HHS Public Access

Author manuscript

Parkinsonism Relat Disord. Author manuscript; available in PMC 2021 March 12.

Published in final edited form as:

Parkinsonism Relat Disord. 2017 January ; 34: 54–58. doi:10.1016/j.parkreldis.2016.11.003.

Emotion Modulation of the Startle Reflex in Essential Tremor: Blunted reactivity to unpleasant and pleasant pictures

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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.

Keywords

essential tremor; startle; emotion; cerebellum; amygdala

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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 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 [4,5,6]

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.

Methods

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.

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 sec, 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 seconds. Custom software was used to synchronize stimulus presentation, variable inter-trial intervals, and acquisition of physiologic data.

Physiologic Recordings

Eyeblinks were measured by recording EMG activity from the inferior arc of the left and right orbicularis oculi muscles using Ag-AgCl electrodes. Raw EMG signals were amplified (30,000 gain) and frequencies <90 and >1000 Hz were filtered using Colbourn bioamplifiers. A Colbourn Contour following Integrator with a time constant of 200 ms was used to rectify and integrate the raw signal, which was directed to a Scientific Solutions A/D board of a personal computer. Digital sampling at 1000 Hz began 50 ms before onset of the auditory startle stimulus and continued for 250 ms after stimulus offset.

Data Reduction and Statistical Analysis

Startle eyeblink data were reduced using custom software designed to eliminate trials with unstable baselines. Each trial was scored for amplitude (peak-baseline in mV) across the 21–130 ms interval following white noise onset. Trials failing to reach peak amplitude during this interval (i.e., no eyeblink response) were rejected. Each trial was also scored for latency in ms between the onset of the white noise burst and the time of the peak amplitude. Because preliminary analyses demonstrated no significant differences between right and left eye responses, a composite startle eyeblink score was computed ([right blink+left blink]/2) and used in subsequent analyses. Data were analyzed using independent sample t-tests and repeated measures ANOVAs.

Results

Baseline startle eyeblink responses

Unprimed startle eyeblink responses during baseline trials were examined for average amplitude and latency in separate independent samples t-tests. Results revealed no significant differences in startle amplitude between the two groups (ET = 108.89 A/D units, SD = 75.45; Control = 124.32 A/D units, SD = 73.69; $t(35) = .63$, $p = 0.51$). Similarly, startle eyeblink latency was similar across both groups (ET = 75.5 ms, SD = 6.9, Control = 74.8 ms, SD = 8.9; $t(35) = .26$, $p = 0.80$).

Emotion-modulated startle eyeblink responses

Startle eyeblink responses elicited during the picture viewing task were converted to T-scores (M = 50, SD = 10) following the procedures of Bradley, Cuthbert, and Lang [16] in order to reduce between-subject variability in the absolute size of the eyeblink response. Average startle responses (T-score metric) were computed for the unpleasant, pleasant, and neutral pictures, and used as dependent variables in subsequent analyses.

To determine whether ET patients had diminished startle reactivity during emotional pictures, we conducted a Group (ET, control) X Valence (unpleasant, pleasant, neutral) repeated measures ANOVA. Results revealed a significant main effect for valence ($F_{2,70}$ =

10.62, $p < 0.01$, $\eta_p^2 = 0.233$), which indicated a significant linear relationship (unpleasant > neutral > pleasant). Bonferroni-corrected post-hoc comparisons showed that startle eyeblink amplitude was significantly greater during unpleasant ($M = 51.4$, $SD = 2.4$; $p < 0.05$) than neutral pictures ($M = 49.9$, $SD = 2.9$; $p < 0.05$); in turn, startle eyeblink amplitude was greater during neutral than pleasant pictures ($M = 48.2$, $SD = 2.6$; $p < 0.05$).

