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Clinical Neurophysiology 111 (2000) 1366–1371

www.elsevier.com/locate/clinph

Abnormalities of the acoustic startle reflex and reaction time in Gilles de la Tourette syndrome

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Accepted 28 April 2000

Abstract

Objective: To study the startle reflex and the effect of the startle reflex stimulus over reaction time (start-react effect) in Gilles de la Tourette syndrome (GTS).

Method: Ten GTS patients and ten matched healthy volunteers underwent a simple RT paradigm (4 blocks of 50 trials). Forty acoustic startle reflex stimuli (110 dB) were randomly delivered with a 20% occurrence probability and presented unexpectedly at the same time as the imperative stimuli of the RT. Variables of interest were: amplitude, onset latency, degree of spread and rate of habituation of the startle response, and RT and the start-react effect caused by the startle stimuli.

Results: GTS patients showed a significantly higher amplitude, a major degree of spread and fewer habituation phenomena of the startle reflex. GTS patients showed poorer non statistically significant RT performance compared to controls, with a significant correlation between RT and severity of the disease. The start-react effect was significantly less pronounced in GTS patients.

Conclusions: The present study confirms that GTS has an exaggerated startle reflex response and extend the spectrum of abnormalities to the start-react effect. A state of dopaminergic hyperactivity may have contributed to these results.

Keywords: Gilles de la Tourette; Startle reflex; Reaction time

1. Introduction

Gilles de la Tourette syndrome (GTS) is a lifelong fluctuating neuropsychiatric disease characterized by the presence of motor and vocal tics and a range of associated behavioral problems that include anxiety, attention-deficit hyperactivity, obsessions and compulsions (American Psychiatric Association, 1994). Deficient pallidal inhibition and hyperdopaminergic mechanisms have been suggested to underlie GTS (Swerdlow et al., 1994; Castellanos et al., 1996a). Acquired cases of GTS with brainstem focal lesions (Sacks, 1982) and neurophysiological studies (Smith and Lees, 1989; Stell et al., 1995) also suggest that the brainstem plays an important role in the pathophysiology of this syndrome.

The startle response is a brainstem reflex that appears mainly modulated by the basal ganglia and the dopamine system (Vidailhet et al., 1992; Delwaide et al., 1993; Valldeoriola et al., 1998). As both GTS and the startle reflex may share anatomical structures and neurotransmission mechanisms, it could be predicted that the startle reflex would be abnormal in GTS patients.

From the time of its description comparisons have been drawn between GTS and the syndromes of excessive startle (Gilles de la Tourette, 1885); however, the status of GTS as a startle syndrome remains controversial. Results of the few studies addressing the relationship between GTS and the startle reflex have been contradictory (Stell et al., 1995; Sachdev et al., 1997). Some methodological problems in obtaining the startle response may underlie these discrepancies.

Recently, a new test for the study of startle response has been developed (Valls-Solé et al., 1995). It consists of delivering a startle stimulus when the subject's attention is focused on reacting to a visual 'go' signal. In normal human subjects, it

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1388-2457/00/$ - see front matter CLINPH 2000507
PII: S1388-2457(00)00343-6

was found that the startle response elicited with this procedure shows larger electromyographic (EMG) responses and less habituation, thus improving the performance of the startle reflex in the laboratory (Valls-Solé et al., 1997). In normal subjects examined with this procedure, the reaction time (RT) is markedly shortened when the startle is delivered simultaneously with the 'go' signal. This physiologic behavior is called the start-react effect (Valls-Solé et al., 1995). This test appears as a useful tool to investigate the startle reflex response and attention and motor preparation, all of which may show abnormalities in GTS (Pitman et al., 1987; Van Woerkom et al., 1988; Eapen et al., 1994; Castellanos et al., 1996; Johannes et al., 1997).

In the present study, we compared the startle reflex and the start-react effect in GTS patients and a control group. We examined the following hypothesis: if a state of hyperdopaminergic activity underlies GTS, the startle reflex of GTS patients should have an exaggerated amplitude and spread, a shorter latency, and a lower rate of habituation. Moreover, there should be a greater facilitation effect of the startle reflex on RT performance.

