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Sensory sensitivity to external stimuli in Tourette syndrome patients

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Abstract

Patients with Tourette Syndrome often state that their sensitivity to sensations is equally or more disruptive than are motor tics. However, their sensory sensitivity is not addressed by standard clinical assessments nor is it a focus of research. This lapse likely results from our limited awareness and understanding of the symptom. In this study we 1) defined the patients' experience of sensitivity to external stimuli in detail, and 2) tested two hypotheses regarding its origin.

First, we administered a lengthy questionnaire and in-depth interviews to adult Tourette patients (n=19) and age-matched healthy volunteers (n=19). Eighty percent of patients described a heightened sensitivity to external stimuli, with examples among all 5 sensory modalities. Bothersome stimuli were characterized as faint, repetitive or constant, and non-salient, whereas intense stimuli were well-tolerated.

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We then determined whether the sensitivity could be due to an increased ability to detect faint stimuli. After measuring the threshold of detection for olfactory and tactile stimuli among the patients and healthy volunteers, we found no significant difference for either sensory modality. These results indicate that patients' perceived sensitivity derives from altered central processing rather than from enhanced peripheral detection.

Lastly, we assessed one aspect of processing: the perception of intensity. When subjects rated the intensity of near-threshold tactile and olfactory stimuli, there was a surprising difference: Tourette patients more frequently used the lowest range of the scale compared with healthy volunteers. Future research is necessary to define the anatomical and physiological basis of the patients' experience of heightened sensitivity.

Keywords

Tourette syndrome; tic; sensory; threshold

Introduction

Although Tourette syndrome (TS) is classified as a movement disorder and defined by the persistent presence of motor and vocal tics, patients frequently describe a sensory disturbance which is equally, if not more, disruptive to their daily lives[1–3]. Disturbing sensations arise both within their bodies and from external sources. The uncomfortable bodily sensations were first described by Joseph Bliss as phenomena which precede motor tics.[4] Subsequent reports reveal that these are experienced by the majority of people with TS.[2, 5–8]

In addition to this increased awareness of internal sensations, people with TS also experience heightened sensitivity to external stimuli, the classic example of which is an intolerance of clothing tags. Cohen & Leckman[2] documented that 13/20 TS patients reported increased sensory sensitivity, with specific examples including bothersome clothing, lights, and sounds. These stimuli do not trigger motor tics, but are a constant source of irritation, discomfort, and distraction. Very little is known about this sensory sensitivity, and clinical and therapeutic approaches do not specifically address it.

Past research into the pathophysiology underlying TS has focused mostly on its motor aspects and on the basal ganglia as a system which regulates movement. The cortico-straital-thalamo-cortical (CSTC) circuit appears to play an important role in the symptom complex of TS.[9–11] Insight into the physiological basis for the sensory symptoms will likely enhance our understanding of the clinical syndrome and of how the CSTC circuit functions.

Here, we report investigations into the way external sensory stimuli are perceived and processed by patients with TS. We first sought to characterize the patients' subjective experience of sensitivity to external stimuli in detail. Three questions were addressed: 1) how universal is it among TS patients, 2) which of the five senses are involved, and 3) is the discomfort in response to faint stimuli, intense stimuli, or both?

We next investigated two mechanisms that could potentially underlie the patients' perceived sensitivity. First, we tested the hypothesis that TS patients have an increased ability to detect external stimuli. Second, we evaluated the hypothesis that faint stimuli are perceived as intense.

Methods

Subjects

The study was approved by the NINDS IRB. We recruited 19 adult subjects meeting DSM-IV criteria for TS and having at least a moderate sensory urge, (≥20 on the Premonitory Urge Tic Scale[12]) and 19 age-matched healthy volunteers (HVs; TS patients 36.2 ± 8.4 years, HVs 32.4 ± 8.3 years). Exclusion criteria for both groups included pregnancy, upper respiratory illness, peripheral neuropathy (and conditions that might cause it), and depression. Subjects with attention deficit hyperactivity disorder (ADHD) or obsessive compulsive disorder (OCD) were not excluded.

