

Autism and Chronic Ill Health: An Observational Study of Symptoms and Diagnoses of Central Sensitivity Syndromes in Autistic Adults

Sarah Louise Grant (✉ sarah.grant@kcl.ac.uk)

King's College London <https://orcid.org/0000-0002-2937-5338>

Sam Norton

King's College London

Ricarda F. Weiland

Vrije Universiteit Amsterdam

Anke M. Scheeren

Vrije Universiteit Amsterdam

Sander Begeer

Vrije Universiteit Amsterdam

Rosa A Hoekstra

King's College London

Research

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Abstract

Background

Autistic adults, particularly women, are more likely to experience chronic ill health than the general population. Central sensitivity syndromes (CSS) are a group of related conditions that are thought to include an underlying sensitisation of the central nervous system; heightened sensory sensitivity is a common feature. Anecdotal evidence suggests autistic adults may be more prone to developing a CSS. This study aimed to investigate the occurrence of CSS diagnoses and symptoms in autistic adults, and to explore whether CSS symptoms were related to autistic traits, mental health, sensory sensitivity, or sex.

Methods

Participants included 982 autistic adults (male = 409, female = 563, other = 9, mean age = 44.5) registered at the Netherlands Autism Register, who completed questionnaires assessing autistic traits, sensory sensitivity, CSS, physical and mental health symptoms. The reliability and validity of the Central Sensitization Inventory (CSI) in an autistic sample was established using exploratory and confirmatory factor analyses. Chi² analyses, independent t-tests, ANOVA, hierarchical regression analysis and path analysis were used to analyse relationships between CSS symptoms, autistic traits, measures of mental health and wellbeing, sensory sensitivity, age and assigned sex.

Results

21% of participants reported one or more CSS diagnoses, and 60% scored at or above the clinical cut-off for a CSS. Nonbinary and female autistics were more likely to report a CSS diagnosis and experienced more CSS symptoms than males. Sensory sensitivity, anxiety, age and sex were significant predictors of CSS symptoms, with sensory sensitivity and anxiety fully mediating the relationship between autistic traits and CSS symptoms.

Limitations

Although this study included a large sample of autistic adults, we did not have a control group or a CSS only group.

Conclusions

CSS diagnoses and symptoms appear to be very common in the autistic population. Increased awareness of an association between autism and CSS should inform clinicians and guide diagnostic practice, particularly for females where CSS is common and autism under recognised.

Background

Autistic people are more vulnerable to a broad range of physical health issues [1], experience more chronic disease and premature mortality [2, 3] and have poorer general health outcomes [4] than the wider population. However, the underlying mechanisms are not yet well established. One group of physical problems colloquially thought to be more prevalent in autistic people are 'central sensitivity syndromes' (CSS) including myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS), fibromyalgia syndrome (FMS), migraine, irritable bowel syndrome (IBS) and temporomandibular joint disorder (TMJD). CSS are thought to have central sensitisation, or augmented sensory signalling of the central nervous system, as a core component [5]; symptoms include fatigue, chronic pain and sensory hypersensitivity. CSS often co-occur with mental health conditions such as anxiety, depression and post-traumatic stress disorder (PTSD) [6].

Individual sensory processing differences are a core feature common to both autism [7] and CSS [8]. While sensory research in autism has been more focussed on altered experience and heightened sensory sensitivity across all modalities [9], CSS research has been centred around pain [10]. Therefore, whilst CSS studies have acknowledged that general sensory sensitivity, and not just pain, is part of central sensitisation [11–13], it is not known whether the sensory sensitivity observed in CSS patients could have preceded their health condition. In autism, altered pain processing has been indicated for both acute [14] and sustained pain [15], but it is not yet clear whether this altered pain perception might indicate a particular vulnerability to central sensitisation.

Research looking directly at an association between autism and CSS is limited. Paediatric studies have highlighted a higher incidence of neurodevelopmental disorders in children with chronic pain [16, 17] or CSS [18, 19], but there is little equivalent research in adults. There is, however, growing awareness of a link between neurodivergence and genetic connective tissue disorders, particularly joint hypermobility-related disorders [20, 21] and the Ehlers-Danlos syndromes [22]. These conditions often co-occur with CSS [23–25], but more research is needed into whether this directly translates to an association between autism and CSS.

