Neural Correlates of Recall of Life Events in Conversion Disorder

Selma Aybek, MD; Timothy R. Nicholson, MD, PhD; Fernando Zelaya, PhD; Owen G. O’Daly, PhD; Tom J. Craig, MD, PhD; Anthony S. David, MD; Richard A. Kanaan, MD, PhD

Conversion disorder (CD), also known as hysteria, is by no means a historical entity, accounting for 16% of neurology outpatients.1 Although current diagnostic criteria highlight the role of physical findings,2 etiological models remain rooted in the past, particularly freudian models postulating the “repression” of psychological conflict and its “conversion” into physical dysfunction.3 This view of CD as psychogenic remains popular4, but biological research has neglected the psychogenic aspect, focusing on the neurological symptoms. Functional magnetic resonance imaging (fMRI) studies of patients with motor CD have compared brain activity5 during attempted, planned, or imagined movement in an affected limb in contrast to the unaffected or recovered limb; results are interpreted6 as evidence of motor network dysfunction, but these do not link symptoms to the hypothesized antecedent psychological stresses.

There is consistent evidence for an association between childhood stressors (particularly sexual abuse) and CD7 but less consistent evidence for the importance of psychological stressors at the time of symptom onset, which may in part be because of the methodological challenges of studying life events,8 especially using self-report checklists. A rigorous and extensive method, the Life Events and Difficulties Schedule (LEDS),9 has been developed to assess stressful life events in psychiatric populations and has been applied successfully to functional and somatoform disorders.10,11 Freud3 argued not only that the key events in CD were painful, leading to their being willfully ignored (or repressed), but also that subsequent illness invariably led to some benefit or “secondary gain” for the patient. The presence of secondary gain in CD has been confirmed by some investigators12-15 and the LEDS allows an operationalized rating of this aspect of events.11
One potential contemporary model for Freudian repression is the voluntary suppression of memory, demonstrated experimentally in healthy volunteers using a think-no-think paradigm. This suppression was associated with a brain activity network involving the dorsolateral prefrontal cortex (DLPFC) correlated with hippocampal deactivation, and with the right inferior frontal cortex (IFC) having a key role when suppressing emotional memories. We hypothesized that an analogous process would be revealed during fMRI of the cued recall of life events considered of causal significance in CD. We also set out to explore whether this process would be associated with activation in symptom-salient brain areas.

Methods

Participants
The study was approved by a London, England, research ethics committee (Bromley 07/H0805/33). After complete description of the study to the participants, written informed consent was obtained. Patients with DSM-IV sensory motor CD (onset within 24 months) were recruited from neurology and neuropsychiatry settings in South East London, with diagnoses established by a fully trained neuropsychiatrist after appropriate neurological exclusion. Age- and sex-matched control subjects were randomly recruited from a primary care clinic in the same area. Nonfluent English speakers and individuals with psychosis, major depression, bipolar affective disorder, or a comorbid neurological disorder were excluded. Recruitment continued until a sufficient number of participants with suitable events (see below) was obtained, namely, 12 patients (8 female; mean age, 38.1 years), and 13 control subjects (10 female; mean age, 36.2 years). We had to assess 42 patients before we concluded recruitment, although many of those excluded were for pragmatic reasons (eg, the potential presence of metal clips from a previous surgical procedure). One-third of each group was taking some medication, usually antidepressants or anxiolytics.

Life Events Assessment
The presence of psychological stressors was assessed using the LEDS, a semistructured interview that covers a wide spectrum of stressful experiences. The LEDS has several advantages over self-report checklist measures, particularly for reducing the risk of recall bias. It is investigator based, and because a participant will be biased in the reporting of his or her experience, it uses a contextual measurement of meaning. In this approach, a panel of raters (S.A., T.R.N., T.J.C., A.S.D., and R.A.K.), blinded to whether they are dealing with a patient or control subject, makes a judgment of the likely effect of the event on an average person with the plans, biography, and circumstances of the participant but ignoring the participant’s report of his or her reaction to the event at the time. Of course, the measure still depends on the accuracy of reporting the facts of the event, but the LEDS has been shown to have excellent psychometric properties, including high levels of interrater reliability for the contextual ratings of meaning in studies of anxiety, depression, and physical illness.