Written informed consent was obtained from all participants. TS subjects and HVs underwent a history and physical exam, including a lengthy interview regarding sensory experiences. TS patients also participated in a structured clinical interview for DSM-IV (SCID) and completed surveys to assess the severity of TS (YGTSS), symptoms of attention-deficit hyperactivity disorder, and symptoms of obsessive-compulsive disorder (Table 1). Six patients were classified as having mild TS due to the motor + vocal portion of the YGTSS being <20 (out of 50).[13] Ten patients had diagnoses or sub-clinical symptoms of OCD. Although the study was not powered to discern differences among these subgroups, exploratory analyses are included in the results.

Both groups completed a questionnaire about sensory stimuli that we adapted from one validated for use in adult autism patients.[14] It included 33 questions relating to all five senses, regarding subjects' perception of their sensitivity to faint and intense stimuli. For statistical analysis of survey responses, chi square tests were used for single questions, and Student's t-tests were used for categories that involved several questions, with significance set at $p < 0.01$.

Threshold measurements

In both TS patients and HVs we assessed the threshold of detection for olfactory and tactile stimuli, modalities most often cited by patients as giving rise to bothersome sensations. On the day of testing, subjects were asked not to chew gum, smoke, or use heavy scents. The olfactory threshold was detected using the validated instrument, "sniffin' sticks" (Burghart GmbH, Germany), which comprises a geometric series of 16 dilutions of n-butanol and control "sticks" containing water.[15] The threshold for detection was determined using a forced choice procedure and the method of limits.[16] While blindfolded, subjects were presented with pairs of "sticks" (odorant and control) in random order 10 seconds apart and asked to identify which of the two contained the test odor. After a 30 second interval, the next pair was presented. This interval has been shown to be adequate for the brain activity triggered by odorant exposure to return to the pre-stimulus baseline.[17] If the subject correctly identified the test odor twice, a lower concentration was presented until the test odor was incorrectly identified twice. This procedure was repeated 10 times. The average of the lowest concentrations to be correctly identified determined the threshold. The thresholds for all subjects within each group (TS or HV) were averaged using the stick number.[15, 18] Statistical significance was assessed using a Student's t-test and $p<0.01$.

Tactile thresholds were determined for two locations in each subject: 1) the distribution of the left peroneal nerve, 5 cm below the knee and 2) the region of the most active tic and sensory urge for each TS patient (matched one-for-one in HVs). The peroneal region, rarely the site of tics, was chosen to test the idea that TS patients have a generalized enhanced capability to detect tactile stimuli. The region of the tic was chosen to assess the possibility that there was a unique alteration of detection threshold in these areas.

To determine tactile thresholds, we used a geometric series of (Semmes Weinstein) VonFrey monofilaments, ranging from 2 to 0.008 grams. Paired presentations included an actual touch by the fiber and a sham with no contact. While blindfolded, subjects were asked to identify which was the touch. Again, sticks were numbered 1 to 16 for threshold averaging and a Student's t-test was used to assess statistical significance (set at $p<0.01$).

Intensity measurements

For the same populations, we evaluated their perception of intensity associated with faint stimuli using a graded labeled magnitude scale.[19] Subjects were instructed that the lowest rating (1) corresponded to a sensation that was barely detectable and that the highest rating (100) corresponded to the strongest sensation imaginable. We presented olfactory stimuli (n-butanol), and tactile stimuli (VonFrey fiber); the latter at both the lower leg and the tic site. While blindfolded, subjects were asked to rate the intensity of 7 successive stimuli of the series, the weakest being the threshold for each subject. The stimuli were presented four times in a different random order. The intensity scores for each of the 7 stimuli were averaged within both TS and HV groups. A Student's t-test was used to determine significance, $p<0.01$.

To determine the range of the scale used by the subjects within each group, we first identified the highest score given by each subject for those stimuli between 1 and 4 levels above threshold, for each stimulus type and location. We then calculated the skew of the distribution of high scores for each group, and the probability that it represented a significant deviation from a normal distribution ($p<0.01$).