In the general population, prevalence estimates of CSS vary 0.2–20% [26–32] depending on type of syndrome and country. CSS are much more commonly diagnosed in women than in men [33], and females are thought to have greater pain sensitivity [34] and heightened central sensitisation [35]. Sex is also an important predictor of an autism diagnosis and physical health in autism. Autism has historically been under recognised [36] and diagnosed later [37] in females, and autistic females appear more vulnerable to a greater range of co-occurring physical conditions than autistic males [38]. Whether CSS are more common in autistic females has not been explored.

Our study aimed to investigate whether the rates of CSS, or CSS symptoms, are high in a sample of autistic adults. We first examined the dimensionality and reliability of the Central Sensitization Inventory (CSI), a widely used CSS measure [39], in this autistic sample. We postulated that higher scores would be associated with more autistic traits, greater sensory sensitivity, higher anxiety and depression scores and poorer physical health and subjective well-being, and we predicted that autistic females would report greater sensory sensitivity and more CSS symptoms than autistic males. We also considered whether sensory sensitivity, anxiety or biological sex might mediate a relationship between autism and CSS, and whether the age at autism diagnosis and/or time since diagnosis might play a role.

Methods

Participants

The sample comprised 982 adults (409 male, 563 female, 9 other) all of whom have been formally diagnosed with autism. The mean age of the sample was 44.5 years (SD = 13.6), with males (Mean = 48.7 SD = 13.42) significantly older than both females (Mean = 41.7 SD = 12.93 $p < .001$) and non-binary individuals (Mean = 31.1 SD = 11.17 $p < .001$). 18.6% of the sample had completed a university degree, 21.5% a higher professional education, 16.3% a vocational education, 20.5% had another type of education and 23.1% had not specified their level of education .

Participants were recruited through the Netherlands Autism Register (NAR www.nederland-sautismeregister.nl/english/), a longitudinal autism research volunteer register that is administered on an annual basis to autistic people and/or their legal representatives. The data collection for this study was self-report only and was part of an ongoing wave of NAR surveys and, as such, participants were asked questions as part of the overall survey rather than being specifically recruited for a study on autism and chronic illness, ensuring we minimised bias in the recruitment process. The inclusion criteria were that participants had completed the CSI in full.

Measures

Central Sensitisation

The Central Sensitization Inventory [40] was developed as a valid and reliable self-report to measure symptoms of central sensitisation, and later posited as a possible screening instrument. Each item in Part A is measured on a five-point Likert scale ranging from 0 'never' to 4 'always' (for item content please see supplementary material). Part B contains a list of CSS diagnoses and related disorders. A cut-off score of 40 on Part A was determined to best distinguish between CSS and non-CSS patients [39]. This study used the Dutch version of the CSI [41] which also uses a cut-off of 40 and has been shown to discriminate well between chronic pain patients and healthy controls, with good internal consistency and test-retest reliability. Several health conditions from Part B – fibromyalgia syndrome (FMS), myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS), irritable bowel syndrome (IBS), migraine and temporomandibular joint disorder (TMJD) - were included in the 2019 wave of the NAR data collection, with participants able to select them as co-occurring conditions if relevant. Participants with one or more formal CSS diagnoses were flagged as “diagnosed CSS” with all others flagged as not diagnosed.

Physical Health

Participants were asked to rate their physical health from 0–10 with 0 being the poorest health and 10 being good physical health. This question is asked in each wave of the Netherlands Autism Register.

Sensory Sensitivity

The 35 item Sensory Perception Quotient (SPQ) was developed to assess sensory sensitivity in adults with and without autism, and shows good internal consistency and validity [9, 42, 43]. It is assessed on a four-point Likert scale across five sensory modalities. Items range from 0 'strongly agree' to 3 'strongly disagree'. Lower scores on the SPQ indicate higher sensory sensitivity, and higher scores lower sensitivity. SPQ data was collected in the 2016 wave of the Netherlands Autism Register.

Autistic Traits

Autistic traits were measured using the 28 item AQ-Short [44], an abridged version of the 50 item Autism Spectrum Quotient or AQ [45]. Items are scored on a four-point Likert scale ranging from 1 'definitely agree' to 4 'definitely disagree'. 13 of the 28 items are reverse scored where 'agree' responses are characteristic for autism. This measure has been evaluated in Dutch and English samples and was found to have good reliability, sensitivity and specificity [44, 46]. The AQ is administered when participants register with the NAR, and therefore the year completed varied per person.