The Group X Valence interaction was also significant ($F_{2,70} = 3.90$, $p < 0.03$, $\eta_p^2 = 0.10$) and is depicted in Figure 1. Decomposing this interaction revealed that while the control group had a significant linear trend for valence (i.e., unpleasant > neutral > pleasant; $F_{1,17} = 57.70$, $p < 0.0001$, $\eta_p^2 = 0.77$), the ET group did not ($F_{1,18} = 2.22$, $p > 0.10$, $\eta_p^2 = 0.11$). Post-hoc comparisons revealed no differences in eyeblink amplitude across the unpleasant, pleasant, and neutral pictures for the ET group. Relative to controls, startle eyeblink responses of the ET participants were significantly smaller in amplitude during unpleasant picture viewing ($t(35) = 2.6$, $p < 0.02$; *M*s: ET = 50.5, controls = 52.4). Conversely, eyeblink responses of the ET participants, relative to controls, were significantly larger during pleasant pictures ($t(35) = 2.5$, $p < 0.02$; *M*s: ET = 49.2, controls = 47.2). There were no group differences in startle amplitude during neutral pictures (t(35) = 0.216, $p = 0.83$; *M*s: ET = 50.0, controls = 49.8).

Ratings of IAPS Pictures

We examined participants' subjective valence and arousal ratings of the pictures in separate Group (2) X Valence (3) repeated measures ANOVAs. Results indicated a significant main effect of Valence ($F_{1.7, 57.9} = 262.40$, $p < 0.001$, $\eta_p^2 = 0.86$), such that participants rated unpleasant pictures as significantly more negative than neutral pictures ($p < 0.05$) and pleasant pictures as significantly more positive than neutral pictures ($p < 0.05$). This pattern was present to the same extent in both groups (i.e., no significant interaction). Similarly, the main effect of Arousal was significant ($F_{1.6, 53.4} = 80.0$, $p < 0.001$, $\eta_p^2 = 0.68$), with participants rating unpleasant and pleasant pictures as significantly more arousing than neutral pictures ($p < 0.05$, both cases). Again, this same pattern was present in both groups (i.e., nonsignificant interaction).

Influence of depression, medications, tremor severity, and symptom duration

To determine whether group difference in emotion modulation of startle were related to self-reported depressive symptoms, we examined within-group bivariate correlations (Pearson) between Beck Depression Inventory - II (BDI-II) scores and startle reactivity. We calculated a difference score between startle amplitudes during unpleasant and pleasant picture conditions to serve as an index of startle reactivity. Correlations between BDI-II scores and startle reactivity were not significant for either group (ET: $r = -0.26$, $p = 0.31$; controls: $r = 0.41$, $p = 0.07$). We also examined the possibility that medication usage may have contributed to dampened modulation of startle responses in the ET participants. To do so, we compared ET participants who were taking antidepressants, anxiolytics, and/or primidone ($n = 10$) to those who were not taking medications ($n = 9$) with an additional Group (2) X Valence (3) repeated measures ANOVA. The main effect of Valence was not significant ($F_{(2,34)} = 0.61$, $p = 0.55$, $\eta_p^2 = .03$), nor was the Group X Valence interaction effect,

indicating that the pattern of diminished modulation was similar in both medication users and non-users.

Lastly, we conducted correlations to examine the relationship between startle reactivity, symptom severity (Fahn-Tolosa-Martin Tremor Rating Scale – Motor Scale), and symptom duration (years with symptoms) in the ET group. Startle reactivity was not significantly correlated with either symptom severity ($r = 0.24$, $p = 0.33$) or symptom duration ($r = -0.01$, $p = 0.96$).

Discussion

Our primary finding was that ET patients responded abnormally in terms of startle reactivity to emotional pictures. They did not show the typical “priming” or enhancement of startle responses when viewing unpleasant pictures; nor did they show the expected “inhibition” of startle responses when viewing pleasant pictures. This outcome contrasted with that of the control group, who showed the typical pattern described in the literature [17]; namely, heightened startle eyeblink responses according to picture valence (i.e., unpleasant > neutral > pleasant). This linear pattern corresponds to the role of the amygdala in priming defensive networks in response to threat [18]. Of note, our findings with ET participants differ from those previously described in individuals with PD who underwent identical procedures [13,19]. In these studies, PD participants only showed blunted startle responses to unpleasant, aversive pictures. Thus, the global blunting of startle responses in our sample of ET participants indicates that both priming and inhibition of the defensive system may be affected in this sample.