Results

Tourette patients report heightened sensitivity to a variety of external stimuli

On the survey, 80% of TS patients indicated that, in general, they experienced heightened sensory sensitivity, compared to 35% of HVs ($X^2 = 8.286$, $p<0.01$, Figure 1A). Within the subgroup analysis, 67% of those patients with mild TS (n=6) and 90% of those with co-morbid OCD (n=10) reported heightened sensitivity. The percent TS subjects endorsing sensitivity to a specific modality was significantly higher than that of HVs for each modality except taste (Sound: TS 55%, HV 15%, $X^2 = 7.032$, $p<0.01$; Light: TS 60%, HV 15%, $X^2 = 8.640$, $p<0.01$; Smell: TS 70%, HV 25%, $X^2 = 8.120$, $p<0.01$; Taste: TS 50%, HV 15%, $X^2 = 5.584$, $p<0.02$, Touch: TS 65%, HV 25%, $X^2 = 6.465$, $p<0.01$).

Responses to specific scenarios revealed that TS patients experience sensitivity to faint stimuli but not to intense stimuli: a pattern which was consistent among all modalities. This difference was statistically significant for questions regarding tactile stimuli (TS 65%, HV 35%, $p<0.01$; Figure 1B). During in-depth interviews, each patient described specific stimuli within a few sensory modalities that were particularly bothersome. Examples of tactile stimuli were nearly ubiquitous. Most patients described irritating aspects of clothing: the rough texture of fabrics or the constant pressure exerted by a shirt collar or a waistband. Many were also bothered by the pressure of the chair or another person's arm draped over them. Several patients could not tolerate sticky substances on their skin. All regions of the body were sensitive, including head/neck, trunk, and extremities. Sensitivity to provocative odors, such as body odor, spoiled food, or mold was frequently described, as was an increased ability to hear faint or far-away sounds. With regard to intense stimuli, patients described a preference for strong tactile stimuli such as massage or having their skin scratched. Several patients described engaging in activities that produce a near-painful sensation, such as pushing the skin back from under the fingernail.

In summary, TS subjects described a heightened sensitivity to repetitive (or constant), non-salient, faint stimuli among all sensory modalities. They did not object to intense stimuli within any modality, and appeared to prefer intense tactile sensations.

TS and HV subjects did not differ significantly in their thresholds of detection

For olfactory stimuli, the average detection threshold for TS subjects was 8.78 ± 1.24 and for HV subjects was 9.23 ± 2.06 (Figure 2). This did not represent a significant difference (p=0.43) and was consistent with published values for healthy volunteers. [18, 20] Thresholds for mild TS patients (9.03 ± 1.22) and moderate/severe TS patients (8.69 ± 1.29) were not significantly different (p=0.29) and there was no correlation between YGTSS score and threshold (R^2 = 0.01, data not shown). Likewise, there was no significant difference in threshold between patients with OCD (8.89 ± 1.12) and those with no OCD (8.68 ± 1.41, p=0.72, data not shown).

Measurements of the tactile threshold at the lower leg revealed that the average detection threshold for TS subjects was 15.11 ± 1.13 and for HV subjects was 14.33 ± 1.61. This difference did not reach statistical significance (p=0.05). The tactile thresholds at this site were not significantly different among subgroups: mild TS =15.57 ± 0.53 vs. moderate/severe TS = 14.92 ± 1.26, p=0.29; TS + OCD = 15.42 ± 0.69 vs. TS only = 14.79 ± 1.41, p = 0.24 (data not shown).

We also assessed the tactile threshold at the site of an active tic, which for TS subjects was 15.45 ± 0.63 and in matched regions for HVs was 15.64 ± 0.57 (p=0.16). The tactile thresholds at the urge site were not significantly different among subgroups: mild TS = 15.43 ± 0.81 vs. moderate/severe TS = 15.46 ± 0.59, p=0.93; TS + OCD = 15.39 ± 0.79 vs. TS only = 15.52 ± 0.45, p=0.67 (data not shown).

