The auditory startle response in relation to outcome in functional movement disorders

Dreissen, Y. E. M.; Koelman, J. H. T. M.; Tijssen, M. A. J.

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Dreissen, Y. E. M., Koelman, J. H. T. M., & Tijssen, M. A. J. (2021). The auditory startle response in relation to outcome in functional movement disorders. *Parkinsonism & Related Disorders*, *89*, 113-117. https://doi.org/10.1016/j.parkreldis.2021.07.012
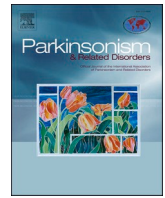
Short communication

The auditory startle response in relation to outcome in functional movement disorders

Y.E.M. Dreissen [a], J.H.T.M. Koelman [a], M.A.J. Tijssen [b],*

[a] *Department of Neurology and Clinical Neurophysiology, Amsterdam University Medical Center, University of Amsterdam, the Netherlands*
[b] *Department of Neurology, University Medical Centre Groningen, University Groningen, the Netherlands*

A R T I C L E   I N F O

A B S T R A C T

Background: The auditory startle reflex (ASR) is enlarged in patients with functional movement disorders (FMD).
Objectives: To study whether the ASR relates to symptom reduction in FMD patients, who participated in a placebo controlled double blind treatment trial with Botulinum Neurotoxin (BoNT).
Methods: Response to treatment in the BoNT study was assessed using the Clinical Global Impression – Improvement scale (CGI-I). The electromyography (EMG) muscle activity of 7 muscles following 110 dB tones was measured in 14 FMD patients before and after one-year treatment and compared to 11 matched controls. The early and a late (behaviorally affected) component of the ASR and the sympathetic skin response (SSR) were assessed.
Results: 10 of 14 patients (71.4%) showed symptom improvement, which was believed to be mainly caused by placebo effects. The early total response probability of the ASR at baseline tended to be larger in patients compared to controls ($p = 0.08$), but normalized at follow-up ($p = 0.84$). The late total response probability was larger in patients vs. controls at baseline ($p < 0.05$), a trend that still was present at follow-up ($p = 0.08$). The SSR was higher in patients vs. controls at baseline ($p < 0.01$), and normalized at follow-up ($p = 0.71$).
Conclusions: On a group level 71.4% of the patients showed clinical symptom improvement after treatment. The early part of the ASR, most likely reflecting anxiety and hyperarousal, normalized in line with the clinical improvement. Interestingly, the augmented late component of the ASR remained enlarged suggesting persistent altered behavioral processing in functional patients despite motor improvement.

1. Introduction

In recent years the research focus in functional movement disorders (FMD) has shifted from a psychological towards a neurobiological basis. Although the etiology and pathophysiology of FMD is unknown, impaired stress regulation is thought to play an important role[1].

In an earlier study we found an augmented early and late response of the auditory startle reflex (ASR) in patients with jerky and tremulous FMD compared to healthy controls[2]. The early component of the ASR is the fastest response of the fear system. It has a fixed rostro-caudal recruitment pattern mediated by the caudal brainstem with onset latencies between 20 and 120 ms (ms)[3]. It is modulated by the amygdala and enlarged in anxiety disorders[4,5]. The enlarged early response of the ASR in FMD patients is accompanied by an increase in autonomic activity, measured with the sympathetic skin response (SSR)[6]. The late component with an onset latency of 100–120 ms, also referred to as the

'orienting response' [7] has a more variable pattern and is associated with behavioral processing. It is less studied and enlarged in culture-specific startle syndromes as Latah [8].

Now, we studied the startle reflex over time in a group of FMD patients who participated in a randomized controlled trial of treatment with botulinum neurotoxin (BoNT)[9]. In this study, a 60% motor improvement was seen in the 4-month RCT-phase in both the BoNT and placebo group, which increased to 80% after one year open-label treatment. As the effect of BoNT was largely considered a placebo effect, we hypothesize there is no specific effect of BoNT on the startle reflex. We suppose that the effects on the ASR reflect hyperarousal and behavioral aspects in relation to the course of FMD symptoms in the studied patients.