The panel for this study included neurologists (S.A.) and psychiatrists (T.R.N., T.J.C., A.S.D., and R.A.K.) with expertise in CD and in the use of the LEDS, who were trained on the contextual measures used. There were between 3 and 6 members present for each rating. First, a rating of the threat of events was made, on a scale of 1 to 4, reflecting the severity of the likely consequences of the event (a severe event was rated 1 or 2). Second, the panel rated the event’s escape potential, a refined version of secondary gain, defined as the extent to which a subsequent illness might reduce the effect or consequences of the stressor, affording a socially sanctioned means to avoid a difficult situation. For example, a spouse’s sudden death would offer minimal escape potential because the individual’s subsequently becoming ill would do little to alleviate the stressor; however, a partner threatening to break off a relationship would have substantial escape potential because the individual’s becoming ill might prevent the partner’s feeling able to abandon the individual when he or she was unwell. This escape component was blindly judged “as if the individual had developed CD,” so that events concerning patients and controls could be rated identically. Our group has previously shown that such escape events are substantially more common in CD than among control subjects and that this becomes increasingly significant toward the time of symptom onset, supporting the causal significance. The panel reached a consensus on events of likely causal significance based on the threat, escape, and proximity of the event to the illness (or the epoch end in controls). Participants who had both a severe escape event (referred to as the escape event hereafter) and at least 1 severe nonevent (referred to as the severe event hereafter) underwent imaging.

Premorbid IQ was estimated with the National Adult Reading Test. Mood was assessed with the Hospital Anxiety and Depression Scale and memory with the Autobiographical Memory Inventory.

fMRI Task
Three weeks before imaging, a follow-up interview was conducted to obtain details of the severe and escape events, as well as of a third neutral event from the same epoch, to generate length-matched statements (24 for each type of event). One-quarter of these were rendered incorrect by changing incidental facts to maximize immersive recall when later asked in the imaging system if true or false. Three blocks of 8 statements were presented in counterbalanced order between conditions (severe, escape, and neutral). Each block began with a 3-second header title. Each statement was shown for 11 seconds, for a total of 88 seconds per block, excluding the period of the header. Reaction times (RTs) for true or false responses (by a button press in the less symptomatic hand) were recorded. After each block, participants rated how upsetting the last 8 sentences had been by moving a cursor on a visual analog scale (VAS) (very upsetting was rated as 0, and not upsetting at all as 10). To minimize carryover effects, the order of presentation was pseudorandomized between participants.
Recall of Life Events in Conversion Disorder

Image Acquisition and Preprocessing

Magnetic resonance imaging was performed on a 3-T system (Signa HDX; GE Medical Systems) with an 8-channel radiofrequency coil. During the task, a temporal series of 291 gradient-recalled, echoplanar image volumes was acquired (repetition time/echo time of 3000/35 milliseconds, 14:33 minutes total, 49 near-axial sections, and 3.4 × 3.4 × 3.0 mm). A high-resolution echoplanar image (1.875 × 1.875 × 3.3 mm) was acquired for coregistration and normalization.

Data were processed using Statistical Parametric Mapping (SPM8; http://www.fil.ion.ucl.ac.uk/spm/) and adjusted for section timing, realigned to the first image of the first run, normalized to the Montreal Neurological Institute (MNI) atlas, and smoothed using an 8-mm gaussian kernel. To correct for movement artifacts, first-level analyses were performed using the SPM8 robust weighted least-squares tool.28

Statistical Analysis

Sex, age, IQ, mood, and memory scores were compared between groups using the Fisher exact test, unpaired t test, and Mann-Whitney test. Behavioral data were analyzed with the Kruskal-Wallis test and repeated-measures analysis of variance with condition (escape, severe, or neutral) as a within-group factor and group as a between-group factor using the Statistical Package for the Social Sciences (PASW Statistics 18.0; SPSS Inc).