In a separate group of subjects (TS=9, HV=10), audiometry testing demonstrated no significant difference in auditory thresholds at 7 distinct frequencies between 250 and 8000 Hz (p>0.25 for each, data not shown).

TS patients used lower intensity ratings to describe faint stimuli compared with HVs

We calculated the average intensity score for each group (TS or HV) for each of the 7 different stimulus strengths within each modality. In none of the pair-wise comparisons (TS vs HV) was there a statistically significant difference. Representative data are therefore given for two stimulus levels: one level above threshold (T+1) and four levels above threshold (T+4, Figure 3A). For T+1 olfactory stimuli, TS patients gave an average intensity rating of 9.0 ± 7.9, and HV subjects gave an average rating of 8.9 ± 7.6 (p=0.97). For T+4 olfactory stimuli the average intensity scores were: TS 27.3 ± 23.7, HV 35.9 ± 28.6 (p=0.34). For tactile stimuli at the leg, average intensity ratings for T+1 were: TS 6.0 ± 10.4, HV 7.2 ± 7.6 (p=0.70) and for T+4 stimuli were: TS 9.4 ± 11.5, HV 16.4 ± 14.1 (p=0.10). For T+1 tactile stimuli at the urge site, the average intensity scores were: TS 6.4 ± 8.5, HV 6.4 ± 5.6 (p=0.98). For T+4 tactile stimuli at the urge site, the average scores were: TS 12.8 ± 16.6, HV 18.8 ± 18.7 (p=0.30). For stimuli of increasing strength, there was a non-significant trend for average intensity scores to be lower among TS subjects than among HVs.

We performed a second analysis to determine whether TS patients used a different range of the scale than did HVs. The set of highest intensity scores given by subjects within each group (TS or HV) was assessed for its skew from a normal distribution. For tactile stimuli at both locations, the distribution of scores for TS patients was skewed toward the lower end of the scale, which was significantly different from a normal distribution (at lower leg: skew 2.38, p<0.0001, at urge site: skew 2.79, p<0.0001). Scores of HVs were slightly skewed as

well, but this did not represent a statistically significant difference from a normal distribution (at lower leg: skew 1.13, p=0.02, at urge site: skew 0.79, p=0.08, Figure 3B). For olfactory stimuli, the scores for neither group were significantly skewed (TS skew: 0.57, p=0.16, HV skew: 0.73, p=0.10).

Discussion

This study reveals that the vast majority of TS patients perceive themselves to have a heightened sensitivity to external stimuli among all sensory modalities. This finding could potentially impact both the clinical and scientific approaches to TS. Clinically, Tourette syndrome has been defined by motor phenomena and identified as encompassing a symptom complex that includes ADHD, OCD, anxiety, mood disorders, and learning disabilities.[21–26] However, the presence of a sensory disturbance has not been recognized as an important or distinct element of the syndrome. Due to the substantial negative impact on quality of life produced by the sensory sensitivity, the fact that it is so pervasive underscores the importance of addressing this symptom both in the clinical setting and as part of the research effort.

The limitations of this study include the relatively small number of patients recruited. Given the robust nature of our results, however, both with respect to the patients' subjective experience of sensory sensitivity and to the lack of difference in threshold detection, we expect that the conclusions reflect the broader population. Second, because we evaluated the threshold and intensity responses for olfactory and tactile stimuli, we cannot be certain that sensitivity among other modalities occurs as a result of the same underlying mechanism. Finally, we included TS patients with co-morbid ADHD and OCD and, given the sample size, cannot determine the extent to which these disorders contribute independently to the findings. It has been hypothesized that these disorders co-occur as a result of a common pathophysiology, but further research is necessary to clarify the sensory processing mechanisms in each.