---

* Corresponding author. Department of Neurology AB 51, University Medical Center Groningen, PO Box 30.001, 9700 RB, Groningen, the Netherlands.
E-mail address: M.A.J.de.Koning-Tijssen@umcg.nl (M.A.J. Tijssen).

2. Methods

2.1. Study population

Included patients participated in the a BoNT treatment study (Table 1)[9]. They were diagnosed by two experienced movement disorder neurologists (JHTMK, MAJT) and fulfilled diagnostic criteria of 'definite' or 'probable' FMD. Healthy gender- and age-matched subjects without neurologic/psychiatric deficit and without usage of central nervous system(cns)-acting medication served as a control group. Both patients and controls with a hearing defect were excluded.

2.2. Treatment

The treatment intervention consisted of two sessions of either BoNT or placebo during the RCT-phase [9]. The injection site was based on clinical examination in combination with polymyographic electromyography (poly-EMG) (Table 1). If there was no effect, the dosage was doubled at the second treatment session. After the RCT-phase, all patients received BoNT treatment in the one year open-label phase.

2.3. Study procedure and outcome assessment

The ASR was recorded twice in patients and control subjects, at baseline and at follow-up after one year. Outcome measures were assessed at these occasions. The primary outcome of the BoNT study was the Clinical Global Impression – Improvement (CGI-I), a 7 point Likert Scale ranging from 1 (very much improved) to 7 (very much worse), which was dichotomized to symptom improvement (score 1-3) vs. same or worse (score 4-7). Motor symptoms were assessed using the Psychogenic Movement Disorder Rating Scale (PMDRS). Both of these outcome measures were rated based on video recordings, by two independent researchers who were blinded to the allocated treatment[9]. Patients also underwent a psychiatric interview by one researcher (YEMD) based on the DSM-IV using the Mini-International Neuropsychiatric Interview - PLUS (MINI-PLUS). Self-assessment scales included the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI). Controls were only screened for a current depressive or anxiety disorder based on the DSM-IV using the relevant part of the MINI-PLUS.

2.4. ASR and SSR assessment

During ASR assessment, subjects were seated on a bed with a headphone and instructed to sit quietly and listen to a series of beeps. After skin preparation, the ASR was recorded using bipolar active cutaneous Ag-AgCl EMG electrodes (Active One System; Biosemi, Amsterdam, The Netherlands) in the following seven muscles: orbicularis oculi (OO), masseter (Mass), sternocleidomastoid (SCM), deltoid (Delt), abductor pollicis brevis (APB), rectus abdominis (RA) and the quadriceps (Quad) muscle. The response in the OO muscle usually contains of two EMG

Table 1

Clinical characteristics of patients before and after treatment. PMDRS = Psychogenic Movement Disorder Rating Scale. BAI = Beck Anxiety Inventory. SCM = sternocleidomastoid. Botulinum Neurotoxin (BoNT) starting dose per muscle (iliopsoas: 160-200 International Units (IU); rectus femoris 100–200 IU; vastus medialis 50 IU; rectus abdominis 120-200 IE; trapezius 50-80 IU; levator scapulae 60-80 IU; SCM 40-80 IU; pectoral major 80-100 IU; deltoid 80 IU; paraspinal 150 IU; semispinal 60 IU).

Patients	Phenomenology	Muscle(s) treated	CGI-I follow-up	PMDRS baseline	PMDRS follow-up	Current anxiety disorder baseline	Current anxiety disorder follow-up	BAI-scores baseline	BAI-scores follow-up
1	jerks abdomen and legs	iliopsoas	1	12	11	no	no	16	18
2	jerks both legs	iliopsoas	1	10	1	no	no	0	0
3	jerks one leg	iliopsoas rectus femoris vastus medialis	1	27	6	no	no	17	11
4	jerks abdomen	rectus abdominis	5	22	22	yes	no	15	6
5	jerks one shoulder	trapezius levator scapulae	4	18	0	no	no	9	0
6	jerks both shoulders	SCM trapezius major pectoral deltoid	4	25	25	no	no	3	4
7	jerks both shoulders	trapezius major pectoral	1	10	9	no	yes	11	15
8	jerks back	paraspinal	3	5	2	yes	no	4	0
9	jerks abdomen	iliopsoas rectus abdominis	3	23	19	no	no	12	20
10	jerks one leg	iliopsoas rectus femoris	3	24	20	no	no	9	6
11	jerks abdomen	rectus abdominis	3	6	3	no	yes	15	22
12	jerks abdomen and shoulder	semispinal rectus abdominis	2	5	0	no	no	16	10
13	jerks one leg	vastus medialis rectus femoris	3	18	9	no	no	5	11
14	jerks abdomen	rectus abdominis	5	11	13	yes	yes	23	31