In light of these findings, it is peculiar that patients with ET do not clinically present with signature emotional flattening and apathy that is often characteristic of individuals with PD. Prior studies have reported increased apathy symptoms in ET relative to healthy controls, as assessed by self-report questionnaires [4,5]. It is unclear whether heightened responses on these questionnaires reflected amotivation per se versus the effects of social withdrawal secondary to embarrassment and/or functional disability. Indeed, embarrassment is commonly reported among individuals with ET and contributes to lower quality of life [20,21].The question arises, then, as to the basis or bases for the aberrant startle modulation observed in ET participants. There are several possibilities.

First, blunted reactivity could be due to aberration in the mechanics of the startle eyeblink response itself. This explanation seems unlikely given our findings that the amplitude and latency of unprimed startle eyeblink responses were similar across groups. A second possibility pertains to the influence of medications on startle modulation, as there is some evidence that antidepressants and benzodiazepines dampen startle reactivity. Findings from studies addressing medication effects have been largely inconsistent, with some observing that psychotropic medications reduce emotion modulation, others finding that they diminish overall startle amplitude, but not emotion modulation, and still others failing to demonstrate these effects altogether [22]. Our results indicate that both medication users and non-users exhibited a similar pattern of diminished startle modulation.

A third possibility is that the ET group failed to appreciate the emotional significance of the pictures they viewed and in turn did not develop an appropriate emotional set. However, our finding that the groups subjectively rated the pictures similarly in terms of arousal and valence argues against this explanation. Another possibility pertains to mood. Indeed, atypical modulation of the startle reflex has also been associated with various mood disorders, particularly depression, though there has been great variability across studies [23]. In our sample, mean scores on a depression scale (BDI-II) were well below the clinical cut-off for mild depression (i.e., below 6.2 in both groups), did not differ between groups, and were not correlated with startle reactivity.

Finally, it is worth considering that diminished responsivity may relate to the influence of cerebellar changes over basic brain stem circuitry involved in the generation of the startle reflex. Tracing studies in animals have shown that the nRPC, a critical mediator in the startle cascade, receives projections from the deep cerebellar nuclei [24,25]. Theoretically, abnormal cerebellar outflow to the nRPC in ET could interfere with the normal startle cascade; however, while lesions of the nRPC are known to markedly attenuate or completely abolish the startle reflex, cerebellar lesions do not abolish the reflex, but instead interfere with associative learning of aversive reactions and startle habituation [26]. Importantly, our study did not employ fear conditioning, but used picture stimuli designed to elicit pre-learned emotional associations. Also noteworthy is our finding that baseline startle magnitudes and latencies (i.e., those elicited without concurrent emotional picture presentation) were not different between the essential tremor and control groups. This suggests that basic startle responses in the essential tremor group were intact and only emotion modulation was affected.

Mechanistically, it is conceivable that ET pathology influences downstream systems involved in the modulation of the startle response. In this view, cerebellar changes alter networks connecting the deep cerebellar nuclei with amygdalar regions responsible for priming the startle response in emotional contexts. Several lines of evidence support this possibility. Early animal studies characterize a putative circuit between the fastigial nuclei of the cerebellum and the basolateral nucleus of the amygdala, which serves as a critical relay between basic startle circuity and the brain’s fear/defensive system [27]. By some means, cerebellar pathology in ET may interfere with the ability of the basolateral nucleus to transcode information corresponding to attention, arousal, and emotional valence. Interestingly, several studies have shown that ET is associated with abnormal cellular changes and volumetric reductions in the vermis, a midline region that has been implicated in a range of emotional functions in humans and animals [28,29]. Given that the vermis houses the fastigial nuclei, it may represent a regional focal point through which ET pathology influences downstream modulatory circuitry.