The physiology underlying the sensory experiences of TS patients has been a matter of debate. Some experts suggest that the urge sensation may be initiated by sensory input from muscles or other bodily tissues, to which the tic is a voluntary response, just as one scratches an itch.[8, 27] Others postulate that the pre-tic sensation is the result of altered basal ganglia physiology that can manifest as both sensory and motor symptoms.[1, 5, 9] Still others hypothesize that the urge sensation emanates from the motor systems generating the tic, representing a projection backwards in time.[7, 28]

Patients' sensitivity to external stimuli has generally not been addressed by these hypotheses. The specific characteristics of the bothersome stimuli, as defined in this study, provide a framework for understanding the relationship between the sensitivity to external stimuli and the pre-tic urge sensations. In both cases, the offending stimuli can be described as faint, repetitive, and non-salient: Published descriptions of the pre-tic sensations include an itch, (muscle) tension, a fullness or pressure[2, 8] and a "hyperawareness of what [the patient's] skin, muscles, and joints feels like."[3]

Normal sensory perception depends on peripheral receptor neurons translating a physical stimulus into neuronal activity and several layers of processing by the central nervous system. Our finding that TS patients did not have an enhanced ability to detect faint stimuli suggests that the experience of heightened sensitivity arises from alterations in central processing, consistent with the understanding that TS is a disorder of the central nervous system. There is general consensus that the syndrome is due to pathology within the basal ganglia and the associated cortico-striatal-thalamo-cortical (CSTC) circuit.[9, 10, 26] However,

which of the many functions of this circuit is disrupted, thereby producing symptoms, is not known. One hypothesis is that tics represent dysfunctional habit formation,[11, 29] although it is unclear how the sensory symptoms fit in with this concept.

Another hypothesis is that TS may result from disrupted sensory gating or filtration by the CSTC circuit.[24, 30–32] This view would explain the heightened sensitivity to both external and internal stimuli and could also account for the observation that bothersome stimuli are faint, repetitive, and non-salient since such stimuli are normally filtered out. Refinement of the hypothesis would be necessary, however, to explain other aspects of the sensory sensitivity. For example, patients are sensitive only to certain stimuli within each modality, and they do not describe simply an increased awareness of faint stimuli, but an associated discomfort.

We tested the idea that faint stimuli may be bothersome due to a perception of increased intensity associated with them. Our finding that TS patients' intensity ratings were skewed toward the low end of the scale was contrary to this hypothesis, but is consistent with the patients' subjective reports that perceived intensity does not generate discomfort. In fact, given that many patients enjoy intense tactile stimuli, it is possible that the lack of perceived intensity is a factor in rendering faint stimuli bothersome. Further investigation is required to elucidate the pathophysiology underlying these sensory experiences.