responses, the early eye-protective blink response and a second response which is part of the ASR. Because of the overlap between the two responses, distinguishing them is almost impossible [6]. The SSR was recorded on the palm of the hand with the reference electrode on the dorsum. Eight consecutive 200 Hz (Hz) auditory stimuli of 110 dB sound pressure level and duration of 55 ms (ms) with a varying interval of 1.5 and 3 min were used to elicit the ASR. This paradigm was identical to our previous study [2], in accordance with the paradigm previous used by our group [6] and with guidelines on the startle reflex by the Psychophysiology committee[10]. All participants gave written informed consent and this study was approved by the local Medical Ethical Committee.

2.5. Data processing

Data analysis was performed off-line using Brain Vision Analyzer version 2.0 (Brain Products GmbH). The different parameters of the ASR were quantified distinguishing between the early component with onset latency of 0–100 ms for the OO and Mass and 0 - 120 ms for the remaining muscles and the late component with onset latencies of 100–1000 ms for the OO and Mass and 120–1000 ms for the remaining muscles [2]. Predefined criteria for classifying a response were used, i.e. a clear increase from baseline with a minimal duration of 30 ms and amplitude of 30 μV (μV). All responses were manually marked by one investigator (YEMD) at the same scale sensitivity (200 μV). The response probabilities were assessed for all the muscles separately by dividing the total amount of responses per muscle by the total amount of trials and multiplying this by 100. The total response probability was calculated as the average response probability of all muscles together. The SSR, which was defined as the largest increase in amplitude from baseline after stimulation within 5 s, was calculated and standardized to the intra-individual maximum (0%–100%).

2.6. Statistical analysis

Baseline characteristics were summarized using descriptive statistics. Possible differences in gender between patients and controls were tested with a Fisher's exact test. A Mann-Whitney *U* test was used to test for differences in age between groups. In the patient group the difference in motor symptoms (PMDRS) between baseline and after treatment was tested using a Wilcoxon signed rank test. A repeated measures analysis (general linear mixed model with fixed effects) was used to assess the effect of group (patients vs. controls) and the repeated stimuli, which is a measure of habituation, on the total response probability for the two different time points (baseline and follow-up) separately. In order to correct for the possible confounding factors cns-acting medication and anxiety disorders, a second model was built in which these factors were added. The same model was also used to determine whether there was a change in ASR between baseline and follow-up (effect of timing of measurement) for patients vs. controls. All tests were two-sided and a p-value of <0.05 was considered statistically significant. The analyses were performed with Statistical Packaging for Social Sciences (SPSS) version 25.

3. Results

3.1. Population characteristics

Fourteen patients and 11 control subjects were included in this study. The majority of both groups was male (n = 9; 64% patients vs. n = 8; 73% controls). The groups did not differ in terms of age, with a median age of 58 (interquartile range (iqr) 46–60) in patients compared to a median of 56 (iqr 46–62) in the control group. Eight (57%) of patients were using cns-acting medication (including amitriptyline, clonazepam, temazepam, diazepam, tramadol and pramipexol).

3.2. Response to BoNT treatment

In total 10 of 14 patients (71.4%) showed motor improvement at follow-up on the CGI-I. A significant improvement of PMDRS-scores was found in patients between baseline and follow-up (median 15 (iqr 9–23) to median 9 (iqr 2–19); p = 0.01). There was no significant change in anxiety symptoms between baseline (BAI median score 12; iqr 5-17) and follow-up (BAI median score 11; iqr 3-19) in the patient group (p = 0.95) nor in the amount of anxiety disorders (baseline (n = 3 (21%) vs. follow-up (n = 3 (21%); p = 1.00).

