J Autism Dev Disord (2017) 47:1183–1192
DOI 10.1007/s10803-017-3041-4

ORIGINAL PAPER

Quantitative Sensory Testing in adults with Autism Spectrum Disorders

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Published online: 3 February 2017

Abstract Altered sensory perception has been found in patients with autism spectrum disorders (ASD) and might be related to aberrant sensory perception thresholds. We used the well-established, standardized Quantitative sensory testing (QST) protocol of the German Research Network on Neuropathic Pain to investigate 13 somatosensory parameters including thermal and tactile detection and pain thresholds in 13 ASD adults and 13 matched healthy controls with normal IQ values. There were no group differences between somatosensory detection and pain thresholds. Two ASD patients showed paradoxical heat sensations and another two ASD subjects presented dynamic mechanical allodynia; somatosensory features that were absent in controls. These findings suggest that central mechanisms during complex stimulus integration rather than peripheral dysfunctions probably determine somatosensory alterations in ASD.

Keywords Autism · Quantitative sensory testing · Sensory thresholds · Hyposensitivity · Hypersensitivity

Introduction

Altered sensory perception is a central clinical finding in patients with autism spectrum disorders (ASD; for reviews see (Baum et al. 2015; Elwin et al. 2012; Marco et al. 2011; Moore 2015)). Up to 96% of (pediatric) patients with ASD report hyper- or hyposensitivity regarding visual, auditory, tactile (Marco et al. 2011) and olfactory stilmuli (Tonacci et al. 2017). However, the existence of unusual sensory perception in ASD was only recently re-incorporated into the new DSM-5 diagnostic criteria for ASD (APA 2013) and have long been under-appreciated (Duerden et al. 2015).

Current literature highlights the integral role of intact lower level unisensory perception for higher order functions such as multisensory integration (for review see (Baum et al. 2015)). Somatosensory perception, e.g., perception of touch or vibration on the skin, seems to be a commonly affected sensory processing domain in ASD patients (Marco et al. 2011). Autobiographical reports (for review see (Elwin et al. 2012)) reveal that many ASD patients experience sensory peculiarities such as aversions of being touched or hugged while experiencing relaxation and relief from tight pressure (Grandin 1995; Cesaroni and Garber 1991).

Odette Fründt and Wiebke Grashorn have contributed equally to the work.

Electronic supplementary material The online version of this article (doi:10.1007/s10803-017-3041-4) contains supplementary material, which is available to authorized users.

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Others provided information on patients with an intense interest in surface textures or the ability to really see and understand things by touching them (Grandin 1995). In the DSM-5 criteria hyper- as well as hypo-reactivity to sensory input or unusual interest in sensory aspects of the environment are mentioned, including many somatosensory peculiarities such as "apparent indifference to pain/temperature, adverse response to specific […] textures, excessive […] touching of objects" (APA 2013). Research on somatosensory perception in ASD has for a long time almost exclusively relied on autobiographical, observational or behavioral measures. Only recently a few studies have started to disentangle the underlying mechanisms of somatosensory dysfunctions in ASD patients using various experimental approaches. There is still no gold standard how somatosensory features in individuals with ASD should be assessed. Previous investigations of somatosensory perception in ASD focusing on sensory detection and pain thresholds yielded mixed results (for reviews see (Baum et al. 2015; Marco et al. 2011; Baron-Cohen et al. 2009)): Regarding vibro-tactile perception, previous findings range from normal perception (Guclu et al. 2007) to raised static vibro-tactile detection thresholds (Tavassoli et al. 2015; Puts et al. 2014) and poorer vibro-tactile amplitude discrimination in children with ASD (Puts et al. 2014). Also in adults contradictory findings ranging from normal vibro-tactile thresholds (Cascio et al. 2008) to vibro-tactile hypersensitivity (Blakemore et al. 2006) were observed. Detection of touch was similar between ASD and healthy adults (Cascio et al. 2008). In children, an increased touch sensitivity (Riquelme et al. 2016) but normal detection discrimination (O'Riordan and Passetti 2006) has been found. Regarding pain perception (for review see (Moore 2015)) paradoxical heat sensations (i.e., gentle cooling is perceived as hot or burning (Magerl and Klein 2006)) occurred in a few ASD adolescents (Duerden et al. 2015). Thermal pain hypersensitivity but normal threshold detection for innocuous thermal stimuli have been found in ASD adults (Cascio et al. 2008) whereas ASD adolescents showed normal thermal pain thresholds, but a hyposensitivity to innocuous thermal stimuli (Duerden et al. 2015). In ASD adolescents/adults normal pain detection thresholds during thermal and electrical stimulation were observed (Yasuda et al. 2016; Bird et al. 2010) whereas pressure pain (Fan et al. 2014) thresholds were lower. The latter finding could also be confirmed in ASD children (Riquelme et al. 2016).

