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Impaired emotion processing in functional (psychogenic) tremor: A functional magnetic resonance imaging study

Alberto J. Espay[a,*], Thomas Maloney[b], Jennifer Vannest[b], Matthew M. Norris[c], James C. Eliassen[c], Erin Neefus[a], Jane B. Allendorfer[d], Anthony E. Lang[e], Jerzy P. Szaflarski[d]

[a] Gardner Family Center for Parkinson's Disease and Movement Disorders, Cincinnati, OH, USA
[b] Pediatric Neuroimaging Research Consortium, Cincinnati Children's Hospital, Cincinnati, OH, USA
[c] University of Cincinnati Center for Imaging Research (CIR), Cincinnati, OH, USA
[d] Department of Neurology, University of Alabama at Birmingham, Birmingham, AL, USA
[e] The Morton and Gloria Shulman Movement Disorders Clinic and the Edmond J. Safra Program in Parkinson's Disease, University Health Network, University of Toronto, Toronto, Canada.

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ABSTRACT

Background: Despite its high prevalence and associated disability, the neural correlates of emotion processing in patients with functional (psychogenic) tremor (FT), the most common functional movement disorder, remain poorly understood.

Methods: In this cross sectional functional magnetic resonance imaging (fMRI) study at 4T, 27 subjects with FT, 16 with essential tremor (ET), and 25 healthy controls (HCs) underwent a finger-tapping motor task, a basic-emotion task, and an intense-emotion task to probe motor and emotion circuitries. Anatomical and functional MRI data were processed with FSL (FMRIB Software Library) and AFNI (Analysis of Functional Neuroimages), followed by seed-to-seed connectivity analyses using anatomical regions defined from the Harvard-Oxford subcortical atlas; all analyses were corrected for multiple comparisons.

Results: After controlling for depression scores and correcting for multiple comparisons, the FT group showed increased activation in the right cerebellum compared to ET during the motor task; and increased activation in the paracingulate gyrus and left Heschl's gyrus compared with HC with decreased activation in the right precentral gyrus compared with ET during the basic-emotion task. No significant differences were found after adjusting for multiple comparisons during the intense-emotion task but increase in connectivity between the left amygdala and left middle frontal gyrus survived corrections in the FT subjects during this task, compared to HC.

Conclusions: In response to emotional stimuli, functional tremor is associated with alterations in activation and functional connectivity in networks involved in emotion processing and theory of mind. These findings may be relevant to the pathophysiology of functional movement disorders.

1. Introduction

Functional (psychogenic) tremor (FT), the most common functional movement disorder, is diagnosed by confirming entrainment or full suppressibility of the oscillatory activity, distractibility, co-activation or co-contraction sign, pause of tremor during contralateral ballistic movements, and variability in tremor frequency, axis, and/or topographical distribution (Espay and Lang, 2015). Despite its frequency and the magnitude of disability it imparts, the pathophysiological underpinnings of FT remain poorly understood and no effective treatments have been established.

Neuroimaging studies have suggested that the basal ganglia and limbic systems are integral parts of the neural pathways for processing emotions (Nowak and Fink, 2009). Recent functional neuroimaging studies of patients with functional movement disorders have demonstrated alterations in regional cerebral blood flow during simple motor tasks (Schrag et al., 2013) or in brain activation of the cerebellar vermis, posterior cingulate cortex, and hippocampus on isometric precision-grip contraction tasks (Blakemore et al., 2016) as well as in brain activation of the right amygdala on simple emotional stimuli (n = 10)

Abbreviations: AFNI, Analysis of Functional Neuroimages; CPT-END, continuous performance task with emotional and neutral distracters; FSL, FMRIB Software Library; FT, functional tremor; fMRI, functional magnetic resonance imaging; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; EPI, echo-planar imaging; MDEFT, modified equilibrium Fourier transform; MINI, Mini International Neuropsychiatric Interview

* Corresponding author at: University of Cincinnati, 260 Stetson St., Suite 2300, Cincinnati, OH 45267-0525, USA.
E-mail address: alberto.espay@uc.edu (A.J. Espay).

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(Voon et al., 2010) or both amygdala on stimulation on fearful emotional stimuli (n = 12) (Aybek et al., 2015). We hypothesized that patients with FT have an impairment and/or disconnection of cortical and subcortical areas involved in motor and emotion control that may be distinguished from those of essential tremor (ET) and healthy controls (HCs). This hypothesis is also complemented by preliminary findings of differences in emotion processing in other neurological disorders (Allendorfer and Szaflarski, 2014; Szaflarski et al., 2014). ET is the most common tremor disorder, diagnosed in the presence of postural and action hand tremor, often in the context of a positive family history. While it follows none of the diagnostic criteria for FT, ET is considered to represent cerebellar dysfunction although with poorly defined neurobiological boundaries (Espay et al., 2017). We chose basic and intense emotion processing fMRI tasks in order to access the emotional state of the observed individual and as a measure of social intelligence, a concept separate from general (or cognitive) intelligence (Bar-On et al., 2003; Bonora et al., 2011). Further, the brain regions responsible for facial emotion recognition and processing, which includes visual (spatial cognition) and executive (attentional control) networks may be involved directly or indirectly in the generation or maintenance of FT (Calarge et al., 2003).