2. Patients

Ten patients (5 men, 5 women) aged 29.8 ± 15.8 years, who fulfilled the diagnostic criteria for GTS according to DMS-IV (American Psychiatric Association, 1994), participated in the experiment. The study protocol was approved by the hospital ethics committee and all patients and volunteers gave informed consent to participate. Six patients had never received treatment for GTS. The other four patients discontinued all medication 15 days before the study. The clinical characteristics and ratings of the GTS subjects on the Tourette's Syndrome Global Scale (TSGS) (Harcherik et al., 1984) are presented in Table 1. None of the patients complained of a symptomatic abnormal startle reflex.

The control group was matched as far as possible for age and sex and was composed of 10 volunteers (28.0 ± 9.5 years). Mean age of both groups was similar ($t = 0.31$, $P = 0.76$). Control subjects were screened for physical or psychiatric disorders, and for an absence of family history of GTS or obsessive-compulsive disorder. None were taking psychotropic drugs. All subjects, patients and controls, were able to hear normal speech properly.

3. Methods

3.1. Experiment conditions

The experiment was conducted in a quiet laboratory with the subject seated in a comfortable chair with arm and back rests, 1 m in front of a computer screen at eye level. The subject's arms were positioned on the padded armrest of the chair with a switch in the dominant hand.

Surface silver-silver chloride electrodes were applied to the right orbicularis oculi, masseter, sternomastoid, biceps and forearm flexors. Due to that audiogenic blink response is not thought to be part of the true startle reflex (Brown et al., 1991), we measured startle reflex parameters using the masseter muscle response. For the masseter, the recording electrode was placed over the midbelly of the muscle and the reference electrode was placed over the angle of the jaw. The EMG activity was analogically recorded using an electromyograph (Grass 8-plus EEG, Quincy, USA). Both the EMG and the signal generated by pushing the switch were all digitized with an A/D converter board and stored for off-line analysis using Neuroscan 3.0 (Herndon, USA) software. Raw EMG from each muscle was rectified and sweeps were performed after each stimulus. The 50-ms period previous

Table 1
Demographic, clinical features and habituation rates of startle reflex in GTS patients and normal controls[a]

GTS patients							Control subjects				
No.	Age	Sex	H	S	TSGS score	Treatment	No.	Age	Sex	H	S
1	25	M	50	4	30.6	None	1	25	M	65	3
2	21	F	30	5	5.0	None	2	28	F	77	3
3	13	M	58	4	16.1	None	3	12	M	82	2
4	42	F	75	4	36.8	Clorpromacine	4	38	F	62	1
5	17	M	30	2	37.1	Paroxetine	5	17	M	78	1
6	24	F	63	4	7.3	None	6	26	F	86	2
7	42	F	44	3	28.0	None	7	41	F	65	1
8	25	M	66	4	51.8	Pimozide	8	27	M	95	2
9	39	F	10	5	6.3	None	9	37	F	75	2
10	33	M	60	5	30.6	Pimozide	10	32	M	74	1
Mean	28.10		48.60	4.00	24.96		Mean	28.30		75.90	1.80
SD	10.57		20.08	0.94	15.70		SD	9.17		10.25	0.79

[a] H, habituation rate %; S, number of active muscles; TSGS, Tourette Syndrome global scale[18].

to the onset of the stimulus was used as the baseline value in each of these sweeps.

3.2. Startle stimuli

Acoustic startle stimuli consisted of 1 kHz square waves of 150 ms duration at 110 dB administered binaurally through air headphones. The choice of the stimulus parameters was based on previous works (Graham, 1979; Stell et al., 1995; Sachdev et al., 1997).

3.3. Reaction time paradigm

A simple RT task without warning stimuli was executed. Each trial began with the presentation of a green square during 150 ms (vertical visual angle approximately 4°. Subject response was awaited until 1000 ms after the imperative stimulus onset. A fixed interstimulus interval of 4 s was used between trials. The subjects received 4 blocks of trials; each block consisting of 50 trials (40 non-startle trials and 10 startle trials). The startle trials were randomly delivered in each block with a 20% occurrence probability. Each block was followed by a short break. Subjects were tested after an initial practice period.

The acoustic startle stimuli were presented unexpectedly at the same time as the imperative stimuli and with the same duration. The subjects were instructed to ignore the presence of auditory stimuli throughout the experiment, and also to respond as quickly as possible with their dominant hand and avoid possible anticipations. A fixation dot in the middle of the screen was visible throughout the experiment. RT paradigm and acoustic startle stimuli were administered using Neurostim (Herndon, USA) software.