In summary, previous studies on somatosensory perception in ASD have yielded mixed results probably due to heterogeneity of participants (e.g. regarding age, ASD symptom severity, comorbidities), the small sample sizes and differences regarding methods and tactile modalities. In addition, most studies only focused on single somatosensory submodalities (e.g. either vibro-tactile, pain or thermal sensitivity).

Here, we used the standardized "Quantitative Sensory Testing" (QST) protocol developed by the German Research Network on Neuropathic Pain (Deutscher Forschungsverbund Neuropathischer Schmerz, DFNS) to assess responses to a battery of 13 somatosensory stimuli (Rolke et al. 2006) in a relatively homogeneous sample of 13 well-characterized, high-functioning ASD participants. Our goal was to obtain potentially disease-specific sensory profiles and compare them to 13 age- and gender-matched healthy subjects. We further aimed at exploring the relationship between potential sensory processing peculiarities and ASD symptom severity.

Methods

Participants

ASD participants were assessed in the outpatient clinic in the Department of Neurology, University Medical Center Hamburg-Eppendorf, Germany. Initially, 16 adult patients (>18 years) with suspected ASD were assessed in an extensive psychiatric interview (D.S.) using the DSM IV criteria ("Diagnostic and Statistical Manual of Mental Disorders, Text Revision"– DSM-IV-TR" (American Psychiatric Association 2000)) and a standard neurologic interview and examination (O.F. and A.M.). When possible, third party medical histories and previous medical records were obtained. ASD participants with the diagnostic categories 299.00 and 299.80 with IQ values > 70 were included. Out of the 16 patients, one was excluded because expected ASD was not confirmed. One patient was excluded because she worked as a dominatrix (an employment associated with regular pain experiences), another patient was excluded because of chronic pain due to ulcerative colitis, two conditions that might alter sensory perception and influence test results. Thus, 13 ASD patients were included in the study and matched with 13 healthy subjects (i.e., without neurologic or psychiatric comorbidities) who were recruited through advertisement. None of the female participants was pregnant. The healthy controls did not take any medication besides contraceptives (2 subjects). None of the participants suffered from a chronic pain disease, had acute pain or had taken any analgesic medication within 24 h prior to the study. Only participants with normal IQ values >70 were included (for IQ testing see below).

The study was approved by the local ethics committee and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all

study participants who were told they were free to withdraw from the study at any time.

Questionnaires and Quantitative Sensory Testing (QST)

All questionnaires were completed by both groups. The Autism Quotient (cut-off 32+ (Baron-Cohen et al. 2006)), the Empathy Quotient (cut-off <30 (Baron-Cohen and Wheelwright 2004)) and the Systemizing Quotient (Baron-Cohen et al. 2003) were used to quantify autistic trait severity. The German Multiple Word Test (MWT-B; (Lehrl 2005)) was used to calculate individual verbal IQ levels. To assess the influence of depression on our results all participants completed the Beck Depression Inventory (BDI, (Beck et al. 1961)).

QST, a subjective psychophysical method, was performed using an established protocol and the standard equipment according to the German Research Network on Neuropathic Pain (Deutscher Forschungsverbund Neuropathischer Schmerz, DFNS) (Rolke et al. 2006). All QST experimenters (O.F., W.G.) were trained to perform QST by the DFNS and our lab acquired the QST certificate (Certkom e.V.; http://www.certkom.com/). All subjects were investigated on the dorsal surfaces of the left and right hand. Thirteen QST parameters were determined: cold and warm detection thresholds, thermal sensory limen (i.e., perception of changing temperatures from warm to cold and vice versa), paradoxical heat sensations (i.e., participants experienced cold as heat; PHS), cold and heat pain thresholds, mechanical detection (MDT) and mechanical pain thresholds, mechanical pain sensitivity (sensitivity to pinprick stimuli), pressure pain threshold, vibration detection thresholds, dynamic mechanical allodynia (i.e., experience of pain during non-painful gentle and moving tactile stimulation; DMA) and the wind-up ratio (temporal pain summation = ratio of pain ratings of a series of painful stimuli / pain ratings of a single painful stimulus). The room temperature was kept between 20 and 25 °C. For a detailed description of the QST procedure please see our supplementary material.