Our findings should be considered in the context of limitations to generalizability. Notably, the ET group was limited to a small sample comprised entirely of candidates for DBS surgery with relatively advanced motor symptoms. It is therefore unclear whether our findings would extend to individuals in earlier stages of disease progression. In theory, more severe motor symptoms in our sample should reflect more advanced underlying cerebellar pathology. Thus, at least according to our overarching hypothesis, increased pathology

would be expected to result in greater disruption of normal amygdala function and startle modulation. Although we were unable to quantify cerebellar changes in this study, we did examine the relationship between startle reactivity, disease duration, and symptom severity, but did not observe significant associations. This is in contrast to previous observations in Parkinson's disease, which showed that startle hyporeactivity was associated with more advanced disease progression [13]. These differences may in part relate to more variable age of onset and gradual symptom progression in essential tremor relative to Parkinson's disease. Indeed, the clinical course of essential tremor is known to vary considerably across individuals [30,31]. Alternatively, our sample size may not have been large enough to detect linear relationships among startle and disease variables. Future studies examining emotion-modulated startle in ET should include larger subgroups of participants at varying stages of the disease to increase generalizability and statistical power.

In summary, the current study of blunted startle reactivity to emotional pictures adds to the growing literature on non-motor changes in individuals with ET. We propose that ET, particularly as it advances, may be associated with changes in emotional circuitry or access to circuitry that is involved in processing and/or reacting to emotionally-salient information. Though the manner via which this occurs is unclear vis a vis precise cerebellar mechanisms, the role of the cerebellum in a variety of non-motor and affective functions is well established [32]. Emotional deficits in ET may well parallel those observed in the cognitive domain in that they are relatively mild and more likely to occur in the later stages of the disease. Nevertheless, they have the potential to reveal new insights related to disease pathogenesis and progression.

Acknowledgements:

Funding: This work was partially supported by the University of Florida Center for Movement Disorders and Neurorestoration, Gainesville, Florida. Mr. Lafo was supported by a NINDS predoctoral training grant (T32 NS82168).

Funding: This work was funded by the National Institutes of Health (R03-MH109336, UH3-NS095553, T32-NS82168 [Lafo, Scott]) and the University of Florida Center for Movement Disorders and Neurorestoration, Gainesville, FL.

Appendix:

Unpleasant IAPS: 1090, 1300, 2120, 3000, 3010, 3100, 3130, 3530, 6230, 6370, 9040, 9050

Pleasant IAPS: 2080, 2650, 4220, 4660, 4680, 5470, 7330, 8030, 8080, 8200, 8370, 8510

Neutral IAPS: 2190, 2200, 5500, 7000, 7010, 7030, 7090, 7130, 7170, 7500, 7550, 7700

References:

[1]. Louis ED, Understanding essential tremor: progress on the biological front, Curr. Neurol. Neurosci. Rep14 (2014) 450. doi:10.1007/s11910-014-0450-z. [PubMed: 24740806]

[2]. Louis ED, From neurons to neuron neighborhoods: the rewiring of the cerebellar cortex in essential tremor, Cerebellum. 13 (2014) 501–512. doi:10.1007/s12311-013-0545-0. [PubMed: 24435423]

[3]. Lafo JA, Jones JD, Okun MS, Bauer RM, Price CC, Bowers D, Memory Similarities Between Essential Tremor and Parkinson's Disease: A Final Common Pathway?, Clin. Neuropsychol 29 (2015) 985–1001. doi:10.1080/13854046.2015.1118553. [PubMed: 26689342]

[4]. Louis ED, Huey ED, Gerbin M, Viner AS, Apathy in essential tremor, dystonia, and Parkinson's disease: a comparison with normal controls, Mov. Disord 27 (2012) 432–434. doi:10.1002/mds.24049. [PubMed: 22183872]

[5]. Miller KM, Okun MS, Fernandez HF, Jacobson CE, Rodriguez RL, Bowers D, Depression symptoms in movement disorders: comparing Parkinson's disease, dystonia, and essential tremor, Mov. Disord 22 (2007) 666–672. doi:10.1002/mds.21376. [PubMed: 17266084]