3.4. Data analysis

Variables of interest were defined as follows:

- Amplitude of the startle response: the averaged (40 trials) amplitude in microVolts of the EMG startle response recorded at the masseter muscle.
- Onset latency: the time interval between onset of acoustic stimulus and the onset (>2 SD difference from the baseline) of the averaged EMG response recorded at the masseter muscle.
- Degree of spread: the number of muscles (maximum 5) in which there were a discernible startle EMG response (>2 SD difference from the baseline) in the global EMG average.
- Rate of habituation: the percentage reduction when comparing the averaged amplitude of the EMG startle response recorded at the masseter muscle obtained at the first block with the averaged response obtained at the fourth block of the RT paradigm.
- Reaction time: the time interval between onset of stimulus and pressing the switch.

A statistical comparative analysis between GTS patients and controls of startle amplitude, onset latency, degree of spread and rate of habituation was performed using t-test. RT results were analyzed using ANOVA, with a within-subject factor: type of trials (non-startle trials vs. startle-trials), and a between-subject or group factor (patients vs. control). Pearson correlation was used in GTS patients to assess the lineal relationship between TSGS score and age, startle reflex amplitude, onset latency, degree of spread, rate of habituation and RT.

4. Results

4.1. Amplitude of the startle response

The mean EMG amplitude of the startle reflex recorded at the masseter was significantly higher in GTS patients (29.22 ± 19 μV) compared to controls (10.94 ± 10.01 μV) ($P = 0.05$). In GTS patients no correlation was found between the severity of TSGS and startle amplitude ($r = 0.089$).

4.2. Onset latency of startle response

No significant differences were found when comparing the mean latency of the startle response recorded at the orbicularis oculi in GTS patients (56.82 ± 16.43 ms) and in controls (57.41 ± 15.70 ms) ($P = 0.913$). In GTS patients no correlation was found between the severity of TSGS and the onset latency of the startle reflex ($r = 0.080$).

4.3. Degree of spread of startle response

The startle response had a more significant degree of spread in GTS patients (mean 4.00 ± 0.94 muscles) than in controls (mean 1.80 ± 0.79 muscles) ($P = 0.0001$). In GTS patients no correlation was found between the severity of TSGS and the degree of spread of the startle response ($r = 0.453$).

4.4. Rate of habituation

The rate of habituation in the startle response was significantly more pronounced in the control group ($75.50 \pm 10.25\%$) compared to GTS patients ($48.40 \pm 20.08\%$) ($P = 0.002$) (Fig. 1). In GTS patients no correlation was found between the severity of TSGS and the rate of habituation of the startle reflex ($r = 0.481$).

4.5. Reaction time task

No significant differences in RT were found between the two groups: patients (260 ± 67 ms) and controls (253 ± 54 ms). The presence of the startle acoustic stimuli in RT trials facilitated voluntary responses in both groups, decreasing mean RT, compared to trials in which startle stimuli was absent ($P < 0.0001$). However, this start-react effect was

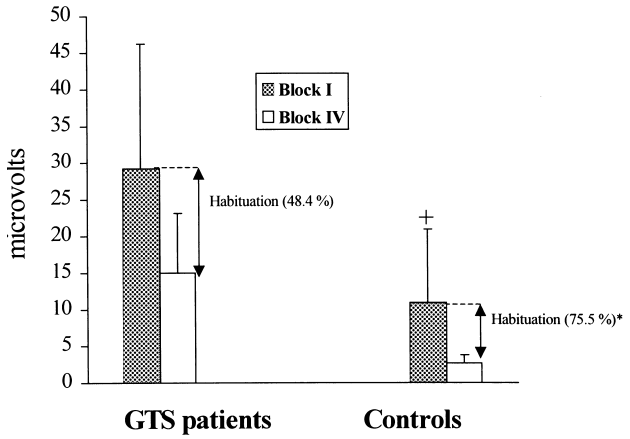

Fig. 1. Mean amplitude (±SD) of the startle reflex response recorded at the masseter muscle. Note the major amplitude ($^{+}P = 0.05$) and the lower habituation rate ($^{*}P = 0.002$) in the GTS group.

significantly ($P = 0.008$) different between GTS patients (mean reduction of 38.08 ± 13.04 ms) and controls (mean reduction of 56.90 ± 1.92 ms) (Fig. 2).

A strong relationship was seen between TSGS and RT, especially in non-startle-trials ($r = 0.678$, $P = 0.031$) (Fig. 3). There was no correlation between RT measures and age.