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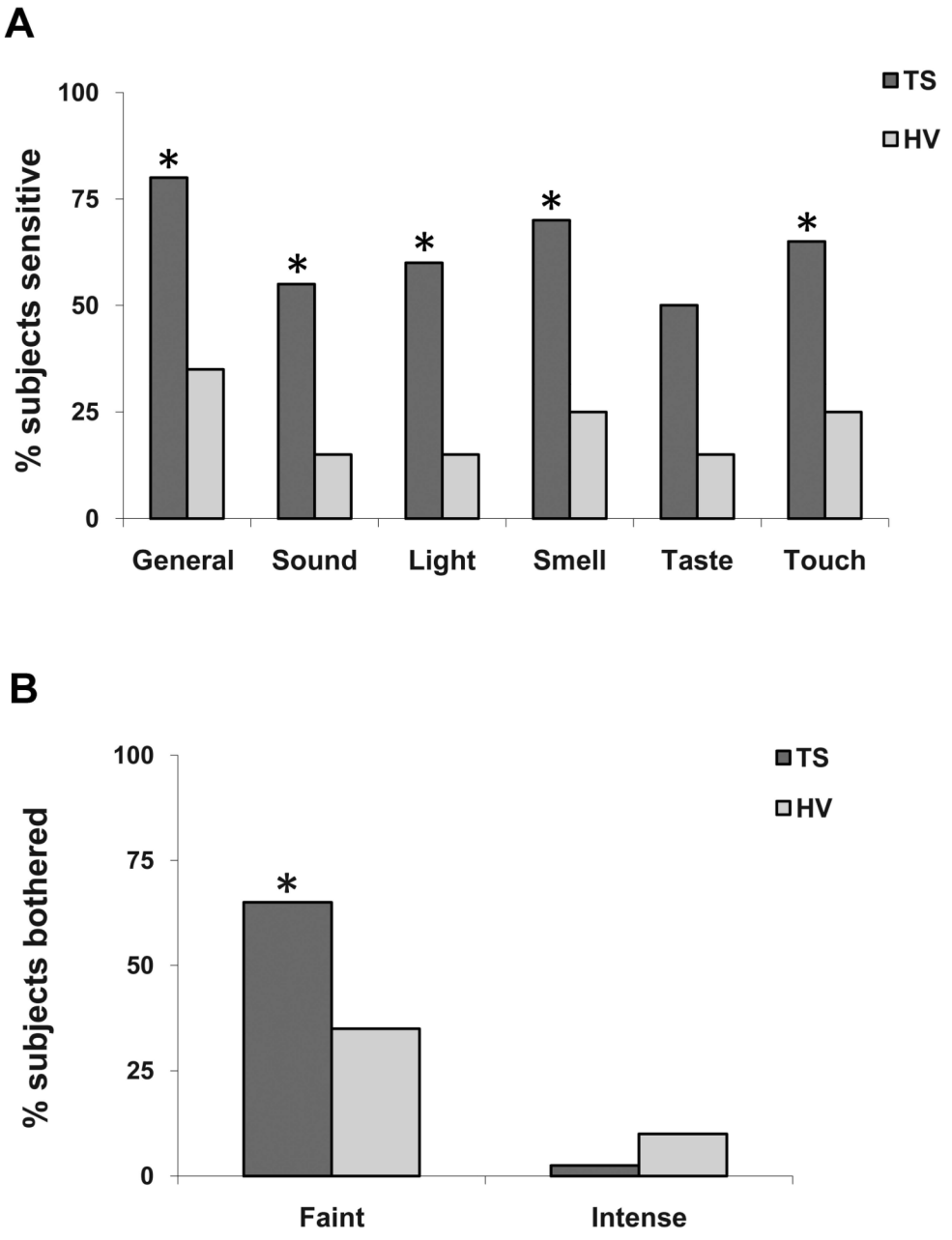

Figure 1. Subjective report of sensitivity to external stimuli

A. Responses to single questions asking if the subject had a heightened sensitivity to external stimuli in general, or sensitivity to specific sensory modalities. Statistically significant differences ($p<0.01$) between TS patients and HVs are indicated by an asterisk. **B.** Responses to questions describing specific scenarios involving tactile stimuli. This pattern of enhanced sensitivity to faint stimuli but not to intense stimuli among TS patients was similar for all sensory modalities.