Anxiety and Depression

The Hospital Anxiety and Depression Scale or 'HADS' [47], consists of two subscales and is used to identify anxiety (HADS-A) and depression (HADS-D) in non-psychiatric patients. Each subscale contains seven items ranging from 0 to 3, with 3 indicating greater symptom severity. The dimensional structure of the HADS has been shown to be stable across groups in Dutch samples, with good sensitivity and specificity [48]. HADS data was collected in the 2018 wave of the Netherlands Autism Register.

Subjective Wellbeing

Subjective wellbeing was assessed using a composite score from three separate measures, the Subjective Happiness Scale [49], the Satisfaction with Life Scale [50] and the Cantril ladder [51]. Previous psychometric research has shown

that combining these measures in a dimensional score of overall wellbeing (range 2 to 73) is reliable and valid [52]. The Subjective Happiness Scale has four items on a Likert scale from 1 'strongly disagree' to 7 'strongly agree', with higher scores indicating greater happiness. The Satisfaction with Life Scale uses the same Likert scale but with five items related to life satisfaction. The Cantril ladder uses an 11-point scale to evaluate general quality of life, with 0 indicating the worst possible life and 10 the best.

Statistical Analyses

The CSI has not currently been validated in the autistic population. To establish the factor structure of the Dutch CSI in this sample of autistic adults, an exploratory factor analysis (EFA) was conducted on a random split half of the sample using a promax rotation and weighted least squares extraction method, with confirmatory factor analyses (CFA) using WLSMV estimator performed on the remaining half of the sample, in which we compared the factor structure indicated by the EFA, and the factor structures reported in previous English CSI [40] and Dutch CSI [41] studies in non-autistic samples. A third CFA model evaluated a bi-factor structure, as proposed by Cuesta-Vargas et al [53], whereby the covariance between CSI items was accounted for through one general factor and four orthogonal factors. Model fit was interpreted using the Root Mean Square Error of Approximation (RMSEA), Comparative Fit Indicator (CFI), and Tucker-Lewis indicator (TLI). Optimal fit is indicated by values of 0 for the RMSEA and 1 for the CFI and TLI. Criteria for an 'acceptable fit' was an RMSEA < .1, CFI/TLI > .9. Criteria for an 'excellent fit' were RMSEA < .06, CFI/TLI > .95 < 1.0 [54]. EFA and CFA analyses were conducted using MPlus version 8.2 [55] and a reliability analysis was conducted in SPSS 25.0 [56]. An ANCOVA with age and sex as covariates was conducted to compare group differences in CSI scores between participants with and without a formal CSS diagnosis.

Two additional variables were created, one to indicate whether a participant scored above or below the clinical cut-off of 40 on Part A of the CSI (high or low CSI) and the second to indicate whether the participant reported a diagnosed CSS of FMS, CFS, IBS and/or TMJD. We used independent samples t tests and Chi² tests to analyse CSS group differences (high versus low CSI, and those with and without a CSS diagnosis), with sex group differences explored using one-way ANOVA with Tukey's (HSD) post hoc tests. Where relevant, analyses were corrected for multiple testing using Bonferroni correction. A four-stage hierarchical regression analysis was used to explore the hypothesis that autistic traits, sensory sensitivity and anxiety might significantly predict CSS symptoms, with age and sex included in stage one as controls, and each construct added in a separate stage to explore their effect on the variance in CSI scores. Further multiple regression was used to explore whether age at diagnosis or time since diagnosis might also be significant predictors of CSI scores. Path analyses were conducted to investigate whether sensory sensitivity or anxiety might mediate the relationship between autistic traits and CSS symptoms.

Results

Descriptive Statistics

Out of all 982 participants, 208 (21%) had a formally diagnosed CSS from the list of included conditions; 41 participants indicated having more than one CSS (see Supplementary Table 1 for full list). 93% of participants with a disclosed CSS diagnosis scored at or above the clinical cut-off of 40 on the CSI; participants with a disclosed CSS scored significantly higher on the CSI than those without [$F(1,977) = 169.96, p < .001$]. 589 participants (60% of the sample) scored at or above the clinical cut-off of 40 on the CSI but only 31% of the 'high CSI' group had a formal CSS diagnosis.