Statistical Analyses

Statistical analyses were performed using the Equista software provided by the DFNS (http://www.neuro.med.tu-muenchen.de/dfns/arzt/qstform.html) and using IBM SPSS software version 20.0 (http://www-01.ibm.com/software/analytics/spss/). As described in a previous study (Schunke et al. 2016), raw values of both groups were log-transformed using Equista to establish normal distribution and mapped onto the distribution of the DFNS reference group (Rolke et al. 2006; Magerl et al. 2010), consisting of 180 healthy subjects, using z transformation ($z\text{-score}_{Participant} = ((QST_{Participant} - QST_{Reference})/\text{standard deviation}_{Reference})$). This method assured comparability of QST results as z scores were adjusted to sex, age and tested body site of the published reference group (Rolke et al. 2006; Magerl et al. 2010). Initially, z scores of the left and right hand were calculated separately and were compared with each other. Finally, the mean z scores of both hands (z mean = mean ($z_{left} + z_{right}$) were used for further analyses. A z score >0 indicated high (gain of function) and a z-score <0 low (loss of function) sensitivity to the external stimulus applied. Z scores exceeding 95% of the confidence interval of the reference group (±1.96 standard deviation (SD)) are considered as pathologic/aberrant (Rolke et al. 2006; Mucke et al. 2014). Paradoxical heat sensations (= experiencing a warm, hot or painfully hot sensation in response to the cold stimulation (Rolke et al. 2010; Magerl and Klein 2006)) and allodynia (= a pain sensation is elicited by gentle non-painful, moving, tactile stimuli (Magerl and Klein 2006)) were analyzed separately as they only occurred in ASD patients but not healthy subjects.

For between group analyses, mean z scores were compared between ASD patients and the control group using parametric Student´s t test. Furthermore, group mean z scores and—for exploratory purposes—individual z scores were compared with the published reference data (Rolke et al. 2006; Magerl et al. 2010) and analyzed with regard to certain neurobiological (topodiagnostic) mechanisms assessing, for example, the function of different types of nerve fibers (e.g. A delta, A beta or C fibers) or more central mechanisms such as sensitization (Mucke et al. 2014). Group comparisons of questionnaire results were analyzed using parametric (t test) and non-parametric (Mann–Whitney-U test) tests. Finally, z scores were correlated with questionnaire scores (IQ, AQ, EQ, SQ and BDI).

Results

13 ASD patients (mean age 31.7 ± SD 8.2 years) and 13 healthy control subjects (32.1 ± 7.1 years) matched by age ($t\ (24) = 0.396$, $p = 0.90$) and gender (each group: 6 female, $\chi^2 = 1{,}0$) were included in the study. Characteristics and questionnaire results of ASD patients and healthy subjects are given in Table 1. As expected, ASD participants scored significantly higher in ASD specific questionnaires.

There was no body side difference between z scores of the left and right hand in both groups (all p values >0.05) in the 11 QST parameters analyzed (apart from DMA and PHS which did not occur in healthy subjects). In one ASD patient we could not calculate the wind-up ratio because despite using the predefined pinprick (256 Nm) no feeling of pain was reported (as required by the DFNS protocol).

Table 1 Clinical characteristics and questionnaire results of patients with autism and healthy subjects

Characteristic	Patients with autism (mean ± standard deviation, [minimum − maximum])	Healthy subjects (mean ± standard deviation, [minimum − maximum])	Statistics (p value or chi square)
No of subjects	13	13	–
Age	31.7 ± SD 8.2 years [21–45]	32.1 ± SD 7.1 years [23–46]	p = 0.900
Gender	6 female, 7 male	6 female, 7 male	$\chi^2 = 1.000$
Comorbidities	4 patients: 1. Depression only 2. Depression & anxiety 3. Depression & tics 4. Depression & ADHD	none	–
Neuropsychiatric medication	2 patients: 1. Opipramol 2. Quetiapine & Moclobemide	No neuropsychiatric medication	–
Verbal IQ	111.6 ± 16.0 [94–143]*	110.2 ± 17.3 [95–145]	p = 1.000 (MWU)
Autism Quotient (AQ)	38.5 ± 9.4 [16–49]*	16.3 ± 6.3 [9–28]*	**p < 0.001** (MWU)
Empathy Quotient (EQ)	22.8 ± 12.7 [6–47]*	43.3 ± 10.0 [25–58]*	**p < 0.001**
Systemizing Quotient (SQ)	39.3 ± 16.8 [11–70]**	28.3 ± 9.5 [10–40]*	**p = 0.032** (MWU)
Beck depression inventory (BDI)	10.5 ± 8.6 [1–24]*	4.7 ± 4.6 [0–15]*	p = 0.054[#]

Characteristics and results of questionnaires of patients with autism (middle left) and healthy subjects (middle right). *n* number of patients

Significant results are marked in bold

Mann–Whitney-U test (MWU) was used in case of non-normal distributions

*Data of 1 participant is missing

**Data of 2 participants are missing

[#]t test corrected for unequal variances

Group comparisons of single QST parameters' mean z scores revealed a significant difference for the mechanical detection threshold (MDT, *t (24)* = 2.650; p = 0.014) with a greater loss of function for mechanical detection in ASD patients that, nevertheless, did not survive Bonferroni correction ($p_{Bonferroni} = 0.05/11 = 0.004$; the same was true for the less conservative Bonferroni–Holm method). Furthermore, mean MDT z scores of both groups ranged within ± 1.96 SD of the DFNS reference group (see Fig. 1).