Table 1. Participant Characteristics, Psychopathology, and Memory Scores

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n = 12)</th>
<th>Controls (n = 13)</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>Female sex, No. (%)</td>
<td>8 (67)</td>
<td>10 (77)</td>
<td>.67a</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>38.10 (11.26)</td>
<td>36.20 (9.14)</td>
<td>.66b</td>
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<tr>
<td>Hospital Anxiety and Depression Scale, mean (SD)</td>
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<tr>
<td>Depression score</td>
<td>11.00 (6.67)</td>
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* Fisher exact test.  
**t Test.  
*Mann-Whitney test.

Results

Participant Characteristics

The patients were all symptomatic at the time of imaging, with lateralized motor deficits in 4 participants (2 left-sided and 2 right-sided) and bilateral deficits in 8 participants (5 paraparesis and 3 tetraparesis). The median duration of symptoms was 13.5 months (range, 3-36 months). Patients and controls did not differ in sex, age, estimated IQ, autobiographical memory, or anxiety scores, but depression scores were significantly higher in patients (mean, 11.0 of 21) than in controls (mean, 5.7 of 21) (P = .03) (Table 1).

Behavioral Findings

The mean true-false errors were low in all conditions (12.5% among patients and 11.7% among controls for the escape condition, 17% among patients and 12.2% among controls for the severe condition, and 12.5% among patients and 14.4% among controls for the neutral condition), with no significant effects of group or condition. The mean (SD) time elapsed from each event to the imaging day was not significantly different between groups and across conditions (15.4 [9.9] months among patients and 14.8 [13.0] months among controls for the escape condition, 20.3 [11.8] months among patients and 16.7

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cape events (3.14 [0.14] seconds) compared with neutral events.
Analysis showed significantly longer mean (SD) RTs for escape events (2.89 [0.13] seconds) compared with neutral events (2.7 [0.3] seconds). A significant group × condition interaction was found. Between groups, the mean (SD) VAS scores (less upsetting) for escape events (3.3 [0.3]) were significantly higher than for severe events (2.7 [0.3]) across groups (F(2,40) = 0.74, P = .47). A significant main effect of condition was observed (F(2,37) = 4.23, P = .03; Greenhouse-Geisser corrected). Post hoc analysis showed significantly longer mean (SD) RTs for escape events (3.4 [0.14] seconds) compared with neutral events (2.89 [0.13] seconds) (P < .001; Greenhouse-Geisser corrected), and there was no significant group × condition interaction (F(2,40) = 0.74, P = .47). A subjectively lower mean (SD) VAS scores (more upsetting) for escape events (3.3 [0.3]) compared with neutral events (3.9 [0.3]) (P < .001) and for severe events (2.7 [0.3]) compared with neutral events (5.9 [0.3]) (P < .001). Significantly higher mean (SD) VAS scores (less upsetting) for escape events (3.3 [0.3]) were found compared with severe events (2.7 [0.3]) (P = .04) across groups. Objective ratings of mean (SD) severity (LEDS threat scores, as judged by the panel) did not differ between escape events (1.56 [0.71]) and severe events (1.64 [0.49]) across groups (P = .24).

**Imaging Findings**
Whole-brain analysis of the group × condition interaction showed significantly increased activation in patients compared with controls during the escape-severe condition in 2 clusters (Table 2 and Figure 1). The first was located in the right sensory motor cortex extending medially into the supplementary motor area (SMA). The second was located in the right superior temporal cortex extending anteriorly to the insula and posteriorly to the angular gyrus and supramarginal gyrus (temporoparietal junction [TPJ]). The opposite whole-brain contrast (escape-severe) revealed significantly decreased activation in a left temporoparietal cluster, including the parahippocampal gyrus and the hippocampus, in patients compared with controls. No main effect of group or condition was detected. The analyses were repeated with depression and anxiety scores as covariates, without altering the results.