3.3. ASR and SSR at baseline

A trend towards a larger early total response probability was found in patients compared to controls (17% vs. 7%; estimate −0.11; 95% CI -0.23 to 0.01; p = 0.08). The total response probability of the late response was significantly larger in patients compared to controls at baseline (16% vs. 7%; estimate −0.24; 95% CI -0.41 to −0.07; p < 0.05). The early (estimate −0.02; 95% CI -0.02 to −0.01; p < 0.01) as well as the late response showed a significant habituation effect in both groups (estimate −0.03; 95% CI -0.05 to −0.01; p < 0.01). The SSR was enlarged in patients (median 0.63; iqr 0.45 to 0.90) compared to controls (median 0.57; iqr 0.36 to 0.81) at baseline (estimate −0.23; 95% CI -0.38 to −0.09; p < 0.01) with a significant habituation effect (estimate −0.07; 95% CI -0.09 to −0.04; p < 0.01). Adding the factors anxiety disorder and cns-acting medication to the different models did not alter the results. However the presence of an anxiety disorder was a significant contributor to the early total response probability, but not the late. For details on response probabilities per muscle for the early and late responses see Tables 2 and 3 of the supplementary data file.

3.4. ASR at follow-up and difference between baseline and follow-up

3.4.1. Early response

Compared to baseline, at follow-up no difference in total early response probability was found between patients and controls (16% vs. 8%; estimate 0.01; 95% CI -0.09 to 0.10; p = 0.84). The early total response probability showed significant habituation per stimulus in both groups (estimate −0.01; 95% CI -0.01 to 0.00; p < 0.05). Also, there was a significant habituation with a decrease between baseline and follow-up in the whole group (estimate −0.05; 95% CI -0.09 to −0.00; p < 0.05). A trend was seen towards a decrease in total response probability between baseline and follow-up in patients (estimate −0.05; 95% CI -0.10 to 0.00; p = 0.06), which was not present in controls (estimate −0.03; 95% CI -0,08 to 0.02; p = 0.22).

3.5. Late response

At follow-up a trend was still seen towards a larger total response probability of the late response in patients compared to controls (22% vs. 6%; estimate - 0.09; 95% CI -0.19 to 0.01; p = 0.08). No habituation effect was found of the stimulus, nor was there a habituation found between baseline and follow-up. The late response did not change between baseline and follow-up in patients (estimate −0.04; 95%CI -0.19 to 0.11; p = 0.54), but a trend was seen towards a decrease in controls (estimate −0.03; 95% CI -0.06 to 0.00; p = 0.06). Fig. 1 shows an example of the startle response before and after treatment in a patient nr 12 (Table 1).