All other QST parameters did not differ significantly between groups either before or after Bonferroni correction for multiple testing (all p > 0.15; see Fig. 1; Table 2). No specific, pathologic QST pattern pointing towards a certain neurobiologic mechanism such as peripheral nerve fiber dysfunction or peripheral/central sensitization (Mucke et al. 2014) was found for either the ASD group or the control group.

Regarding explorative individual analyses of MDT z scores (see Fig. 2), there was an outlier with an exceptionally low MDT z score (MDT = −3.99). Excluding this outlier from the analysis still revealed a significant group difference (*t (23)* = 2.552; p = 0.018), which again did not survive Bonferroni correction. In sum, we observed an overall larger variance of z scores (see Fig. 2) in the ASD group with more z scores outside the 95% confidence interval of the reference data in the ASD (n = 28, allocated to ten out of the 13 ASD patients and pertaining to all somatosensory thresholds measured here) as compared to the control group (n = 6, allocated to six out of the 13 control subject). Thus, after Bonferroni correction there was only a significant difference in z-score variance for the pressure pain threshold (F = 18.137, p < 0.001).

Furthermore, four patients (30.8%) showed sensory distinctive features: two ASD patients (= 15.4%, one with depression only and one with depression and tics) showed paradoxical heat sensations (= experiencing a warm, hot or painfully hot sensation in response to the cold stimulation) that usually do not occur in healthy subjects (Magerl et al. 2010; Rolke et al. 2006) and another two ASD patients (= 15.4%, one with depression and anxiety, one without comorbidities) felt allodynia to non-painful stimuli (no overlap). However, T-tests of the raw values corrected for unequal variances revealed no significant group differences for either paradoxical heat sensations (*t (13.0)* = *−1.439*, p = 0.174) nor dynamic mechanical allodynia (*t (13.0)* = *−1.465*, p = 0.167).

In the ASD group, questionnaire scores of IQ, AQ, EQ, SQ and BDI did not correlate with any of the QST