The hypothesis-driven analysis (a priori regions of interest) showed no main effect of group but demonstrated a significant main effect of condition in the left DLPFC, with greater activation (MNI −34, 36, 30; P = .04, familywise error corrected) during the escape condition compared with the severe condition across groups (Figure 2A). This effect was driven by the patients because the group × condition interaction revealed greater activation in the same area (Figure 2C) during the escape condition relative to controls. No significant results were found in the right DLPFC.

A main effect of group was significant in the rIFC. Patients showed significantly less activation (MNI 44, 28, 8; P = .004, familywise error corrected) than controls in this region across both conditions (Figure 2B).

Because the whole-brain interaction analysis revealed a significant peak of activation in the right SMA, we conducted a connectivity (psychophysiological interaction) analysis with the seed volume of interest as a 5-mm-radius sphere around this identified peak. This analysis revealed a significant main effect of group, with patients demonstrating greater connectivity between the right SMA and 2 significant clusters across both escape and severe conditions relative to controls. Those clusters included the left amygdala and the cerebellum andpons (Figure 2E). No main effect of condition or group × condition interaction was found.

**Discussion**
The fMRI data during recall of autobiographical traumatic events revealed 4 main findings. First was increased left DLPFC activity during the escape condition relative to the severe condition in patients vs controls, together with decreased hippo-
campal and parahippocampal activity, a pattern compatible with memory suppression. Second was increased right SMA and right TPJ activity, possibly representing symptom-salient areas. Third is decreased rIFC activity in patients relative to controls across both conditions, compatible with impaired emotional inhibition. Fourth is enhanced connectivity between right SMA and left amygdala in patients relative to controls across both conditions, suggesting abnormal limbic-motor interaction.

**Suppression of Unwanted Memories: Role of the DLPFC**

Escape events elicited significantly longer RTs than neutral events and were perceived as less upsetting than severe events, although both types of events were of matched objective threat. These findings are compatible with Freud's concept of repression, such that the painful aspects of the emotional stimuli presented during the escape condition are reduced at a cost of increased cognitive processing. The fMRI results confirmed differential neural processing of escape events, with increased left DLPFC during the escape condition relative to the severe condition. This is consistent with memory suppression, as in the think–no think paradigm, in which participants either think or avoid thinking of a cued stimulus.\(^{17}\) Most important, this main effect of condition was largely driven by the patient group, and the results revealed a group × condition interaction in the same region of the left DLPFC, together with reduced brain activity in the left hippocampus and parahippocampal gyrus. This is additional evidence that patients process escape events in a manner akin to suppression,\(^{17}\) possibly through the mechanism of “direct suppression.”\(^{17}\) In direct suppression, the conscious recollection of an unwanted memory (mediated by the hippocampus) is disrupted by top-down regulation (mediated by the DLPFC) (both right\(^{17}\) and left\(^{17,27}\)); by contrast, in “thought substitution,” the other principal mechanism, unwanted memories are replaced by competing

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Figure 1. Whole-Brain Analysis

Statistical parametric maps showing significant clusters of activation (\(P < .05\), familywise error and cluster corrected). Red indicates group × condition interaction in the contrast escape > severe in patients > controls showing peak activations in the right supplementary motor area (SMA) and the right temporoparietal junction (TPJ). Blue indicates group × condition interaction in the contrast escape < severe in patients > controls showing decreased activation in the left hippocampus and parahippocampal gyrus. On the right are contrast estimates (y-axis) at right SMA (Montreal Neurological Institute [MNI] 12, −8, 68), right TPJ (MNI 40, −58, 24), and left hippocampus (MNI −28, −42, 2) (as indicated in the circles on the left). CD indicates patients with conversion disorder; Ctrl, healthy controls; Esc, escape condition; and Sev, severe condition.
thoughts, mediated by the left caudal and midventral prefrontal cortex.32

The involvement of the DLPFC in CD has been previously reported in motor CD34-37 and interpreted as reflecting abnormal top-down influence of prefrontal regions on lower-order sensory motor functions. Although previous investigations have used motor tasks, our study is the first to date to link this region to a causally relevant task (recall of a traumatic event) and gives greater justification to an etiological interpretation, namely, that this prefrontal dysregulation arises from, or is prompted by, a painful memory.