Validation & Reliability of the Central Sensitisation Inventory (CSI)

We analysed the psychometric properties of the CSI since it had not been used before in an autistic sample. Exploratory factor analysis in a randomly selected half of the sample indicated a five-factor solution provided the best explanation of the CSI inter-item covariances (RMSEA 0.051, SRMR 0.037). However, one factor contained only two items and there was some support on the scree-test for a four-factor solution. Confirmatory factor analysis in the other half of the sample considered this five-factor solution (RMSEA = 0.069; CFI = 0.931; TLI = 0.921), along with a four-factor solution identified in previous studies of the CSI [40] and Dutch CSI[41] (RMSEA = 0.073; CFI = 0.921; TLI = 0.912), and a bifactor solution proposed by Cuesta-Vargas et al [53], comprising one general factor and four orthogonal factors (RMSEA = 0.063; CFI = 0.945; TLI = 0.934). Model fit was acceptable for all models but marginally better for the bifactor model. The bifactor model provides support for the use of the CSI as a total score since this model involves the presence of a general factor. This is further supported by the CSI items showing excellent internal consistency (Cronbach's $\alpha = 0.907$ with all inter-item correlations highly significant ($p < .01$)). Taken together these results indicate that the CSI total score provides a valid and reliable assessment of the central sensitisation in autistic adults.

Group Differences

In the diagnosed CSS versus no CSS groups, CSI scores were significantly higher and physical health ratings significantly lower, as expected (Table 1). The diagnosed CSS group also reported significantly lower SPQ scores, indicating greater sensory sensitivity. Participants with a CSS reported significantly more anxiety and depression, and lower subjective wellbeing, than those without a CSS. There was no significant group difference in autistic traits. As some measures were completed in different waves of the NAR and/or some participants had not completed them, the sample sizes differed across measures.

Table 1
Group differences between low and high CSI, diagnosed CSS and no diagnosis

		Group					
Measure		No CSS	Diagnosed CSS	T value / Cohen's d	Low CSI	High CSI	T value / Cohen's d
CSI	N	774	208	-13.08** / -1.02***	393	589	-41.27** / -2.69***
	Mean Score	40.6	55.3		28.4	53.9	
	SD	14.69	13.41		8.45	10.07	
Physical Health	N	774	208	12.06** / 0.94***	393	589	14.60** / 0.95***
	Mean Score	6.6	5.2		7.1	5.8	
	SD	1.47	1.52		1.22	1.57	
SPQ	N	313	80	4.13** / 0.52**	173	220	7.63** / 0.78**
	Mean Score	45.9	38.3		50.5	39.5	
	SD	14.99	13.8		14.89	13.4	
AQ-Short	N	774	208	-2.08 / -0.16	393	589	-5.91** / -0.38*
	Mean Score	83.3	85		81.2	85.3	
	SD	10.9	10.69		11.12	10.4	
HADS-A	N	510	129	-5.79** / -0.57**	276	363	-13.67** / -1.09***
	Mean Score	9.2	11.7		7.3	11.5	
	SD	4.37	4.12		3.89	3.9	
HADS-D	N	510	129	-4.73** / -0.47**	276	363	-9.39** / -0.75**
	Mean Score	7.0	9.2		5.5	8.9	
	SD	4.84	4.79		4.28	4.83	
Subjective Wellbeing	N	336	82	4.36** / 0.54**	185	233	8.66** / 0.85***
	Mean Score	29.9	25.6		32.6	26.2	
	SD	8.03	7.39		7.33	7.53	

Bonferroni corrected p value = .007. * p < .007 ** p < .001. Effect size d *small effect **medium ***large. CSI = Central Sensitization Inventory; SPQ = Sensory Perception Quotient; AQ-Short = Autism Quotient – Short; HADS-A = Hospital Anxiety and Depression Scale – Anxiety; HADS-D = Hospital Anxiety and Depression Scale - Depression

The descriptive statistics of all outcome measures are displayed in Table 2. Sex differences were significant for CSI, physical health, SPQ, anxiety and subjective wellbeing, with women obtaining more severe scores for each of these

instruments, and non-binary participants also scoring higher on the CSI than males. Chi square tests of independence were used to analyse the relationship between sex, CSS diagnosis, and CSI score group (see Table 1). Women were significantly over-represented in both the diagnosed CSS group, $X^2(2, N = 982) = 36.35, p < .001$ and the High CSI group, $X^2(2, N = 982) = 90.3, p < .001$.