[6]. Fabbrini G, Berardelli I, Falla M, Moretti G, Pasquini M, Altieri M, Defazio G, Biondi M, Berardelli A, Psychiatric disorders in patients with essential tremor, Parkinsonism Relat. Disord18 (2012) 971–973. doi:10.1016/j.parkreldis.2012.05.005. [PubMed: 22658234]

[7]. Blatt GJ, Oblak AL, Schmahmann JD, Cerebellar Connections with Limbic Circuits: Anatomy and Functional Implications, in: Schmahmann JD, Koibuchi F, Rossi F (Eds.), Handbook of the Cerebellum and Cerebellar Disorders. Springer Science+Business Media, Dordrecht, Netherlands, 2013, pp. 479–496.

[8]. Lang PJ, Davis M, Emotion, motivation, and the brain: reflex foundations in animal and human research, Prog. Brain Res 156 (2006) 3–29. doi:10.1016/S0079-6123(06)56001-7. [PubMed: 17015072]

[9]. Hitchcock JM, Davis M, Efferent pathway of the amygdala involved in conditioned fear as measured with the fear-potentiated startle paradigm, Behav. Neurosci 105 (1991) 826–842. [PubMed: 1663757]

[10]. Funayama ES, Grillon C, Davis M, Phelps EA, A double dissociation in the affective modulation of startle in humans: effects of unilateral temporal lobectomy, J. Cogn. Neurosci 13 (2001) 721–729. doi:10.1162/08989290152541395. [PubMed: 11564317]

[11]. Anand BK, Malhotra CL, Singh B, Dua S, Cerebellar projections to limbic system, J. Neurophysiol 22 (1959) 451–457. [PubMed: 13673296]

[12]. Heath RG, Harper JW, Ascending projections of the cerebellar fastigial nucleus to the hippocampus, amygdala, and other temporal lobe sites: Evoked potential and histological studies in monkeys and cats, Exp. Neurol 45 (1974) 268–287. doi:10.1016/0014-4886(74)90118-6. [PubMed: 4422320]

[13]. Bowers D, Miller K, Mikos A, Kirsch-Darrow L, Springer U, Fernandez H, Foote K, Okun M, Startling facts about emotion in Parkinson's disease: blunted reactivity to aversive stimuli, Brain. 129 (2006) 3356–3365. doi:10.1093/brain/awl301. [PubMed: 17095520]

[14]. Louis ED, Ford B, Lee H, Andrews H, Cameron G, Diagnostic criteria for essential tremor: a population perspective, Arch. Neurol 55 (1998) 823–828. [PubMed: 9626774]

[15]. Lang PJ, Bradley MM, Cuthbert BN, International Affective Picture System (IAPS): Instruction manual and affective ratings (Technical Report A-5), Gainesville: University of Florida, Center for Research in Psychophysiology, 2001.

[16]. Bradley MM, Cuthbert BN, Lang PJ, Pictures as prepulse: attention and emotion in startle modification, Psychophysiology. 30 (1993) 541–545. [PubMed: 8416082]

[17]. Lang PJ, Bradley MM, Cuthbert BN, Emotion, motivation, and anxiety: brain mechanisms and psychophysiology, Biol. Psychiatry 44 (1998) 1248–1263. [PubMed: 9861468]

[18]. Davis M, Neural systems involved in fear and anxiety measured with fear-potentiated startle, Am. Psychol 61 (2006) 741–756. doi:10.1037/0003-066X.61.8.741. [PubMed: 17115806]

[19]. Miller KM, Okun MS, Marsiske M, Fennell EB, Bowers D, Startle reflex hyporeactivity in Parkinson's disease: an emotion-specific or arousal-modulated deficit?, Neuropsychologia. 47 (2009) 1917–1927. doi:10.1016/j.neuropsychologia.2009.03.002. [PubMed: 19428424]

[20]. Musacchio T, Purrer V, Papagianni A, Fleischer A, Mackenrodt D, Malsch C, Gelbrich G, Steigerwald F, Volkmann J, Klebe S, Non-Motor Symptoms of Essential Tremor Are Independent of Tremor Severity and Have an Impact on Quality of Life., Tremor Other Hyperkinet. Mov. (N Y) 6 (2016) 361. doi:10.7916/D8542NCH. [PubMed: 26989573]