Conversion Symptoms: Role of the TPJ and SMA
Alongside this activation pattern of memory suppression, the interaction analysis revealed increased activity in the right SMA and right TPJ in the whole-brain analysis. According to Freud’s theory, the repression of memories comes at the cost of somatic symptoms, and this finding might reflect such a conversion into somatic symptoms.

The SMA is key to motor execution, and lesions in this region38 have been associated with motor neglect, which shares some clinical similarities with functional conversion paresis. The SMA has a role in self-initiated action39,40 and, most important, in inhibiting prepotent responses at conscious levels41 and unconscious levels.42 The increased SMA activity we found in patients may reflect an impaired ability to select the correct automatic motor plan at an unconscious level. Our study design did not permit us to conclude whether the increased right SMA activity represents a general process in CD or whether it is directly related to the symptom, and a subgroup analysis of the patients with left-sided (contralateral) symptoms was not feasible because of the few participants with hemiparesis in our sample. The right SMA has already been linked to CD43; enhanced connectivity between the right SMA and the right amygdala was found during an emotionally salient task,43 and lower connectivity between the left SMA and bilateral DLPFC was found during a self-initiated motor task.35

Statistical parametric maps showing significant clusters of activation (P < .05, familywise error and small-volume corrected). Blue indicates left dorsolateral prefrontal cortex (DLPFC) activation. Purple indicates right inferior frontal cortex (rIFC) activation. A, Contrast estimates in left DLPFC (Montreal Neurological Institute [MNI] −34, 36, 30; z = 2.75; P = .04, familywise error corrected). B, Contrast estimates in rIFC (MNI 44, 28, 8; z = 3.73; P = .004, familywise error corrected). C, Contrast estimates in left DLPFC (MNI −32, 36, 30; z = 2.77; P = .03, familywise error corrected).
The right TPJ is important in sensory integration and is operative in bodily self-location, self-consciousness, and self-person perspective, having a key role in out-of-body experiences, for example. In CD, it has been suggested that abnormal right TPJ activity is linked to abnormal multisensory integration of bodily schema.

However, although this interaction effect was mainly driven by increased activity in the SMA and TPJ during the escape condition in patients, it was also partly driven by an opposite effect in controls, who showed greater activity during the severe condition (Figure 3). This challenges a specifically conversion interpretation of these clusters somewhat because healthy controls do not report functional symptoms during recall of severe events. At the least, it suggests that the activity is not sufficient in itself to produce such effects in patients and must be part of a wider process. This activity may represent a consequence, rather than a cause, of symptoms because most of our patients had long-standing sensorimotor difficulties, although it would in that case represent a consequence that was only present when events thought to be of causal significance were recalled.

**Cognitive Control of Emotion: Role of the rIFC and Amygdala**

We found decreased activity in the rIFC in patients relative to healthy controls across both escape and severe conditions. The rIFC is important for inhibiting prepotent responses among several modalities, including motor, cognitive, and possibly emotional. The results of a study of an emotional think–no think task suggest that the suppression of emotional memory involves 2 pathways with staggered phases: the first involves cognitive control by the rIFC over sensory components of memory representation, and the second involves cognitive control by the right middle frontal cortex over emotional components of memory representation. Our finding of decreased rIFC activity in patients relative to controls suggests that patients with CD fail in this physiological attempt to control, inhibit, or reappraise an emotional memory that requires early engagement of the rIFC.

