Parkinsonism and Related Disorders xxx (2016) 1–5

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Emotion modulation of the startle reflex in essential tremor: Blunted reactivity to unpleasant and pleasant pictures

Jacob A. Lafo [a], Ania Mikos [a, c], Paul C. Mangal [a], Bonnie M. Scott [a], Erin Trifilio [a], Michael S. Okun [b], Dawn Bowers [a, b, *]

[a] Department of Clinical and Health Psychology, College of Public Health & Health Professions, University of Florida, PO Box 100165, Gainesville, FL 32610-0165, USA
[b] Department of Neurology, University of Florida College of Medicine, University of Florida, HSC Box 100236, Gainesville, FL 32610-0236, USA
[c] Institute for Regenerative Medicine, University of Zurich, Center for Prevention and Dementia Therapy, Wagistrasse 14, 8952 Schileren, Switzerland

ARTICLE INFO

Article history:
Received 11 October 2016
Received in revised form
9 November 2016
Accepted 11 November 2016

Keywords:
Essential tremor
Startle
Emotion
Cerebellum
Amygdala

ABSTRACT

Background: Essential tremor is a highly prevalent movement disorder characterized by kinetic tremor and mild cognitive-executive changes. These features are commonly attributed to abnormal cerebellar changes, resulting in disruption of cerebellar-thalamo-cortical networks. Less attention has been paid to alterations in basic emotion processing in essential tremor, despite known cerebellar-limbic interconnectivity.
Objectives: In the current study, we tested the hypothesis that a psychophysiologic index of emotional reactivity, the emotion modulated startle reflex, would be muted in individuals with essential tremor relative to controls.
Methods: Participants included 19 essential tremor patients and 18 controls, who viewed standard sets of unpleasant, pleasant, and neutral pictures for six seconds each. During picture viewing, white noise bursts were binaurally presented to elicit startle eyeblinks measured over the orbicularis oculi.
Results: Consistent with past literature, controls' startle eyeblink responses were modulated according to picture valence (unpleasant > neutral > pleasant). In essential tremor participants, startle eyeblinks were not modulated by emotion. This modulation failure was not due to medication effects, nor was it due to abnormal appraisal of emotional picture content.
Conclusions: Neuroanatomically, it remains unclear whether diminished startle modulation in essential tremor is secondary to aberrant cerebellar input to the amygdala, which is involved in priming the startle response in emotional contexts, or due to more direct disruption between the cerebellum and brainstem startle circuitry. If the former is correct, these findings may be the first to reveal dysregulation of emotional networks in essential tremor.

1. Introduction

Essential tremor (ET) is a highly prevalent, slowly progressive movement disorder characterized by kinetic tremor of the arms, and in some cases the neck, head, and occasionally other body regions. Disease pathogenesis remains poorly understood, though neuroimaging and post-mortem findings most consistently implicate abnormal changes within the cerebellum and cerebello-thalamo-cortical outflow pathways [1]. Structural abnormalities in Purkinje cells and surrounding areas, in the context of insidious disease onset, are now thought to reflect a neurodegenerative process; however, specific pathological changes have only recently been characterized [2].

Over the past two decades, the long-held view of ET as a "benign," pure motor disorder has been challenged by mounting evidence detailing cognitive and mood disturbances. Indeed, ET is associated with a fronto-executive cognitive phenotype similar to that observed in Parkinson's disease (PD) [3]. Mood symptoms

* Corresponding author. Department of Clinical and Health Psychology, College of Public Health & Health Professions, University of Florida, PO Box 100165, Gainesville, FL 32610-0165, USA.
E-mail addresses: jlafo@phhp.ufl.edu (J.A. Lafo), mikos.ania@gmail.com (A. Mikos), pmangal@phhp.ufl.edu (P.C. Mangal), bonnie.m.scott@phhp.ufl.edu (B.M. Scott), etrif07@phhp.ufl.edu (E. Trifilio), okun@neurology.ufl.edu (M.S. Okun), dawnbowers@phhp.ufl.edu (D. Bowers).

http://dx.doi.org/10.1016/j.parkreldis.2016.11.003
1353-8020/

accompanying ET, such as depression, anxiety, and apathy have also been documented, but it is unclear whether these symptoms are biologically based or secondary adjustment difficulties related to functional limitations of the disease [4–6].

Despite evidence suggesting that cerebellar outflow influences activity in a range of limbic and para-limbic regions, including the amygdala and hypothalamus [7], few, if any, studies have examined basic emotion-related circuity in ET. As such, the goal of the present study was to learn whether individuals with ET would exhibit normal reactivity of a well-known marker of amygdalar function involving heightened startle eyeblink responses to aversive stimuli. Extensive research over the past 25 years has shown that startle eyeblink responses are enhanced during aversive contexts (e.g., viewing horror scenes) and minimized during pleasant contexts (e.g., viewing erotica) [8]. Why does this occur? In brief, the startle response evolved as a protective reflex to potentially harmful stimuli (e.g., a loud, abrupt noise), and includes raising of the shoulders and brief eye-lid closure, the startle eyeblink. While basic startle reflex circuity is mediated entirely at the level of the brainstem (i.e., the nucleus reticularis pontis caudalis; nRPC), this circuitry can be primed via direct projections from the central nucleus of the amygdala [9]. One effect of amygdalar lesions, both in humans and animals, is reduction or abolition of the fear-potentiated startle response [10]. Such lesions do not eliminate the basic startle response itself, but do abolish "priming" of the response in emotional contexts.