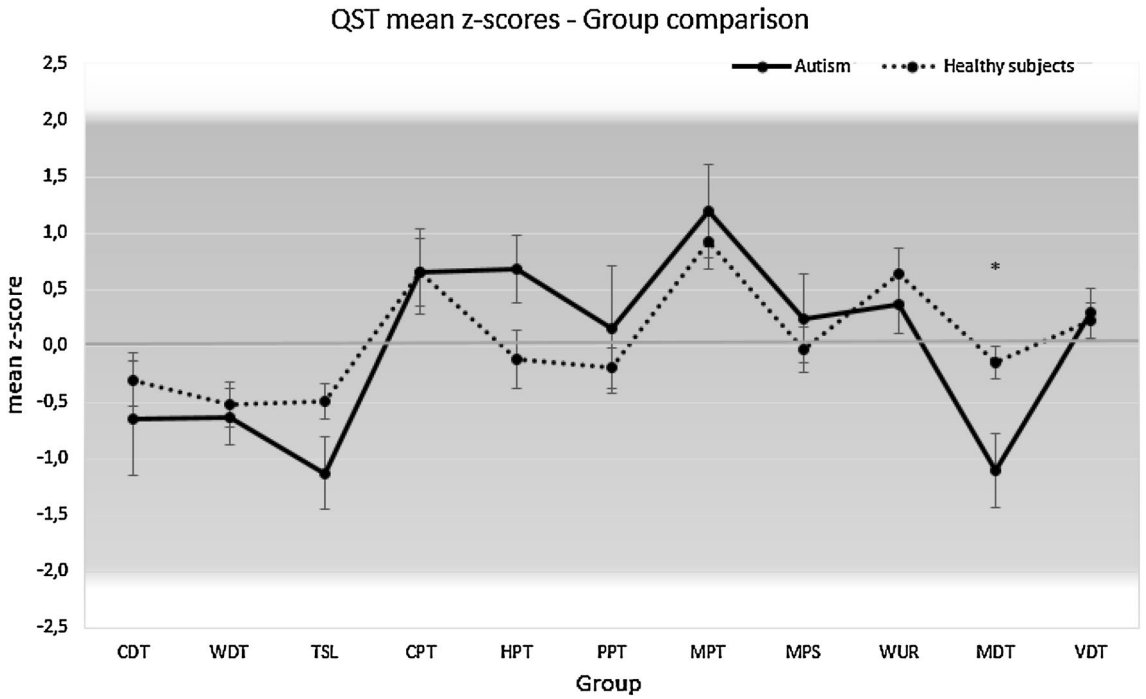

Fig. 1 Group comparison results of Quantitative sensory testing (QST). Results of quantitative sensory testing are given as mean z scores of autism patients (*solid line*) and healthy subjects (*dotted line*) including standard error of means (SEM). Baseline (z = 0) and the *grey area* represents the 95% confidence interval of the DFNS reference group. Abbreviations: *CDT* cold detection threshold, *WDT* warm detection threshold, *TSL* thermal sensory limen, *CPT* cold pain threshold, *HPT* heat pain threshold, *PPT* pressure pain threshold, *MPT* mechanical pain threshold, *MPS* mechanical pain sensitivity, *WUR* wind-up ratio (data of one patient missing), *MDT* mechanical detection threshold, *VDT* vibration detection threshold. Allodynia and paradoxical heat sensation were calculated separately. *Significant group difference (uncorrected for multiple testing)

parameters (all $p > 0.1$). As expected, the AQ and EQ scores as well as EQ and SQ scores correlated significantly with each other (all $p \leq 0.001$) even after Bonferroni correction whereas there was only a trend for AQ and SQ ($p = 0.006$).

Discussion

This study investigated somatosensory perception of patients with ASD to assess the hypothesis that altered thresholds for externally applied somatosensory stimuli contribute to unusual sensory perception in ASD. To this end, the standardized QST experimental test battery quantifying 13 relevant somatosensory thresholds was used in a sample of 13 ASD adults and 13 healthy control subjects matched by age and gender. Although we did find group differences for mechanical detection thresholds (MDT) in direct group comparison with a loss of A-beta-fiber (Grone et al. 2012) function in ASD participants, these did not survive correction and mean MDT z scores were within the range of the DFNS reference data (Rolke et al. 2006; Magerl et al. 2010). Thus, the isolated MDT difference in conjunction with normal z scores for other clinically related QST parameters—especially normal and comparable vibration detection thresholds in both groups also representing A-beta-fiber function (Grone et al. 2012; Hoitsma et al. 2004)—should not be interpreted as a pathological finding. In neither of the groups did we observe a consistent, pathologic QST pattern suggesting a defined neurobiological (topodiagnostic) mechanism (e.g. peripheral nerve fiber dysfunction or peripheral/central sensitization (Mucke et al. 2014)).

This notwithstanding, individual analyses revealed a greater inter-individual variance with more occasional QST z scores outside the 95% confidence interval of the DFNS reference group in the ASD (n = 28) compared to the control group (n = 6, see Fig. 2). This variance, although it was only statistically significant for a few QST parameters (see results), was present in all QST parameters by trend and was not driven by single participants. Interestingly, greater variability in ASD participants has also been found in previous studies (e.g. subtests of IQ scores revealed a greater variability in ASD than would be expected by chance (Siegel et al. 1996). This might be explained by the general heterogeneity of ASD participants. Others studies

Table 2 Group comparison of quantitative sensory testing (QST) z scores

Parameter (Mean ± Standard Deviation)	Patients with autism	Healthy subjects	Statistics (uncorrected p value)
QST parameters (z scores)			
Cold detection threshold (CDT)	−0.64 ± SD 1.85	−0.30 ± SD 0.85	0.550
Warm detection threshold (WDT)	−0.63 ± SD 0.91	−0.52 ± SD 0.72	0.745
Thermal sensory limen (TSL)	−1.13 ± SD 1.17	−0.49 ± SD 0.58	0.089
Cold pain threshold (CPT)	0.66 ± SD 1.37	0.56 ± SD 1.08	0.991
Heat pain threshold (HPT)	0.68 ± SD 1.08	−0.12 ± SD 0.92	0.054
Pressure pain threshold (PPT)	0.15 ± SD 2.02	−0.19 ± SD 0.65	0.574[#]
Mechanical pain threshold (MPT)	1.19 ± SD 1.49	0.93 ± SD 0.88	0.592[#]
Mechanical pain sensitivity (MPS)	0.24 ± SD 1.43	−0.03 ± SD 0.73	0.541
Wind-up ratio (WUR)	0.37 ± SD 0.88*	0.63 ± SD 0.85	0.466
Mechanical detection threshold (MDT)	−1.10 ± SD 1.19	−0.15 ± SD 0.53	**0.014****
Vibration detection threshold (VDT)	0.29 ± SD 0.80	0.22 ± SD 0.57	0.800
QST parameters (mean raw values)			
Dynamic mechanical allodynia (DMA)	0.008 ± SD 0.02	0.00 ± SD 0.00	p = 0.167
Paradoxical heat sensation (PHS)	0.357 ± SD 0.93	0.00 ± SD 0.00	p = 0.174