Another clue to abnormal emotional regulation in CD comes from our connectivity analysis, which showed increased amygdala–SMA and cerebellum connectivity in patients across both conditions. This suggests that patients are more prone to emotional arousal when recalling traumatic events and that this arousal may modulate motor function. Both the SMA and the cerebellum have a role in movement planning, with the SMA involved in preparation and the cerebellum involved in sensorimotor prediction. A connection between amygdala activation and motor execution has been shown in healthy volunteers, suggesting a role for the amygdala in implementing protective behavior in threat situations.
and has already been implicated in CD. Moreover, recent evidence suggests a role for cerebello-thalamocortical (including the SMA) loops in cognitive control, and additional studies should explore these circuits in CD.

Strengths and Weaknesses

A strength of our study is the sample size compared with many imaging studies in CD and the relative symptom homogeneity of the patients, who all had weakness (with a preponderance of paraparesis) rather than abnormal movements or non-epileptic seizures. However, this limits the generalization of our findings to other subtypes of CDs.

Robustly assessing the response to autobiographical recall is challenging because this requires participants to reexperience a memory that cannot be verified. Most studies have used script-driven tasks to elicit autobiographical memories, but we used a modified variant requiring true or false responses that has been found to generate equivalent reexperiencing and allows monitoring of participants’ compliance.

The process of identifying and rating of adverse life events is profoundly challenging, and although we used a validated method that minimizes recall bias from the participants and interviewer bias, the true nature of an individual’s response to events and the possible causal role can never be known with certainty. Our classification of escape events is also novel, and further work to confirm the role in CD is required.

Conclusions

This study offers support for the notion that the way adverse events are cognitively processed can be associated with physical symptoms in CD. When a negative emotion is triggered by recall of a threatening event, it induces increased arousal, mediated by the amygdala. This prompts cognitive control mechanisms mediated by the rIFC that act early in modulating and suppressing those aversive memories. Our finding of enhanced connectivity between the amygdala and motor regions in patients with CD suggests that they have an abnormal response to emotional stress and that regulation by the rIFC is impaired. Furthermore, when subjected to a specific stressor (recall of an escape event), mechanisms to control the emotional content of the event are triggered that increase left DLPFC and decrease hippocampal and parahippocampal activation. This seemed to succeed in making the memory less upsetting, as measured by the VAS subjective scores, but at a cost because the escape events were also associated with abnormal activity in the TPJ and SMA, which may represent neural correlates of a patient’s physical symptoms. This would fit with the Freud metaphor because the cognitive reappraisal of threatening reminiscences would be successful in attenuating the affect but lead to the conversion of this “energy” into physical symptoms. The fact that this pattern of brain activation is specifically induced by events of an escape nature (defined by the outcome being potentially influenced advantageously by the presence of an illness) also fits within phylogenetic or social psychological frameworks. We speculate that this mechanism might be a reflexive adaptation to threat but that in healthy individuals rapid regulation occurs. The reason why patients fail to engage their rIFC in inhibiting those primitive mechanisms still needs to be elucidated, as does the increased connectivity between emotion arousal regions (amygdala) and motor regions (SMA and cerebellum) in patients. It could be related to the illness condition itself and represent a state condition or may be a trait vulnerability that might derive from a developmental perturbation such as childhood abuse.

ARTICLE INFORMATION

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Author Contributions: Dr Aybek had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Aybek, Nicholson, Zelaya, Craig, David, Kanaan.

Acquisition of data: Aybek, Nicholson, Zelaya, Craig.

Analysis and interpretation of data: All authors.

Drafting of the manuscript: Aybek, Nicholson, Zelaya, Craig, David, Kanaan.

Critical revision of the manuscript for important intellectual content: Aybek, Nicholson, Zelaya, Craig, David, Kanaan.

Administrative, technical, and material support: Aybek, Nicholson, Zelaya, Craig, David.

Study supervision: Zelaya, Craig, David, Kanaan.

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