Turning to ET, it is possible that altered cerebellar input to the amygdala resulting from cerebellar pathology may detract from the amygdala's normal response to novelty/threat, and/or influence amygdala outflow to brainstem startle circuitry. In turn, this may lead to abnormal priming of the startle eyeblink response. This hypothesis is based on evidence from a series of early animal studies revealing connections between the cerebellum and amygdala [11]. Namely, electrical stimulation of the cerebellum evoked responses in the basolateral nuclei of the amygdala [12]. Correspondingly, lesions of the cerebellar fastigial nuclei resulted in focal, bilateral synaptic fiber degeneration within the same amygdalar nuclei. Taken together, these findings suggest that the amygdala may be in some way responsive to cerebellar outflow.

To address the hypothesis that emotion priming of the startle eyeblink reflex is abnormal in ET, we modelled an experimental task on one previously used by Bowers et al. [13] in individuals with PD. Given the amygdala's role in fear potentiated priming, we predicted that participants with ET would show reduced priming of startle eyeblink responses while viewing unpleasant vs. neutral pictures.

2. Methods

2.1. Participants

Participants included 19 individuals with ET and 18 healthy controls. Sample characteristics for the two groups are presented in Table 1. Essential tremor participants were drawn consecutively from a convenience sample of patients undergoing candidacy evaluations for Deep Brain Stimulation (DBS) surgery at the University of Florida Center for Movement Disorders and Neurorestoration. Controls were recruited from the local community. Informed consent to participate in this research was obtained following University of Florida Institutional Review Board guidelines. Essential tremor was diagnosed by fellowship-trained movement disorder neurologists according to Louis criteria [14]. The groups did not significantly differ with respect to age, education, gender distribution, depression scores, or cognitive screening status.

Table 1
Sample characteristics[a].

	Essential Tremor = 19		Control = 18		
	M (*SD*)	Range	*M* (*SD*)	Range	*p*-value
Demographics					
Age (years)	68.1 (11.4)	47–84	64.7 (5.9)	56–75	0.28
Gender (m/f)	11/8	–	12/6	–	0.42
Education (years)	13.9 (3.2)	8–20	13.4 (0.9)	12–15	0.57
Mood					
BDI-II	6.1 (3.3)	1–12	4.9 (3.7)	0–12	0.31
General Cognitive					
MMSE	28.6 (1.1)	27–30	28.2 (1.3)	26–30	0.24
Clinical Characteristics					
Disease duration (years)	23.3 (14.2)	4–60	–	–	–
TRS Total Score	52.7 (14.9)	21–80	–	–	–
Motor TRS	36.0 (10.0)	16–55	–	–	–
ADL TRS	16.6 (6.0)	5–25	–	–	–
Medications (tremor, mood)					
Primidone	$n = 5$	$n = 0$			
SSRI	$n = 5$	$n = 2$			
SNRI	$n = 0$	$n = 2$			
Benzodiazepine	$n = 2$	$n = 1$			
Total *n* taking meds*	$n = 10$*	$n = 5$			

Note: ADL = activities of daily living; BDI-II = Beck Depression Inventory-II; MMSE = Mini-Mental State Examination; SSRI = Selective Serotonin Reuptake Inhibitor; SNRI = Serotonin and Norepinephrine Reuptake Inhibitor; TRS = Tremor Rating Scale.

[a] There were no-significant differences between groups on any variable using independent *t*-test comparisons or χ^2 tests (gender distribution).* Of ten unique essential tremor participants taking tremor and/or mood medications, one was taking primidone plus escitalopram; one was taking paroxetine plus alprazolam.

2.2. Stimuli and design

Thirty-six pictures (12 unpleasant, 12 pleasant, 12 neutral) were selected from the International Affective Picture System (IAPS; see Appendix) [15] based on normative 1–9 ratings of valence (unpleasant/pleasant) and arousal (low/high). The unpleasant ($M = 6.5$, $SD = 0.65$) and pleasant ($M = 6.1$, $SD = 0.69$) picture sets were equivalent in arousal ratings ($p > 0.10$), though both were significantly more arousing than the neutral picture set ($M = 3.0$, $SD = 0.54$; $p < 0.05$, both cases). Contentwise, unpleasant pictures depicted scenes of mutilation, physical violence, vicious animals, etc., while pleasant pictures included erotic scenes, babies, food, and sports activities. Neutral pictures depicted furniture, plants, buildings, office scenes, etc.

Testing was conducted within an electrically shielded and sound attenuated room in the Cognitive Neuroscience Laboratory of the McKnight Brain Institute. Each trial began with presentation of a picture, shown for 6 s, on a 20-inch monitor. Participants sat in a reclining chair directly in front of the monitor. To elicit startle eyeblink responses, a single 50 ms burst of white noise (95 dB, instantaneous rise time) was binaurally presented through Telephonics headphones while participants viewed pictures. Startle probes were randomly presented at three intervals after picture onset (4200, 5000, or 5800 ms) and equivalently distributed across each valence category (unpleasant, pleasant, and neutral). Following picture offset, the participants rated each picture's content according to valence and arousal using two independent 1–9 ordinal scales. Prior to beginning the picture viewing task, baseline measures of unprimed startle eyeblink amplitude were obtained by presenting 12 white noise bursts and measuring blink amplitude. The white noise bursts were randomly delivered at inter-stimulus intervals ranging from 10 to 18 s. Custom software was used to synchronize stimulus presentation, variable inter-trial intervals, and acquisition of physiologic data.

Please cite this article in press as: J.A. Lafo, et al., Emotion modulation of the startle reflex in essential tremor: Blunted reactivity to unpleasant and pleasant pictures, Parkinsonism and Related Disorders (2016), http://dx.doi.org/10.1016/j.parkreldis.2016.11.003