[21]. Louis ED, Rios E, Embarrassment in essential tremor: prevalence, clinical correlates and therapeutic implications, Parkinsonism Relat. Disord 15 (2009) 535–538. doi:10.1016/j.parkreldis.2008.10.006. [PubMed: 19028131]

[22]. Kaviani H, Gray JA, Checkley SA, Raven PW, Wilson GD, Kumari V, Affective modulation of the startle response in depression: influence of the severity of depression, anhedonia, and anxiety, J. Affect. Disord 83 (2004) 21–31. doi:10.1016/j.jad.2004.04.007. [PubMed: 15546642]

[23]. Grillon C, Baas J, A review of the modulation of the startle reflex by affective states and its application in psychiatry, Clin. Neurophysiol 114 (2003) 1557–1579. doi:10.1016/S1388-2457(03)00202-5. [PubMed: 12948786]

[24]. Carpenter MB, Batton RR, Connections of the fastigial nucleus in the cat and monkey, Exp. Brain Res. Suppl 6 (1982), S250–291.

[25]. Davis M, Gendelman DS, Tischler MD, Gendelman PM, A primary acoustic startle circuit: lesion and stimulation studies, J. Neurosci. 2 (1982) 791–805. [PubMed: 7086484]

[26]. Leaton RN, Supple WFJ, Cerebellar vermis: essential for long-term habituation of the acoustic startle response, Science. 232 (1986) 513–515. [PubMed: 3961494]

[27]. Campeau S, Davis M, Involvement of the central nucleus and basolateral complex of the amygdala in fear conditioning measured with fear-potentiated startle in rats trained concurrently with auditory and visual conditioned stimuli, J. Neurosci 15 (1995) 2301–2311. [PubMed: 7891168]

[28]. Louis ED, Faust PL, Ma KJ, Yu M, Cortes E, Vonsattel JP, Torpedoes in the cerebellar vermis in essential tremor cases vs. controls, Cerebellum. 10 (2011) 812–819. doi:10.1007/s12311-011-0291-0. [PubMed: 21656041]

[29]. Shin H, Lee DK, Lee JM, Huh YE, Youn J, Louis ED, Cho JW, Atrophy of the Cerebellar Vermis in Essential Tremor: Segmental Volumetric MRI Analysis, Cerebellum. 15 (2016) 174–181. doi:10.1007/s12311-015-0682-8. [PubMed: 26062905]

[30]. Elble RJ, Diagnostic criteria for essential tremor and differential diagnosis, Neurology. 54 (Suppl 4) (2000) S2–6.

[31]. Louis ED, Jurewicz EC, Watner D, Community-based data on associations of disease duration and age with severity of essential tremor: implications for disease pathophysiology, Mov Disord. 18 (2003) 90–93. [PubMed: 12518305]

[32]. Schmahmann JD, The role of the cerebellum in cognition and emotion: personal reflections since 1982 on the dysmetria of thought hypothesis, and its historical evolution from theory to therapy, Neuropsychol. Rev 20 (2010) 236–260. doi:10.1007/s11065-010-9142-x. [PubMed: 20821056]

Highlights:

- Essential tremor associated with abnormal emotion modulation of the startle reflex
- Modulation failure not due to medication effects, depression, or a defect in eyeblink mechanics
- Diminished modulation may reflect aberrant cerebellar input to limbic circuitry

