NeuroImage: Clinical 6 (2014) 333–339

Contents lists available at ScienceDirect

NeuroImage: Clinical

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

Functional neuroimaging of conversion disorder: The role of ancillary activation

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ARTICLE INFO

Article history:
Received 9 July 2014
Received in revised form 24 September 2014
Accepted 26 September 2014
Available online 30 September 2014

Keywords:
Conversion disorder
Functional neuroimaging
Sensory

ABSTRACT

Background: Previous functional neuroimaging studies investigating the neuroanatomy of conversion disorder have yielded inconsistent results that may be attributed to small sample sizes and disparate methodologies. The objective of this study was to better define the functional neuroanatomical correlates of conversion disorder.
Methods: Ten subjects meeting clinical criteria for unilateral sensory conversion disorder underwent fMRI during which a vibrotactile stimulus was applied to anesthetic and sensate areas. A block design was used with 4 s of stimulation followed by 26 s of rest, the pattern repeated 10 times. Event-related group averages of the BOLD response were compared between conditions.
Results: All subjects were right-handed females, with a mean age of 41. Group analyses revealed 10 areas that had significantly greater activation ($p < .05$) when stimulation was applied to the anesthetic body part compared to the contralateral sensate mirror region. They included right paralimbic cortices (anterior cingulate cortex and insula), right temporoparietal junction (angular gyrus and inferior parietal lobule), bilateral dorsolateral prefrontal cortex (middle frontal gyri), right orbital frontal cortex (superior frontal gyrus), right caudate, right ventral-anterior thalamus and left angular gyrus. There was a trend for activation of the somatosensory cortex contralateral to the anesthetic region to be decreased relative to the sensate side.
Conclusions: Sensory conversion symptoms are associated with a pattern of abnormal cerebral activation comprising neural networks implicated in emotional processing and sensory integration. Further study of the roles and potential interplay of these networks may provide a basis for an underlying psychobiological mechanism of conversion disorder.

1. Introduction

Conversion disorder is a controversial and challenging diagnosis that lies on the interface between neurology and psychiatry. It can manifest as a wide spectrum of symptoms, from deficit states such as paresis, blindness and anesthesia to hyperactive states such as tremor and non-epileptic seizures. There have been many recent studies trying to utilize neuroimaging in an attempt to understand the underlying functional neuroanatomical bases of conversion disorder (Carson et al., 2012). Motor conversion disorder has been the most frequently studied sub-type, however, there have been concerns that concurrent emotional and motivational responses generated during active motor tasks may complicate interpretation of results from such paradigms (Price and Friston, 2002).

Anesthesia has long been embedded at the core of conversion disorder and was described by Pierre Janet as "clear, easily appreciable and very characteristic… the typical symptom of hysteria" (Janet, 1901)". With regard to functional neuroimaging, passive somatosensory stimulation is readily testable in scanners (Graham and Staines, 2001) and the resultant task-relevant somatosensory neural activations are well understood (Staines et al., 2002). This makes anesthesia a favorable and feasible sub-type for investigating conversion disorder. Similar to the field as a whole, previous sensory conversion neuroimaging studies have yielded inconsistent results that may be attributed to small sample sizes and disparate methodologies. This author group previously utilized

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http://dx.doi.org/10.1016/j.nicl.2014.09.016

fMRI to study a sample of three sensory conversion patients (Ghaffar et al., 2006). We observed increased activity in multiple brain regions outside of the primary somatosensory cortex and described them as "ancillary" areas of activation. However, due to individual participant differences and a small sample size that precluded an appropriate group analysis; we were limited in our ability to draw conclusions for such activations. Other studies investigating a range of conversion symptoms have also observed ancillary activation but the specific areas reported, which broadly include the anterior cingulate cortex (ACC), insula, frontal cortex, parietal cortex, basal ganglia and thalamus, have varied considerably between studies (Browning et al., 2011). As a result, attempts to reconcile findings and formulate common unifying mechanisms have posed challenging.

The purpose of the present study is to utilize fMRI to conduct a within-subject group analysis on 10 subjects with sensory conversion disorder in an attempt to better define the functional neuroanatomical correlates of sensory conversion symptomatology with a particular focus on the role of ancillary areas of activation. It should be noted that the raw data from the three subjects previously studied (Ghaffar et al., 2006) has been included in our ten subject group analysis.

2. Methods

2.1. Participants

Ten subjects meeting Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for unilateral conversion disorder, sensory subtype participated in this study. All subjects were right-handed and female with a mean age of 41 years (range 25–58 years). Conversion sensory loss was localized to the left side for seven subjects and the right side for three subjects. Three subjects had co-morbid depression with one of the three also diagnosed with PTSD. The other seven subjects had no known psychiatric comorbidity. Absence of neurological disease was ascertained by neurologists using clinical examination and investigations including structural brain MRI, EMG/NCS, and evoked potentials. Experimental procedures were approved by the Sunnybrook Health Sciences Centre Ethics Committee. After complete description of the study to the subjects, written informed consent was obtained from all subjects.