Results of quantitative sensory testing (QST) are given as mean z scores (respectively mean raw values for allodynia and paradoxical heat sensation) of patients with autism (middle left) and healthy subjects (middle right)

*Data of 1 patient is missing

**Significant result (uncorrected for multiple testing)

[#]Corrected for unequal variances.

found a greater intra-individual trial-to-trial variability in behavioral and neuro-/electropsychological responses in ASD (David et al. 2016; Milne 2011) and suggested that ASD subjects might have increased neuronal noise. This is an interesting aspect that is worth to shed more light on.

Furthermore, four of the 13 ASD patients showed distinctive, sensory perceptive features in addition to classic QST threshold testing such as paradoxical heat sensations (n = 2) and allodynia (n = 2), typically not present in healthy subjects including our healthy control group. Given the normal peripheral nerve fiber function as indicated by the normal group mean z scores of other, classic QST parameters, this finding points towards the potential relevance of central rather than peripheral mechanisms for altered sensory perception in ASD.

Paradoxical heat sensation (PHS) is a phenomenon where gentle cooling is perceived as hot or burning (Magerl and Klein 2006) during application of cold and warm stimuli in an alternating manner. PHS can occur in healthy subjects (Davis et al. 2004; Susser et al. 1999) but is not very frequent especially on the hand (see supplement of (Magerl et al. 2010) and (Klauenberg et al. 2008)). Our finding is in line with a previous observation in ASD adolescents reporting PHS in 30% of ASD children tested (Duerden et al. 2015). The authors suggested that this might reflect peripheral nerve fiber alterations (i.e. number of small fibers, or degree of small-fiber myelination) in adolescents with ASD (Duerden et al. 2015). According to previous studies PHS can result from (1) disinhibition of heat-sensitive C-fiber pathways either by blockade or loss of A-fiber input and (2) facilitation of disinhibited C-fiber pathways by sensitization of primary afferents (Craig and Bushnell 1994; Susser et al. 1999; Wahren et al. 1989). Given the nature of our behavioral experimental investigation we can only speculate about the neurobiological mechanisms underlying PHS in our patients. However, given that the analysis of different QST parameters, particularly the different sensory thresholds, did not reveal any specific signs of nerve fiber dysfunction, we believe that central mechanisms (e.g. central disinhibition of nociceptive pathways (Magerl and Klein 2006) or disruption of central thermosensory integration) rather than peripheral mechanisms determine PHS in our ASD sample. However, QST cannot fully distinguish between central and peripheral alterations (Mucke et al. 2014).

In an investigation of neural mechanisms underlying PHS in healthy subjects, the right anterior-mid insular cortex has been found to be activated when subjects perceived PHS at their right hand (Davis et al. 2004). Interestingly, the right anterior insula is consistently found to be hypo-activated in patients with ASD (for reviews see (Di Martino et al. 2009; Uddin and Menon 2009)). It is, therefore, tempting to speculate that insular activation might be involved in altered somatosensory processing in ASD, but this has to be investigated in future studies.