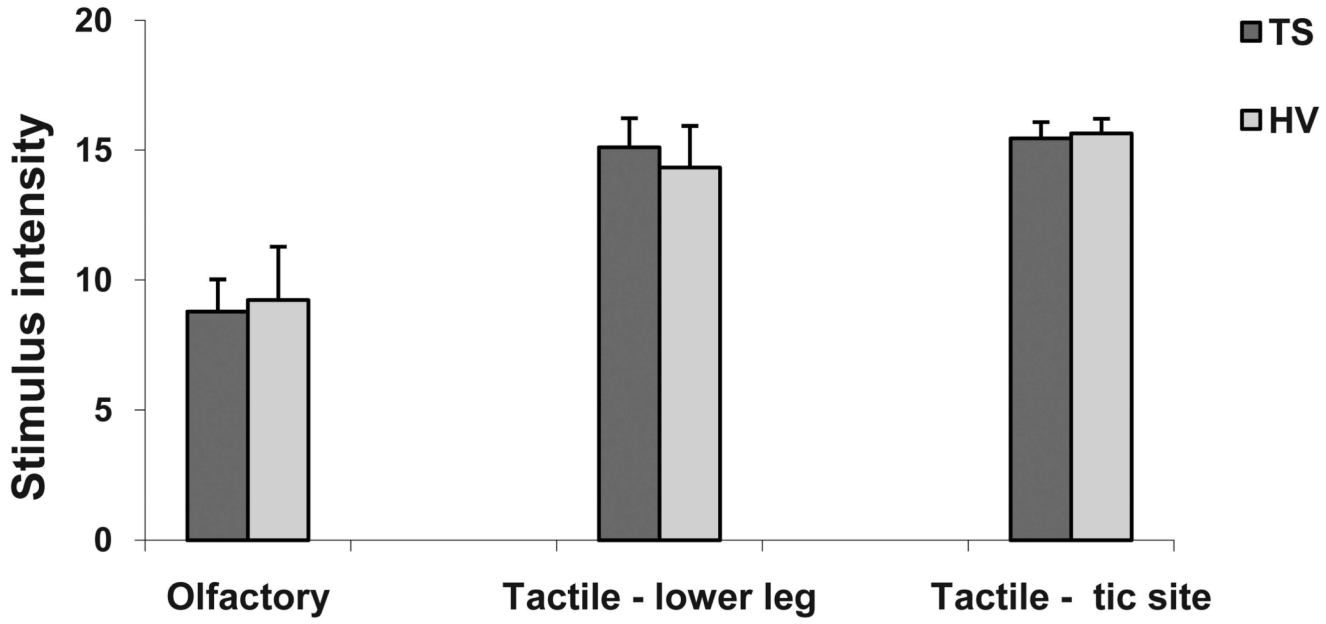

Figure 2. Thresholds of detection for olfactory and tactile stimuli

Tactile stimuli were presented both to the lower leg, and to the site of an active tic in each TS patient, matched 1:1 in HVs. Stimulus strength number corresponds to its order within the geometric series: a higher value represents a weaker stimulus. There was no significant difference between the thresholds for TS patients and HVs ($p>0.01$) Error bars indicate SD.