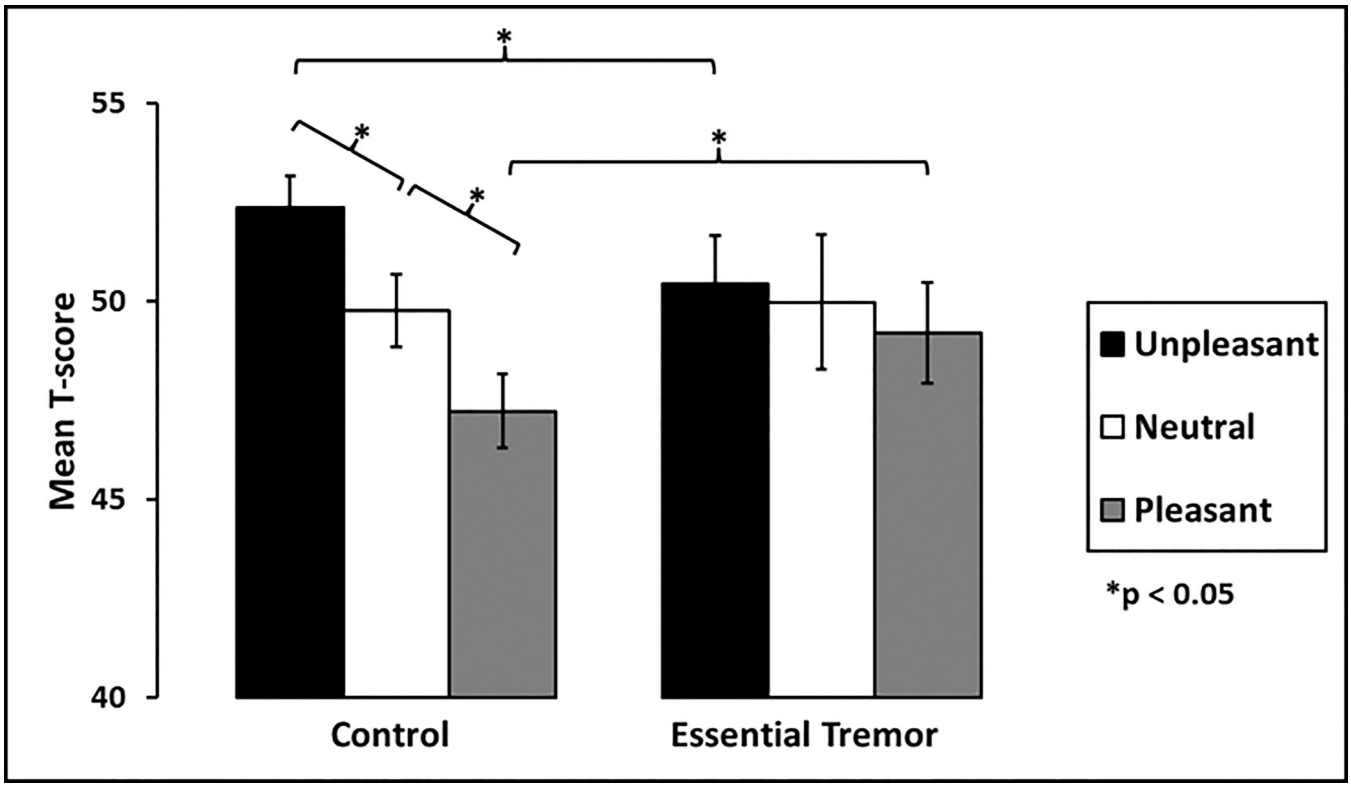

Figure 1.

Peak amplitude (T-score) of startle eyeblink responses during unpleasant, neutral, and pleasant picture viewing

Note: Error bars represent the 95% confidence interval. Asterisks refer to significance at $p < 0.05$ level.

Table 1.

Sample Characteristics

	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
Education (years)	13.9 (3.2)	8–20	13.4 (0.9)	12–15	0.57
Gender (M/F)	11/8		12/6		0.42
Mood					
BDI-II (depression)	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: No significant differences between ET and control groups on any variable using independent t-test comparisons or χ^2 tests (gender distribution); M = Mean; SD = standard deviation; BDI-II = Beck Depression Inventory-II; MMSE = Mini-Mental State Examination; TRS = Tremor Rating Scale; ADL = activities of daily living; SSRI = Selective Serotonin Reuptake Inhibitor; SNRI = Serotonin and Norepinephrine Reuptake Inhibitor

* Of the 10 ET patients taking tremor and/or mood medications, one personl was taking both primidone and escitalopram; another was taking both paraoxetine plus alprazolam.