Table 2
Sex differences in questionnaire measures.

		Group Mean/SD Scores				Anova		Tukey's HSD		
		Male (M)	Female (F)	Non-Binary (NB)	TOTAL	F	Partial Eta ²	M & F	M & NB	F & NB
CSI	N	410	563	9	982		η^2	p=	p=	p=
	Mean	37.1	48.3	51.8	43.7**	70.683	0.126**	< .001***	0.009**	0.761
	SD	14.94	14.39	14.88	15.63					
Physical Health	N	410	563	9	982		η^2	p=	p=	p=
	Mean	6.6	6.1	6.0	6.3**	9.11	0.018*	< .001***	0.533	0.965
	SD	1.55	1.59	1.66	1.58					
SPQ	N	186	207	0	393		η^2	p=	p=	p=
	Mean	47.1	41.8	-	44.3**	12.522	0.031*	< .001***	-	-
	SD	15.5	14.24	-	15.07					
AQ-Short	N	410	563	9	982		η^2	p=	p=	p=
	Mean	83.4	83.8	83.65	83.7	0.378	0.001	0.872	0.726	0.782
	SD	11.61	10.34	9.20	10.87					
HADS-A	N	276	360	3	639		η^2	p=	p=	p=
	Mean	8.5	10.5	12.7	9.7**	17.646	0.053*	< .001***	0.226	0.672
	SD	4.55	4.14	0.58	4.43					
HADS-D	N	276	360	3	639		η^2	p=	p=	p=
	Mean	7.1	7.7	7.7	7.5	1.276	0.004	0.248	0.978	1.000
	SD	5.00	4.83	6.35	4.91					
Subjective Wellbeing	N	199	219	0	418		η^2	p=	p=	p=
	Mean	30.4	27.8	-	29.0*	10.819	0.025*	0.001**	-	-
	SD	8.53	7.45	-	8.08					

ANOVA F significant at Bonferroni adjusted * p < .007 ** p < .001. Effect size η^2 *small effect **medium ***large. CSI = Central Sensitization Inventory; SPQ = Sensory Perception Quotient; AQ-Short = Autism Quotient – Short; HADS-A = Hospital Anxiety and Depression Scale – Anxiety; HADS-D = Hospital Anxiety and Depression Scale - Depression

The relationships between the main variables were analysed using a four-stage hierarchical multiple regression with CSI score as the dependent variable. Stage one included age and sex, stage two added autistic traits (AQ), stage three sensory sensitivity (SPQ) and stage four anxiety (HADS-A).

Table 3
Hierarchical Regression Analysis (n = 356)

	Stage One			Stage Two			Stage Three		
	Beta	t	p	Beta	t	p	Beta	t	p
(Constant)		7.765	0.00***		0.090	0.928		3.723	0.00***
Sex	0.388	7.628	0.00***	0.377	7.633	0.00***	0.208	5.211	0.00***
Age	0.148	2.912	.004**	0.124	2.499	0.013*	0.106	2.747	0.006**
AQ Score				0.231	4.819	0.00***	0.052	1.340	0.181
Anxiety							0.483	11.884	0.00***
SPQ Score							-0.263	-6.565	0.00***

Note. R² = .142 for Model 1: ΔR² = .053 for Model 2 (p < .001): ΔR² = .320 for Model 3 (p < .001). *p < .05, **p < .01, ***p < .001.

Stage one of the regression analysis showed that sex and age were both significantly associated with CSS symptoms and accounted for 14.2% of the variability in CSI scores. Stage two accounted for 18.8% of the variability in CSI scores and contributed significantly to the regression model, $F(3,355) = 28.67, p < .001$, with AQ scores explaining 5.3% additional variance in CSI scores. Sensory sensitivity contributed to a further 12.6% of the variance ($F(4,354) = 41.92, p < .001$) and anxiety to 19.4% of the variance ($F(5,353) = 75.09, p < .001$). In total the model accounted for 50.9% of the variance in CSI scores. Level of autism traits (AQ) was not a significant predictor when anxiety and sensory sensitivity were included. A moderated multiple regression, conducted on mean centred scores, showed that the interactions between SPQ and AQ and HADS-A and AQ were not significant. This indicated that sensory sensitivity and anxiety were not moderating the relationship between autistic traits and CSS symptoms but did not exclude the possibility that they were acting as mediators.