5. Discussion

Overall, this controlled study shows that GTS patients have a disinhibition of the startle reflex, showing a greater amplitude of the response, a greater degree of spread and fewer habituation phenomena. It concurs with previous results of abnormal startle reflex in these patients. Findings of normal latencies of the startle response and normal pattern of muscle activation, suggest that GTS patients have no disturbances of the intrinsic neural pathways mediating the reflex. Moreover, our results also demonstrate that there is an abnormal start-react effect in GTS patients.

From the time of its initial description, comparisons have been drawn between GTS and the syndromes of excessive startle (Gilles de la Tourette, 1885). Clinical studies have suggested that at least 20% of GTS patients have an exaggerated startle response (Murray, 1978). However, available neurophysiological data looking to confirm this clinical impression are contradictory (Stell et al., 1995; Sachdev et al., 1997). This may be partially due to the variability in the clinical expression of GTS and to methodological issues. In fact, the results of our study are in concordance with clinical evidence (Murray, 1978) and with the findings of Stell et al. (1995) who found that GTS patients have an exaggerated audiogenic startle response. In contrast, Sachdev et al. (1997) found that GTS subjects did not differ from controls in any parameter of the startle reflex. Methodological improvements could provide a better discriminability for the procedure. In our case, utilization of the start-react effect paradigm may have improved sensitivity for detecting the possible abnormalities of the startle reflex in GTS patients.

We failed to demonstrate a positive correlation between abnormalities of the startle reflex and severity of the GTS. This may be due to methodological or pathophysiological reasons. A type II error due to an insufficient sample of patients might have biased the present negative results. Alternatively, the clinical rating scale we used might be not sensitive enough to detect a positive relationship between those aspects of GTS in close relationship with an abnormal startle response. In this respect, it is well known that GTS is characterized by a large spectrum of symptoms ranging from predominantly motor to predominantly sensory tics (a motor tic preceded by an urge to move) with many intermediate possibilities that many times are difficult to clearly separate (Kurlan et al., 1989; Kulisevsky et al., 1998). It might be that an abnormal startle reflex was only related to those motor tics without a clear underlying sensory urge, a type of tics that are not distinguished in the TSGS. Moreover, the abnormalities of the startle reflex may lack a correlation with tic severity; instead, an abnormal startle reflex may have a gating effect on tics, acting with an all-or-nothing facilitatory effect. Finally, the abnormal startle response might be present as an associated (co-morbid) phenomena in some but not all GTS patients as it occurs with stuttering, obsessive-compulsive disorder or attention-deficit hyperactivity disorder (Robertson et al., 1993).

Both GTS and abnormal startle reflex may share common pathophysiological mechanisms. The startle reaction is considered a vestigial expression of a basic physiological reaction common to all mammals. The anatomical structures generating the startle reaction have been identified in the brainstem of the cat (Davis et al., 1982). The movement that accompanies a startle reaction is considered a reflex movement not under voluntary control. However, there is evidence that the modulation of the startle response arises

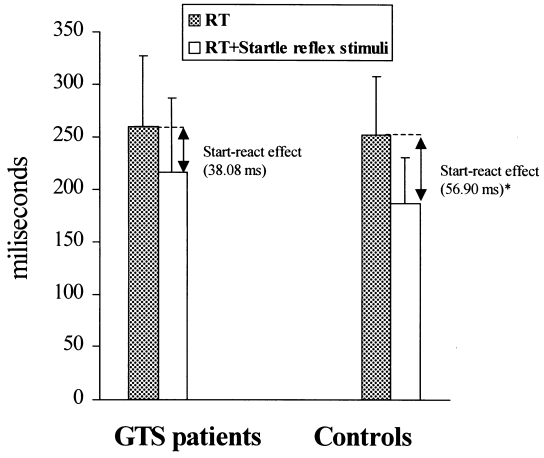

Fig. 2. Mean values of simple RT (±SD) without and with acoustic startle stimuli (start-react effect). Note that the start-react effect is more pronounced in the control group ($^{*}P = 0.008$).