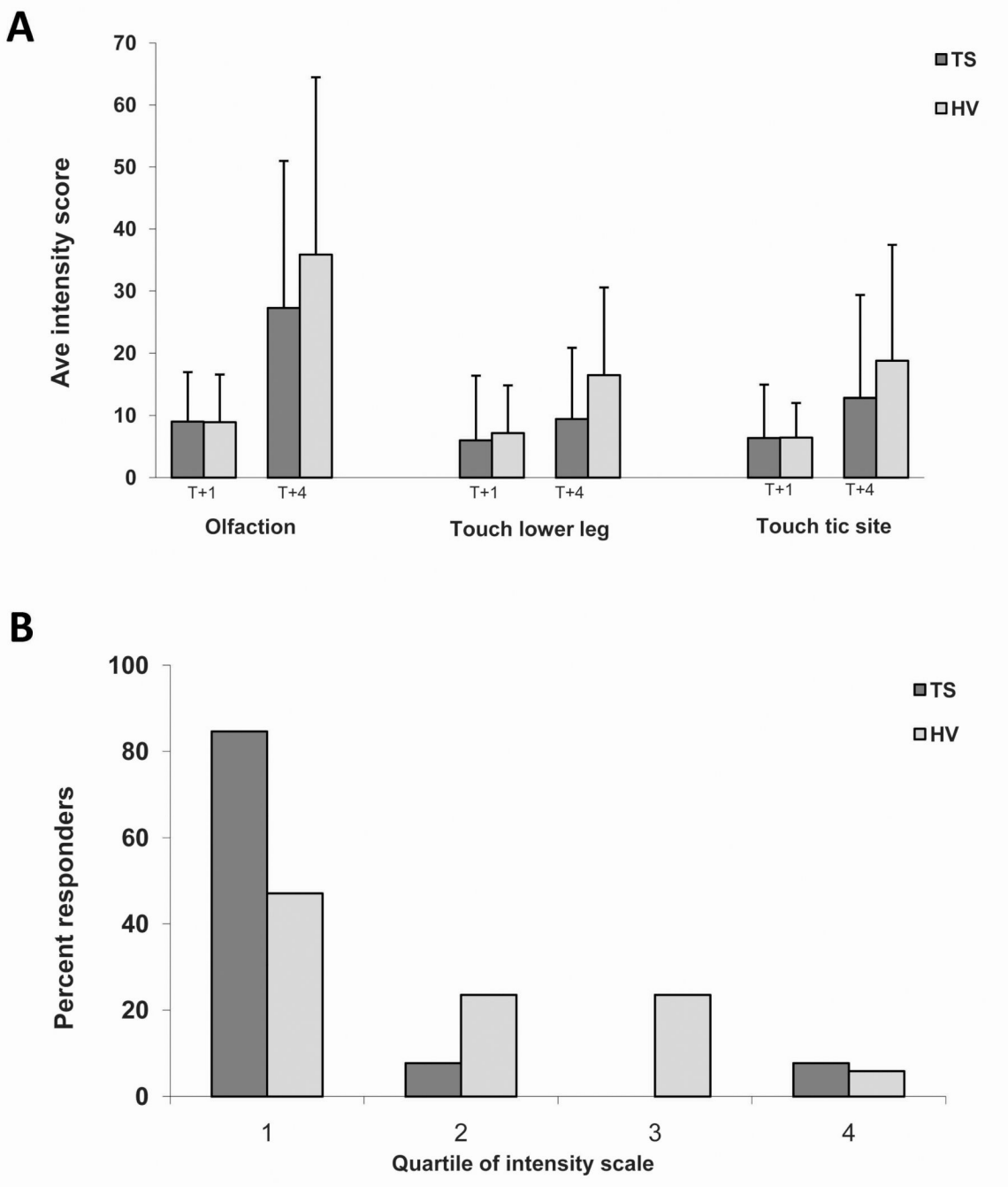

Figure 3. Subjective intensity ratings of near-threshold stimuli

A. The average scores for stimuli one level above threshold (T+1) and four levels above threshold (T+4) are shown. There was no significant difference between TS and HV groups ($p>0.01$). Error bars indicate SD. **B.** The distribution of high scores in each group is plotted for tactile stimuli at the tic site. Quartiles of the intensity scale are: 1=0–25, 2=26–50, 3=51–75, 4=76–100. Note that, in contrast to HVs' scores, the TS patients' scores were significantly skewed toward the low end of the scale ($p<0.0001$).

Table 1

Patient Baseline Characteristics

YGTSS, Yale Global Tic Severity Score; PUTS, Premonitory urge tic scale; Meds, Medications taken by the patient prior to the study, withheld for at least 48 hours; ADHD was a known diagnosis in 6, with 11 others endorsing symptoms by survey; OCD based on SCID with “subclinical” indicating symptoms present that did not meet DSM-IV criteria; N/A, information not available.

Pt #	Age	Sex	Handedness	Motor YGTSS	PUTS	Meds	ADHD	OCD
1	30	Male	Right	21	26	None	Yes	No
2	45	Male	Right	25	24	Klonopin	No	No
3	31	Male	Right	N/A	26	None	N/A	No
4	24	Male	Right	16	23	None	Yes	Yes
5	50	Female	Right	22	34	None	N/A	No
6	38	Male	Right	17	25	None	Yes	Yes
7	33	Male	Left	17	32	None	No	Yes
8	30	Male	Right	14	34	None	Yes	Yes
9	37	Male	Right	22	22	Provigil, Mirapex	Yes	No
10	34	Female	Right	27	28	None	Yes	sub-clinical
11	33	Male	Right	31	35	Risperdal, Zoloft	Yes	Yes
12	36	Male	Right	20	30	None	Yes	No
13	46	Male	Right	19	25	Lexapro	Yes	Yes
14	39	Male	Right	22	24	Klonopin	Yes	sub-clinical
15	45	Male	Left	23	36	None	Yes	sub-clinical
16	47	Male	Right	18	28	None	No	No
17	24	Male	Right	34	35	None	No	Yes
18	23	Female	Right	25	30	orap	N/A	N/A
19	45	Male	Right	27	31	Adderall	No	No