Sensitivity analyses replacing chronological age with age at diagnosis and time since diagnosis showed very similar results.

A path model was estimated to help understand whether sensory sensitivity (SPQ), autistic traits (AQ) and anxiety (HADS-A) explained the association between sex and CSS symptoms (CSI). In this model, sex significantly predicted sensory sensitivity ($p < .001$), anxiety ($p < .001$), and CSS symptoms ($p < .001$). Autistic traits significantly predicted both sensory sensitivity ($p < .001$) and anxiety ($p < .001$). Sensory sensitivity significantly predicted CSI scores ($p < .001$) as did anxiety ($p < .001$), but autistic traits did not ($p = .129$). Anxiety, sensory sensitivity and sex together accounted for 50.5% of the variance in CSI scores, $R^2 = .505$. The only indirect effect that was insignificant was that of sex on CSS symptoms via autistic traits. These findings supported the hypothesised model in Fig. 1.

An alternative model was estimated to explore whether sex and CSS symptoms might predict autistic traits, when mediated by sensory sensitivity and anxiety, however the model was not parsimonious. Neither CSI nor sex acted as a significant predictor of autistic traits, and anxiety SPQ and sex together accounted for only 9.8% of the total variance in AQ. Altogether, these path analysis findings suggest that a relationship between autistic traits and CSS symptoms might relate to heightened sensory sensitivity and anxiety in the autistic population.

Discussion

This is the first study, to our knowledge, that directly considers an association between autism and CSS. In our large sample of autistic adults, 21% reported an included CSS diagnosis of FMS, ME/CFS, IBS or TMJD and 60% scored at or above the clinical cut-off for a CSS on the CSI, suggesting that CSS symptoms are very common in autistic people.

A factor analysis of the CSI [40] was undertaken to test the measure's construct validity in an autistic sample, as previous studies have focussed on chronic pain and control groups [39, 41, 53]. The results supported the bi-factor model [53], and a highly internally consistent scale. In our sample, the mean CSI score for those with a diagnosed CSS was 55.3, slightly higher than the mean score of 52.4 Neblett et al. [39] found in their study of CSS patients establishing the clinical cut-off of 40 on the CSI. However, the mean CSI score for autistic participants without a diagnosed CSS was 40.6; a score far higher than that of Neblett's control group (30.9) and closer instead to the mean score of 40.9 in the non-CSS chronic pain patients. This suggests that CSS symptoms such as pain and fatigue are very common in autistic individuals and possibly more prevalent than in the general population.

Our results also showed that, as predicted, higher scores on the CSI were associated with greater sensory sensitivity, greater anxiety and lower subjective well-being, with females reporting greater sensory sensitivity and scoring higher on the CSI than males. Whilst higher scores on the CSI also appeared to be associated with higher autistic traits, we found that sensory sensitivity and anxiety fully mediated this relationship. Further analysis showed that, just as previously reported in the general population [33, 39], there were clear sex differences, with women over-represented for both CSS diagnoses and severity of CSS symptoms. Women also showed greater sensory sensitivity and reported greater anxiety, depression and lower subjective wellbeing. Previous research into sensory sensitivity in autism has been mixed when considering sex differences [9, 57]. Recent studies on the SPQ, both on data within the Netherlands Autism Register (of which this dataset is a subsample) and outside, found that autistic females had higher sensory sensitivity than both autistic males [42] and non-autistic females [43]. Research within the general population also suggests that females may be more sensitive than males across a range of modalities [34, 58], with hormones thought to play a key role [59]. The path analysis we conducted suggests that sensory sensitivity and anxiety, as well as biological sex by itself, all contribute to CSS symptoms such that autistic females might be more vulnerable to CSS than autistic males and non-autistic females. Given that the non-binary participants in this study seemed to show the same vulnerability, and autistic individuals are less likely to identify with their assigned gender at birth [60–62], gender-focussed research is needed to explore this further.