2.2. Data acquisition

Each subject underwent functional and anatomical imaging on a research-dedicated MRI scanner operating at 3.0 T (GE HealthCare, Milwaukee, WI) using a standard birdcage head coil. High-resolution T1-weighted anatomical images were acquired using axial 3D volume imaging (fast spoiled gradient echo pulse sequence; echo time (TE)/flip angle (θ) = 5.4 ms/35°, 124 slices 1.4 mm thick, 256 × 192 matrix, field of view (FOV) 22 cm anterior to posterior, 16 cm left to right, 6 min). Subsequent fMRI acquisitions utilized heavily T2*-weighted fast gradient echo imaging with single-shot spiral in–out readout (θ/TE/TR = 70°/30/2000 ms, 26 slices, 5 mm thick, 64 × 64 matrix, FOV 20 cm, 5 min) to obtain blood oxygen level dependent (BOLD) contrast. Total scan time was approximately 40 min.

2.3. Somatosensory stimulation

For each of the participants, somatosensory stimuli were presented during the acquisition of fMRI data. Vibrotactile stimulation was applied in a block design (4 s stimulation/26 s no-stimulation/10 repeats) in separate 5 minute scans under the following conditions: 1) unilateral stimulation of the symptomatic limb and 2) unilateral stimulation of the asymptomatic limb. Stimulation was targeted to the body part that had the greatest sensory loss reported by the patient (upper limb/hand or lower limb/foot). For the asymptomatic side, the mirror region was stimulated. Specific stimulation sites differed across participants with 6 having stimulation sites in the upper limb/hand and 4 in the lower limb/foot.

Somatosensory stimuli consisted of discrete vibrations at a constant frequency of 25 Hz delivered by a customized MRI-compatible device (Graham and Staines, 2001). Vibrotactile stimulation was controlled by converting digitally generated waveforms to an analog signal (DAQCard 6024E, National Instruments, Austin, Texas) and then amplifying the signal (Bryston 2B-LP, Peterborough, Ontario) using a custom program written in LabVIEW (National Instruments, Austin, Texas). Varying the amplitude of the driving voltage to the vibrotactile device produced proportional changes in vibration amplitude in the MR environment (Graham and Staines, 2001). Output from the computer was routed through a penetration panel to the magnet room using a filtered 9-pin D sub-connector and shielded cable to ensure that no perceptible torque was produced by currents induced by radio-frequency transmit pulses or time-varying magnetic field gradients during imaging. The proper functioning of the vibrotactile stimulation device was manually verified by two researchers at the beginning and end of each experiment to ensure accurate stimulus delivery. During each verification procedure, a researcher positioned at the scanning bed, applied the device to himself, while a second operator activated it from the control room. Further details concerning the ability of this device to activate somatosensory processing have been described in previous research (Graham and Staines, 2001; Staines et al., 2002), and occasionally, some individuals have not shown S1 activation.

2.4. Data analysis

Raw data was reconstructed offline and a time series of 154 images per slice was generated for each functional scan. The resulting time courses were analyzed using BrainVoyager QX software (Brain Innovation, Maastricht, Netherlands). The first 4 volumes of each time series were excluded to prevent artifact from transient signal changes as the brain reached a steady magnetized state. Prior to co-registration, the functional data was pre-processed by linear trend removal, temporal high pass filtering to remove non-linear low frequency drift, and 3-dimensional motion correction using trilinear interpolation to detect and correct for small head movements during the scan by spatially realigning all subsequent volumes to the fifth volume. Estimated translation and rotation measures were visually inspected and never exceeded 1 mm and 1°, respectively. The functional data sets were transformed into Talairach space (Talairach and Tournoux, 1988) by coregistering the functional data with the anatomical data for each subject. The resulting volume time courses were filtered using a 6 mm Gaussian kernel at full-width half-maximum.

In order to statistically evaluate the relative differences across the two main experimental conditions, stimulation to the symptomatic limb and stimulation to the asymptomatic limb, a multiple regression approach was employed using two predictors: 1) stimulation of the symptomatic side and 2) stimulation of the asymptomatic side, with the 26 s of no stimulation serving as a baseline. Two stimulation protocols using dummy-predictors (for those predictors not included in a given scan) were adopted and convolved with a boxcar hemodynamic response function (Boynton et al., 1996) to account for the expected shape and temporal delays of the physiological response. The resulting reference functions served as the model for the response time course functions used in the general linear model. A random effects analysis was used to investigate regions that were sensitive to the experimental manipulations. Contrast maps were created using a voxel-based approach to show relative changes for stimulation of the symptomatic versus the asymptomatic side. Activated voxels were considered significant if the threshold exceeded $p < 0.001$ uncorrected and formed a cluster of 14 contiguous voxels, based on a cluster size threshold estimator simulation BrainVoyager QX software (Brain Innovation, Mastricht, The Netherlands), corresponding to a corrected threshold of $p < 0.05$ (Forman et al., 1995). The center of gravity and t-statistics were extracted for each significant cluster. Event-related averaging was applied to each cluster to determine the BOLD response characteristics for each