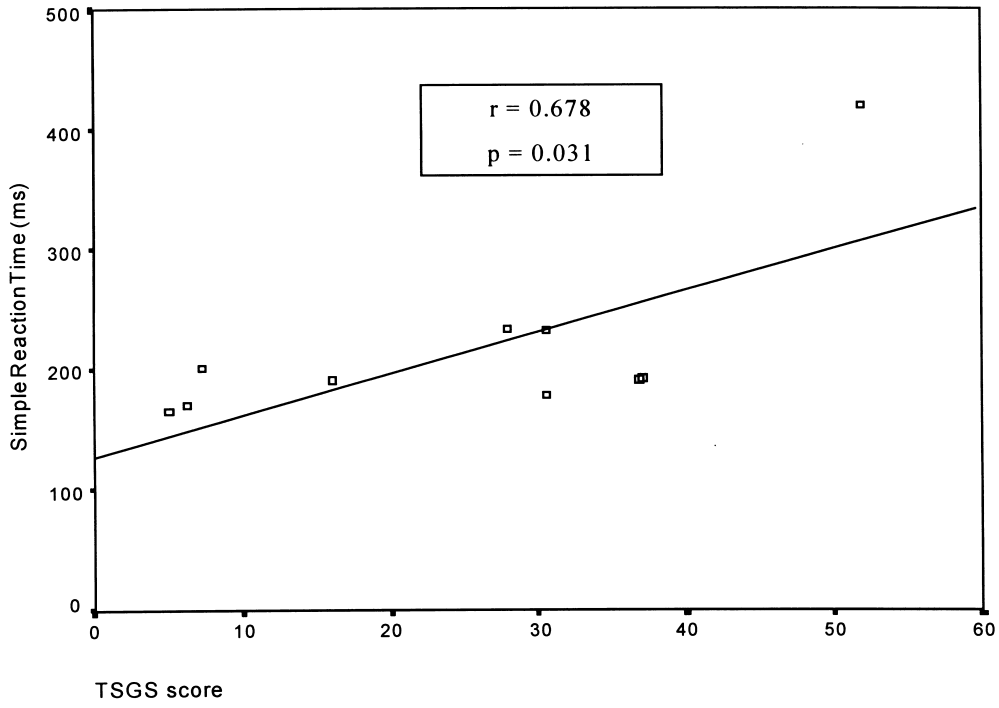

Fig. 3. Correlation between TSGS scores and simple RT performance in GTS patients.

from several cortical and subcortical structures, principally the basal ganglia (Davis, 1984; Brunia, 1993). Dopamine has been involved in the pathophysiology of the startle reflex. Human studies have shown that the startle reflex is abnormal in Parkinson's disease, an hypodopaminergic state (Vidailhet et al., 1992; Valldeoriola et al., 1998). Moreover, the auditory facilitation of the soleus H-reflex is increased by levodopa in humans (Delwaide et al., 1993). Our results of an exaggerated startle response may reflect a disinhibition of this reflex in a hyperdopaminergic state such as GTS.

It is well known that GTS patients are easily captured by external stimuli, as demonstrated by echo phenomena and increased distraction, forcing them to react immediately with a higher basic level of background activity (Pitman et al., 1987; Van Woerkom et al., 1988; Eapen et al., 1994). This may explain the difficulty in concentrating on an easy task, such as simple RT paradigm. Some results of our study support this idea. Although not statistically significant, our patients showed more delayed RT performance than controls. We found a significant negative correlation between RT and the severity of the disease, as measured by means of TSGS score.

On the other hand, if dopamine favors movement in the basal ganglia, one would expect that GTS patients would show an exaggerated start-react effect. The opposite was found in our study. This apparently contradictory effect could be explained on the basis of the particular fine tuning of dopamine action in the central nervous system. Both too little or too much dopamine stimulation results in detrimental task performance (Arnsten and Goldman-Rakic, 1998). In fact, the collision of the startle stimuli on the RT paradigm might act as an stress inductor further increasing dopamine (Arnsten and Goldman-Rakic, 1998) in an hyperdopaminergic state, leading to a poorer task performance.

In conclusion, this study confirms that GTS patients have an exaggerated startle reflex response, possibly due to a state of hyperactivity or disinhibition secondary to an excessive dopaminergic stimulation. That hyperdopaminergic state might underlie the less pronounced start-react effect in GTS patients. Further studies, preclasifying patients by their tics characteristics, by the state of their dopaminergic receptors, and studied before and after antidopaminergic treatment are needed.

Acknowledgements

This study was supported in part by grant FIAP/96-9.501 from the Comisió Interdepartamental de Recerca i Tecnologia, Generalitat de Catalunya, Spain (Dr A. Gironell); and by grant FIS 97/20.27 (Dr M. Berthier). We are grateful to Ignasi Gich, M.D., from Biometrics of the Institut de Recerca, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, for his assistance with statistics and to Maria A. Funes for her help in the preparation of the manuscript.

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