3.6. SSR

No difference in SSR was detected between patients and controls at follow-up. Also, no change between baseline and follow-up was found in controls as well as patients.
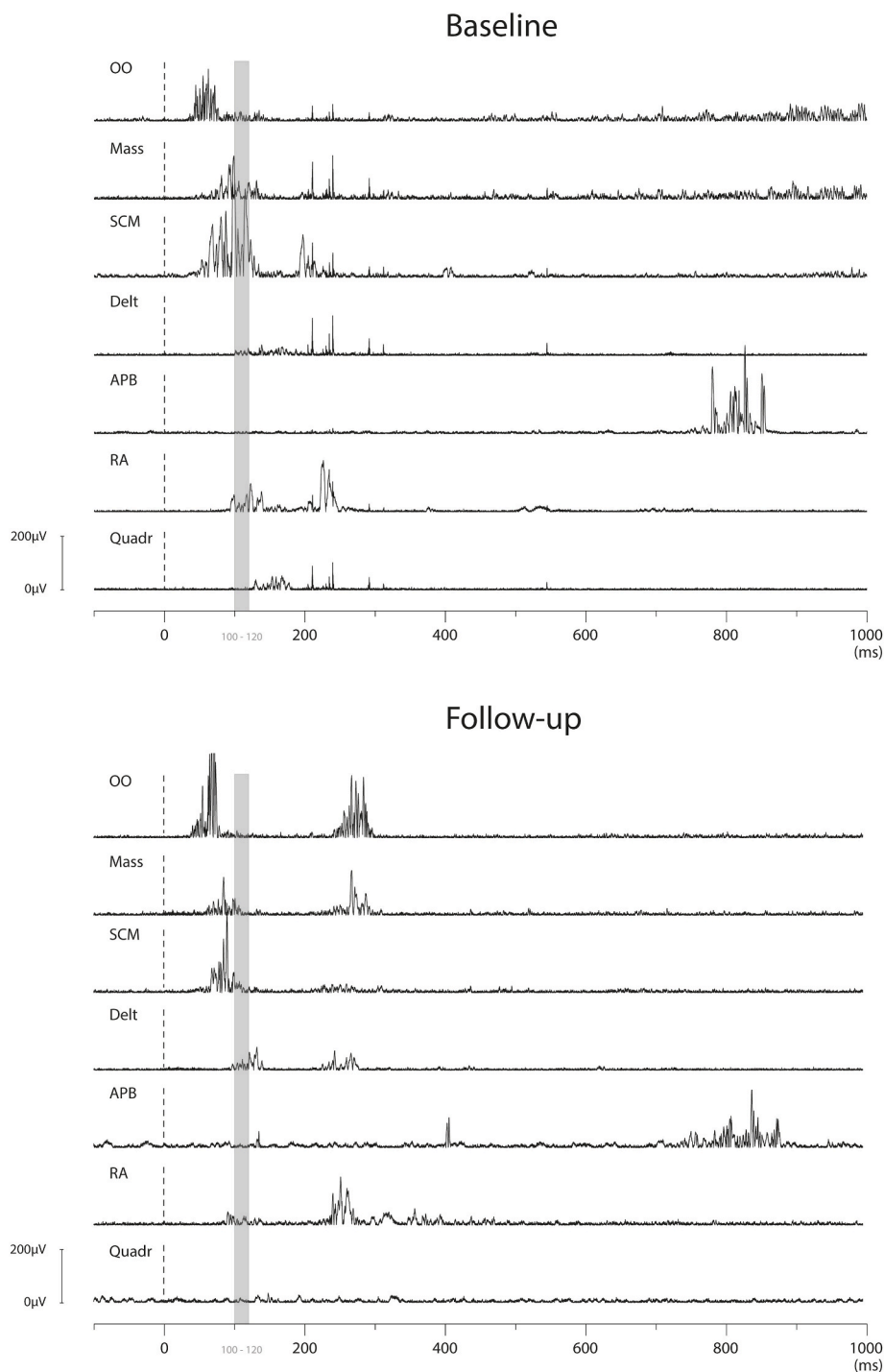
Baseline

Follow-up

Fig. 1. An example of the ASR before (above) and after treatment in patient nr 12 (see Table 1). The gray bar marks the beginning of the late response. Especially the late response, remains prominent after treatment.

4. Discussion

In this study we report on the ASR in relation to outcome in FMD patients and found a tendency for the early component of the ASR to normalize with clinical improvement, whereas the late, behaviorally affected component remained enlarged in patients compared to controls.

In patients, the early motor total response probability showed a trend to be enlarged at baseline, which normalized at follow-up. A similar study showed that the ASR decreased in children with anxiety disorders who responded well to Cognitive Behavioral Therapy (CBT) [11]. Imaging studies have shown that the magnitude of pre-treatment amygdala

activation in general predicts better treatment response[12]. In line with this, the early motor ASR could potentially serve as an outcome measure and/or biomarker in patients with FMD. The stable findings in controls indicate that the test-retest reliability is high.

At baseline the late response was enlarged in patients compared to controls which tended to remain enlarged at follow-up despite motor improvement in a large proportion of patients. The lack of normalization of the late response might reflect a persisting general disorder in the regulation of behavioral aspects which is thought to play a key role in FMD.

Other related neurophysiological studies have shown impaired

prepulse inhibition of the blink reflex in FMD [13], suggesting abnormal preconscious processing of somatosensory inputs, which may also play a role in our results on the ASR given the pathophysiology of FMD.

Regarding limitations, the patient group was too small to compare patients with and without motor improvement. Further, the ASR is determined by a large number of factors including cns-active medication and anxiety disorders which could influence results, despite correction. Lastly, habituation could have influenced the results of the ASR at follow-up.

