistently present regardless of stimulation types (both script reading and imagination). In addition, we observed increased activity in the right parahippocampal gyrus ($p = 0.0037$), the right cuneus (BA 19, $p = 0.0075$), the left middle temporal gyrus (BA 4; $p = 0.0158$), and the cerebellum ($p = 0.0048$) Table 1.

In a second step, we compared activity during mental pain and suicide action conditions. The suicide action condition

Table 1
Neural activity during script-driven recall of the suicidal episode vs. neutral condition.

Region		Contrast	*t*	*p*	Talairach			Extension [mm^3]
					X	Y	Z	
Middle frontal gyrus (BA10)		MP + SA < N	-6.74	0.0003	39	47	13	1092
	R	SA < N	-6.4	0.0004				
		MP < N	-5.93	0.0006				
Middle frontal gyrus (BA 46)		MP + SA < N	-4.68	0.0023	-42	35	22	1830
	L	SA < N	-5.37	0.001				
		MP < N	-4.02	0.0051				
Medial PFC (BA 6)		MP + SA < N	-3.58	0.009	-21	-4	55	375
	L	SA < N	-2.78	0.0274				
		MP < N	-3.58	0.0089				
Parahippocampal gyrus		MP + SA > N	4.27	0.0037	30	-49	1	317
	R	SA > N	3.82	0.0065				
		MP > N	3.78	0.0069				
Cuneus (BA 19)		MP + SA > N	3.71	0.0075	6	-82	28	461
	R	SA > N	1.35	n.s.				
		MP > N	3.78	0.0069				
Middle temporal gyrus (BA 4)		MP + SA > N	3.17	0.0158	-57	-4	-17	371
	L	SA > N	2.22	n.s.				
		MP > N	4.43	0.0031				
Cerebellum		MP + SA > N	4.07	0.0048	0	-40	-14	217
		SA > N	3.34	0.0124				
		MP > N	4.15	0.0043				

MP = mental pain, SA = suicide action, N = neutral activity.

Table 2
Neural activity in mental pain vs. suicide action.

Region		Contrast	t	p	Talairach			Extension [mm^3]
					X	Y	Z	
Medial PFC (BA 6)	L	sas>mps	4.24	0.0038	-21	-4	55	973
ACC/medial frontal gyrus (BA 6, 32)	R	sas>mps	2.83	0.0255	3	23	43	437
Hippocampus BA (35)	L	sas>mps	4.81	0.002	-24	-22	-14	229

Sas = suicide action, script modality, mps = mental pain, script modality.

(script modality) was associated with an increased activation in the left medial prefrontal cortex (BA 6; $p = 0.0038$, Fig. 1B), the right anterior cingulate cortex (BA 32 and BA 6, $p = 0.0255$), and the left hippocampus (BA 35, $p = 0.002$) Table 2.

4. Discussion

The main findings of this neuroimaging study are: a) deactivation in frontal cortical areas (BA 46, 10, and 6) in mental pain plus suicide action, and b) increased neural activity in the medial PFC, the anterior cingulate cortex and the hippocampus during the recall of the suicide action in comparison to mental pain. To our knowledge this is the first neuroimaging study investigating the neural correlates of script-driven recall of a suicidal crisis. It is based on the concept of the suicidal mode (Rudd, 2000) as a state-dependent phenomenon that can be triggered by a specific stimulus. Our results have close similarities with the results from neuroimaging studies employing script-driven imagery with sexual abuse- and combat-related PTSD patients (Lanius et al., 2001; Bremner et al., 1999), which found reduced activity in the left medial prefrontal cortex (BA 6, 10/11) and the anterior cingulate gyrus (BA 32) associated with the re-activation of the traumatic experiences. This suggests that what our patients experienced during the suicidal crisis may have the quality of an acute traumatic state. The traumatic nature of the suicidal mode is supported by the high level of dissociative symptoms reported by our patients. The mean scores of the PDI were in the same range as those reported from Vietnam Veterans (Marmar et al., 1994).

Our results are in line with other studies. For instance, Orbach (1994) argued that dissociative symptoms such as emotional numbing, detachment from body, and indifference to physical pain, may be necessary to facilitate self-harming behavior. Furthermore, our findings are consistent with models of suicide that suggest hypofunction in the ventral prefrontal cortex as a critical parameter of suicidal behavior (Mann et al., 1999; Oquendo et al., 2003).

We had hypothesized that once the emotionally stressed individual shifts his or her mind to suicide as a solution to the traumatic mental pain condition, this would in some areas of the frontal lobes be associated with a shift from deactivation to increased neural activation, consistent with goal-directed behavior. This hypothesis was supported by the findings of increased mPFC, ACC and hippocampus activity during the recall of the goal-directed actions related to the suicide attempt. Both, mPFC and the ACC play a central role in the regulation of emotional and behavioral responses to stressful events (Amat et al., 2005; Simons et al., 2008; Oddo et al., 2010; Botvinick et al., 2001). These areas have been associated with self-reflection, crucial for coping with emotionally charged situations (Ochsner et al., 2002). It is plausible that in the suicidal mode, due to cortical deactivation, the ability to access autobiographical memory, considered to be crucial for mindful problem-solving, is seriously impaired, leaving the suicidal individual victim to unreflected short-term action selection aimed at immediately putting an end to a subjectively unbearable traumatic state of mind. Unfortunately, in this goal-directed process, the "horizon of consciousness is confined to the here-and-now of an egocentric perspective", leaving little capacities for thought, foresight, choice, innovation, or interpretation (Marsel Mesulam, 2002). Furthermore, because an act of self-harm is associated with a reduction of unbearable mental pain, self-destructive behavior is likely to be established as contingent response to this state of mind.

In summary, the results support a model of suicidal behavior as a state-dependent condition. We assume that, once, after a first suicide attempt, the suicidal mode is stored in the neural circuitry, it can be "switched on" by the recall of the mental pain experience. The results also suggest that the suicidal mode has the quality of a traumatic state, with a deactivation in frontal cortical areas. Planning and acting out suicidal impulses is associated with increased activation in the medial prefrontal cortex, the cingulate cortex, and the hippocampus.

4.1. Limitations

Our study used a within-subject design, without a control group. This method was chosen because it would have been virtually impossible to find a homogenous control group representing a serious emotional crisis of similar quality, but without suicidal behavior. The study has a relatively small number of subjects and thus has pilot character. It should be replicated with larger numbers of subjects. Furthermore, we cannot exclude an influence of the antidepressants on the results.

Role of funding source

This study was carried out within a clinical context without special funding. G. Schroth, head of the Department of Neuroradiology, University Hospital Bern, supported the study and allowed the authors to use the MRI scanner as a quasi-clinical procedure. G. Schroth had no influence on the study procedures or data analysis.

Conflict of interest

T. Reisch, E. Seifritz, F. Esposito, R. Wiest, L. Valach and K. Michel report no conflict of interest.

Acknowledgments

This study was carried out within a clinical context without special funding. We thank G. Schroth, head of the Department of Neuroradiology, University Hospital Bern, for supporting us in

using the MRI scanner for this investigation. We also thank our patients for agreeing to be re-exposed to their suicidal crisis.

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