2. Methods

2.1. Subjects

Twenty-seven consecutive consenting patients with FT met established clinical criteria (Espay and Lang, 2015; Fahn and Williams, 1988; Gupta and Lang, 2009). Tremor needed to be absent or minimal at rest in order to avoid interference with the scanning procedure. Patients were excluded if they had any comorbid neurological disorder or severe depression or anxiety as measured by a Hamilton Depression Rating Scale (HAM-D) > 24 and a Hamilton Anxiety Rating Scale (HAM-A) > 25. Subjects were also excluded if they were on benzodiazepines for any reason. We also prospectively recruited 16 consecutive patients with ET as active controls (given the common misdiagnosis of FT with ET and vice versa), and 25 HCs with no history of neurological or general medical conditions. This study was approved by the local IRB and all subjects provided informed consent.

To reach the subject goal of 27 FT patients completing all assessments and rendering high-quality dataset for analyses, we screened a total of 35 FT subjects. Eight screened subjects, 6 with FT and 3 with ET were not recruited due to the following reasons (one each for FT, unless otherwise specified): malingering (rather than conversion), not meeting criteria for FT, patient unwilling to provide consent, unacceptance of diagnosis, prior neurosurgical procedure (unable to undergo fMRI), excessive tremor during scanning, obesity beyond scanner's capacity (1 ET), and inability to get comfortable in scanner (2 ET, 2 FT). Data from 10 subjects was excluded from final analysis due to non-completion of the task or for data quality issues: basic-emotion processing task: 1 HC; intense-emotion processing task: 1 FT, 1 HC; VBM analysis: 4 HCs, 1 ET; volumetric analysis: 2 HCs.

2.2. Clinical measurements

All subjects underwent a 15-minute structured diagnostic interview (Mini International Neuropsychiatric Interview; MINI) (Pinninti et al., 2003) developed to screen for axis I DSM-IV and ICD-10 psychiatric disorders (Sheehan et al., 1998). In addition, we administered the 17-item HAM-D (Williams, 1988) to assess depressed mood and vegetative and cognitive symptoms of depression; and the 14-item HAM-A (Maier et al., 1988), to evaluate for psychic and somatic anxiety. These scales were administered as part of a structured interview (Williams et al., 2008).

2.3. Functional MRI procedure

Anatomical and functional brain images were obtained using a 4T MRI/MRS system (Varian Inc.). The behavioral experiment was programmed in E-Prime, version 1 (www.pstnet.com). All participants wore MR-compatible VGA goggles and headphones (Resonance Technologies, Inc.). For each imaging session, once the participant was positioned in the scanner, a three-plane scout scan was performed to confirm isocenter positioning prior to each of the functional tasks. An echo-planar imaging (EPI) was performed while subjects carried out the behavioral paradigms using a T2*-weighted gradient-echo EPI pulse sequence: TR/TE 3000/29 ms, FOV 256 × 256 mm, matrix 64 × 64, slice thickness 4 mm, flip angle 75°. A multi-echo reference scan was performed to correct for geometric distortion and Nyquist ghost artifacts. After completion of all functional MRI (fMRI) tasks a T1-weighted three-dimensional anatomical high-resolution scan using modified equilibrium Fourier transform (MDEFT) sequence (TR/TE 13/6 ms, T(MD) 1.1 s, FOV 192 × 256 × 256 mm, matrix 192 × 256 × 265, slice thickness 1 mm, flip angle 20°) was acquired (Lee et al., 1995). The MRI system triggered the behavioral paradigms to ensure precise timing of the task with respect to image acquisition.

2.4. Imaging paradigms

Three paradigms were used during the functional scans to examine differences in motor and emotional processing between the three groups. The paradigms, a finger-tapping motor task, a basic-emotion task, and an intense-emotion task were presented to each participant in the same order.

Finger-tapping motor task was designed to assess and monitor the motor system while in the scanner. This paced task consisted of a 30-second block of right-only finger tapping, followed by a 30-second block of left-only tapping, followed by a 30-second block of rest, all repeated 4 times. Subjects were instructed to adhere to the provided rate with the visual prompt presented every second. The task required subjects to move a lever using their right or left index finger, according to whether the "R" or "L" was flashing. The total task duration was 6 min. Task adherence was monitored visually. The task was modeled such that the blocks of rest were treated as "baseline" in the analyses.

The "*basic-emotion*" *face recognition task* was designed to assess response to basic emotional stimuli. Over the span of 14 min, subjects were presented with 120 different faces, corresponding to unique (non-repeating) facial identities each depicting a particular emotion (sadness, happiness, or fear) or a neutral expression (Szaflarski et al., 2014). Processing of emotional expressions is thought to occur subliminally and automatically but is dependent on attention (Pessoa et al., 2002b; Rees et al., 1997). To monitor attention to the task, subjects were instructed to decide the gender of each face by pressing one of two buttons with the right thumb. Subjects were exposed to 30 prototypically happy, 30 sad, 30 fearful and 30 neutral expressions presented in random order selected from the NimStim set of facial expressions (Tottenham et al., 2009). Each stimulus was presented for 2 s with variable inter-stimulus interval of 3.9 ± 2.4 s; during the delay subjects viewed a fixation cross. Subjects were asked to press button "1" for males and button "2" for females while viewing each image. It is well recognized that activation by faces in some brain areas is strongly affected by attentional condition while in other brain areas it is not (e.g., amygdala response to fearful stimuli) (Bentley et al., 2003; Pessoa et al., 2002a). The event-related design with variable inter-stimulus delay was used to reduce habituation of the activation in regions such as the amygdala, since habituation may occur in block designs with highly repetitive and predictable stimulus presentation (Breiter et al., 1996).

The "*intense-emotion*" *task* (continuous performance task with emotional and neutral distracters; CPT-END) consisted of a series of offensive or disgusting images probing intense emotional circuitry (Yamasaki et al., 2002). This task utilized a visual oddball paradigm