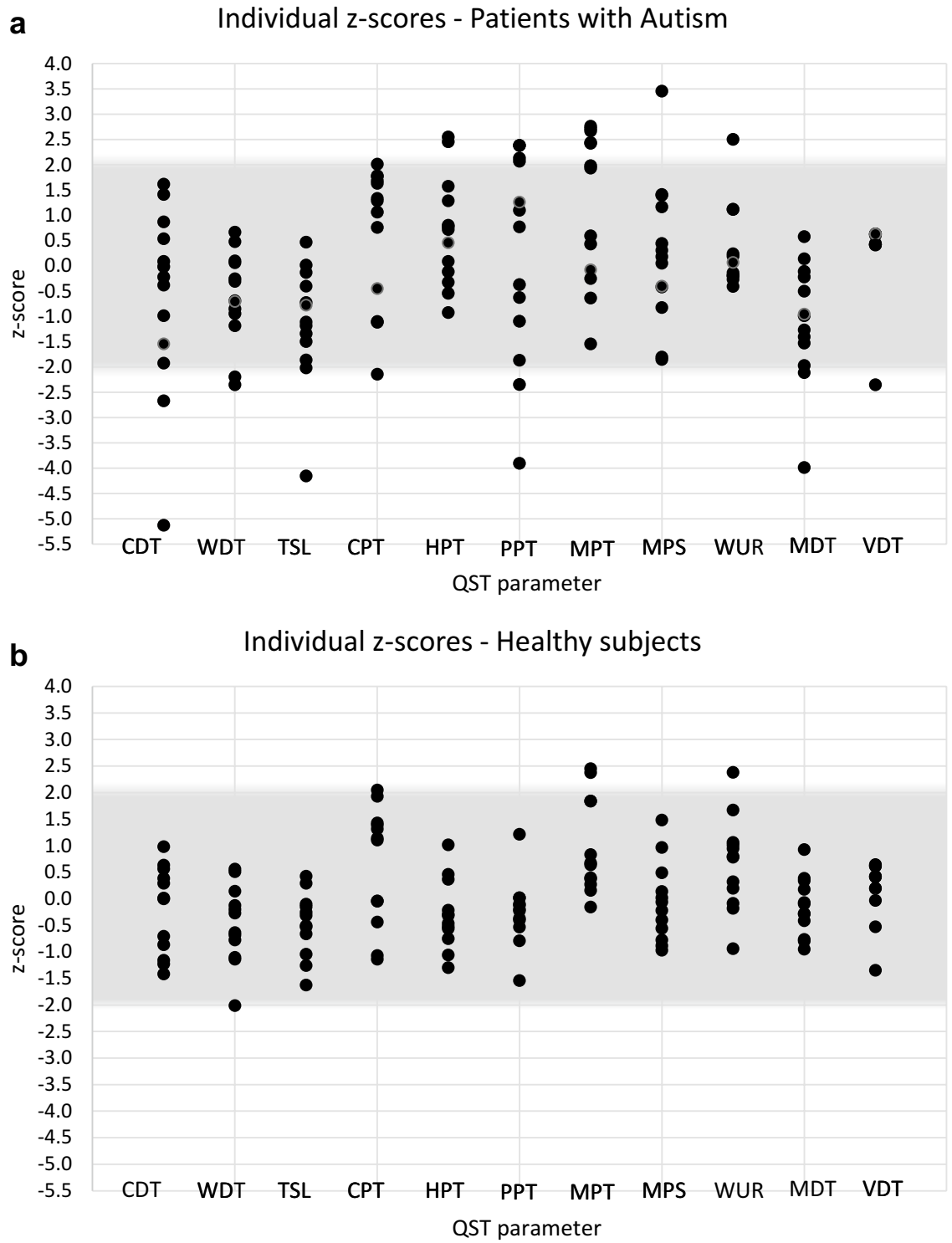

Fig. 2 Individual results of Quantitative Sensory Testing (QST). Individual results of quantitative sensory testing are given as z scores of patients with autism (**a**) and healthy subjects (**b**). Baseline (z = 0) and the *grey* area represent z scores of the DFNS reference group. *CDT* cold detection threshold, *WDT* warm detection threshold, *TSL* thermal sensory limen, *CPT* cold pain threshold, *HPT* heat pain threshold, *PPT* pressure pain threshold, *MPT* mechanical pain threshold, *MPS* mechanical pain sensitivity, *WUR* wind-up ratio (data of one patient missing), *MDT* mechanical detection threshold, *VDT* vibration detection threshold. Allodynia and paradoxical heat sensation were calculated separately

To our knowledge, our study is the first one explicitly and experimentally investigating dynamic mechanical allodynia (DMA) in ASD. DMA was present in two ASD patients but not in controls, and reflects a phenomenon wherein a pain sensation is elicited by gentle non-painful, moving, tactile stimuli (e.g. brushing; (Magerl and Klein 2006; Gierthmühlen and Baron 2013)). DMA must be distinguished from hyperalgesia, i.e., increased pain perception of stimuli that usually provoke pain (Jensen and Finnerup 2014) and from tactile hypersensitivity, i.e., excessive perception of tactile stimuli (Baron-Cohen et al. 2009) with "strong reactions and heightened apprehension in reaction to external (tactile) stimuli, sometimes together with overfocused attention" (Elwin et al. 2012) and an overreaction to sensory stimuli (Blakemore et al. 2006; Kientz and Dunn 1997). DMA usually does not occur in healthy subjects (Rolke et al. 2006). Silva and Schalock (Louisa MT Silva and Schalock 2013, 2012) found that "allodynia" was frequently reported by parents (100%) and therapists (98%) of children with ASD in the Sense and Self-regulation Checklist (SSC). It is noteworthy, that in their study the term "allodynia" was defined as a withdrawal or avoidance of gentle touch and that there was no explicit linkage to a pain perception. Therefore, and in contrast to our approach (and the DFNS definition), the phenomenon described in their study cannot distinguish genuinely painful allodynia from hypersensitivity leading to merely unpleasant or disturbing tactile sensations.