5. Conclusions

This is the first study to assess the ASR in relation to treatment outcome in FMD. The early response appears to relate to motor improvement after treatment. The abnormalities in the behavioral (late) component of the ASR persisted despite clinical improvement, and may indicate a more general disorder in the regulation of behavioral aspects in FMD.

Contributors

YEMD, MAJT and JHTM designed the study. YEMD collected, analyzed. YEMD, MAJT and JHTM interpreted the data. YEMD wrote the paper and designed the figures and tables. MAJT and JHTM drafted and critically revised the paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2021.07.012.

References

[1] J.F. Baizabal-Carvallo, M. Hallett, J. Jankovic, Pathogenesis and pathophysiology of functional (psychogenic) movement disorders, Neurobiol. Dis. 127 (2019) 32–44.
[2] Y.E.M. Dreissen, T. Boeree, J. Koelman, M.A.J. Tijssen, Startle responses in functional jerky movement disorders are increased but have a normal pattern, Park. Relat. Disord. 40 (2017) 27–32.
[3] Y.E. Dreissen, M.J. Bakker, J.H. Koelman, M.A. Tijssen, Exaggerated startle reactions, Clin. Neurophysiol. 123 (1) (2012) 34–44.
[4] M.J. Bakker, M.A. Tijssen, J.N. van der Meer, J.H. Koelman, F. Boer, Increased whole-body auditory startle reflex and autonomic reactivity in children with anxiety disorders, J. Psychiatry Neurosci. 34 (4) (2009) 314–322.
[5] A. Angrilli, A. Mauri, D. Palomba, H. Flor, N. Birbaumer, G. Sartori, P.F. di, Startle reflex and emotion modulation impairment after a right amygdala lesion, Brain 119 (Pt 6) (1996) 1991–2000.
[6] M.J. Bakker, F. Boer, J.N. van der Meer, J.H. Koelman, T. Boeree, L. Bour, M. A. Tijssen, Quantification of the auditory startle reflex in children, Clin. Neurophysiol. 120 (2) (2009) 424–430.
[7] P. Gogan, The startle and orienting reactions in man. A study of their characteristics and habituation, Brain Res. 18 (1) (1970) 117–135.
[8] M.J. Bakker, J.G. van Dijk, A. Pramono, S. Sutarni, M.A. Tijssen, Latah: an Indonesian startle syndrome, Mov. Disord. 28 (3) (2013) 370–379.
[9] Y.E.M. Dreissen, J.M. Dijk, J.M. Gelauff, E. Zoons, D. van Poppelen, M. F. Contarino, R. Zutt, B. Post, A.G. Munts, J.D. Speelman, D.C. Cath, R.J. de Haan, J.H. Koelman, M.A.J. Tijssen, Botulinum neurotoxin treatment in jerky and tremulous functional movement disorders: a double-blind, randomised placebo-controlled trial with an open-label extension, J. Neurol. Neurosurg. Psychiatry 90 (11) (2019) 1244–1250.
[10] T.D. Blumenthal, B.N. Cuthbert, D.L. Filion, S. Hackley, O.V. Lipp, A. van Boxtel, Committee report: guidelines for human startle eyeblink electromyographic studies, Psychophysiology 42 (1) (2005) 1–15.
[11] M.J. Bakker, M.A. Tijssen, J.H. Koelman, F. Boer, Normalization of the auditory startle reflex after symptom reduction in children with anxiety disorders, J. Psychiatr. Res. 45 (6) (2011) 796–802.
[12] H. Klumpp, J.M. Fitzgerald, Neuroimaging predictors and mechanisms of treatment response in social anxiety disorder: an overview of the amygdala, Curr. Psychiatr. Rep. 20 (10) (2018) 89.
[13] Z. Hanzlikova, M. Kofler, M. Slovak, G. Vechetova, A. Fecikova, D. Kemlink, T. Sieger, E. Ruzicka, J. Valls-Sole, M.J. Edwards, T. Serranova, Prepulse inhibition of the blink reflex is abnormal in functional movement disorders, Mov. Disord. 34 (7) (2019) 1022–1030.