Different mechanisms have been suggested to underlie DMA ranging from molecular, cellular, synaptic, nerve fiber (e.g. C, A-delta and A-beta fiber mediated (Gierthmühlen and Baron 2013)), spinal, network and central pathologies (for review see (Sandkuhler 2009)). Other studies presumed that central processes underlie DMA (Baron and Saguer 1995) such as central sensitization (Gierthmühlen and Baron 2013). As nerve fiber function in our study does not seem to be impaired, central processes might be responsible for DMA occurrence in ASD here. Interestingly, both PHS and DMA include rather dynamic than static stimulus presentation: PHS can be induced by alternating cold and warm temperatures and DMA is prompted by innocuous, moving tactile stimuli. The processing of these complex somatosensory stimuli obviously requires the integration of information at a central, higher-order level (Blakemore et al. 2006; Bertone et al. 2003; Minshew and Goldstein 1998), which might be affected by ASD. Note, however, that there was no relation between sensory thresholds within the ASD group and IQ levels, autism symptom severity or depression scores.

These findings should be viewed in the light of at least three limitations. First, the sample size was small (which seems to be a characteristic of the field when analyzing sample sizes of previous studies e.g. Güclü with n = 6 (Guclu et al. 2007), Cascio with n = 8 (Cascio et al. 2008) or Blakemore with n = 10 (Blakemore et al. 2006)). Hence, it might be possible, that inter-group differences might be masked by within-group variabilities. Second, neither the patients nor the controls were screened for any other types of unisensory hyper- or hypo-sensitivities, such as to light, sound, odor or taste which might also be affected or might influence multisensory integration within overall sensory perception in ASD (Marco et al. 2011). Third, psychiatric medication (n = 2) or the existence of comorbid psychiatric diseases (n = 4) might have influenced the results. In particular, because three out of the four patients with DMA or PHS had depression. Future studies should focus on ASD participants without psychiatric comorbidities or larger sample sizes to allow subgroup analyses. However, psychiatric comorbidities in ASD are frequent (Joshi et al. 2013) and previous studies neither found differences in PHS in depressive as compared to healthy subjects (Klauenberg et al. 2008) nor regarding other QST parameters (Schneider et al. 2015). As we focused on adult ASD patients with normal IQ levels, generalization regarding the heterogeneous ASD patient collective should be made cautiously. On the other hand, inclusion of a well-characterized adult ASD sample with normal IQ values (IQ >70) ensured adequate task comprehension.

To conclude, using the comprehensive, well-established QST test battery, single QST parameters did not differ between groups. However, within-group variance for some QST parameters was larger in the ASD group. Also, dynamic mechanical allodynia and paradoxical heat sensations were present in some ASD patients. Central processing and integration of sensory information rather than peripheral perception appears to be altered in ASD patients. As QST basically is a rather subjective, psychophysical method that is based on the cooperation of the participant, future studies with bigger sample sizes should focus on more objective measurements of somatosensory function (e.g. sensory (laser) evoked potentials, nerve conduction velocity etc.) and should combine these measurements with neuroimaging to detect probable processing differences between ASD and control subjects.

Acknowledgments This work was supported by the Else Kröner-Fresenius-Stiftung (Grant 2011_A37; A.M.) and by the EU (FP7-ICT-270212, ERC-2010-AdG-269716, H2020-641321; A.K.E.). We would like to thank all the patients investigated in this study for their support and commitment. Thanks to Jan Vollert (University Medical Center Bochum) and Tina Mainka (University Medical Center Hamburg-Eppendorf) for their advice.

Author Contributions OF and WG equally participated in the conception and design of the study, performed data acquisition, analysis and interpretation, drafted and reviewed the manuscript. DS, IP, ND, AM and AKE participated in the conception and design of the study, performed data interpretation and manuscript revision for important

intellectual content. KF and NW participated in the conception and design of the study, performed data analysis and interpretation as well as manuscript revision for important intellectual content. UB participated in the conception and design of the study, performed data interpretation and manuscript drafting as well as manuscript revision for important intellectual content. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of interest All authors declare that there are no conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Human and Animal Research Information Our research involved human participants.

Informed Consent Informed consent was obtained from all individual participants included in the study. They were told to be free to withdraw from the study at any time.

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