There are many theoretical reasons why autism and CSS might be linked with each other. Sensory processing differences are a core feature of autism [7] with autistic people reporting greater sensory sensitivity [9] than the general population. People with CSS also experience pain and sensory sensitivity [8] but in this case it is associated with central sensitisation [5]. The multisensory integration mechanisms responsible for the development of sensory sensitivity in chronic pain patients could also explain a relationship in the opposite direction i.e. chronic pain in autistic people with sensory processing differences. Indeed, migraine is included under the CSS umbrella, and is thought by some to be a form of "sensory dysmodulation" [63]. Our results demonstrated that autistic people with greater sensory sensitivity also had more CSS symptoms. Since sensory processing differences tend to be present from a young age [7], we can hypothesise that sensory sensitivity is a risk factor for developing CSS, however further research is needed to explore the direction of this relationship.

Autism and CSS may also be related through neuroimmune and genetic differences, particularly the recently recognised "trifecta" of conditions, including Mast cell Activation Syndrome (MCAS) [64], dysautonomia, including Postural Orthostatic Tachycardia Syndrome (POTS) [65], and joint hypermobility disorders including Hypermobility

Ehlers-Danlos Syndromes (hEDS) [66]. These conditions often appear together [67] and are increasingly found to be co-morbid with or underlying CSS diagnoses [25]. They have also been recognised to be associated with autism and other neurodevelopmental conditions [20, 22], particularly through the work of Eccles et al [21, 25, 68, 69], and Casanova et al (2019) recently theorised that some forms of autism could even be hereditary connective tissue disorders [70]. Autism and fibromyalgia are directly associated through the FRM1 gene mutation [71] associated with Fragile X syndrome [72], the most common single gene cause of autism.

Our findings suggest that mental health conditions in the autistic population could contribute to CSS symptoms, with anxiety being a significant predictor of CSS symptoms in this sample. Autistic traits alone were not a significant predictor of CSS symptoms, with our path analysis indicating that higher anxiety and sensory sensitivity in the autistic population might explain the higher incidence of CSS symptoms. Existing research supports this theory; high anxiety [73], chronic stress [74] and PTSD [73, 75] have all been associated with CSS, and are also more common in the autistic community [76–79] than the general population. Other psychological factors could provide a basis for a possible link; some research suggests chronic illness severity might be affected by illness beliefs and coping mechanisms [80]. If this is the case, then cognitive differences in autistic people, such as a lower tolerance for uncertainty [81], might affect their experience of CSS symptoms, and this is something that could be explored in future research.

Diagnostic issues might also explain why an association between autism and CSS has thus far been largely overlooked. Historically, autism has been classified as a social and communication disorder [82], with sensory issues only included in the most recent DSM criteria [83]. An autism diagnosis is still predominantly based on behaviour in childhood, with a considerable sex bias such that females tend to be underdiagnosed [36] or diagnosed later [37]. This is in contrast to CSS, which is more often diagnosed in adulthood and where females are more likely to be diagnosed than males [33]. Increased understanding of the lived experience of autism has improved awareness of the many co-occurring health issues autistic people experience [84] but this is not reflected in the current diagnostic criteria [83, 85]. It could be the case that the CSI has captured physical symptoms that have always been common in the autistic population, but not recognised because they were not obvious to the external observer.

Clinically, this study has important implications. We found that the relationship between autistic traits and CSS symptoms was fully mediated by anxiety and sensory sensitivity. Autistic people often struggle to access mental health support or occupational therapy, particularly in adulthood [86, 87]. Our research suggests that increased anxiety and sensory sensitivity could have wider physical health implications, and longitudinal research could explore further whether interventions focussed on these aspects might mitigate the risk of autistic people developing a CSS later in life.

Limitations

A strength of this study is that these data were reported as part of an ongoing data collection in the NAR volunteer register, with participants not explicitly primed as to the aims of the CSI data collection. Therefore, it is unlikely that these findings are inflated due to selection or attrition bias.

In terms of limitations, firstly, although we were able to include a large sample of autistic participants, we did not have a control or CSS only group. Future research including these groups would add additional power and allow for a greater exploration of the relationships between the main variables in the wider population. Secondly, it could be the observed association between autism and CSS relates more to the wording of the questions in the CSI [40] and reflects an overlap of symptoms rather than a true co-occurring condition (e.g. sensory sensitivities, anxiety attacks,

child trauma). Further studies could utilise different illness-specific instruments and alternative instruments to the CSI to establish whether a relationship between autism and CSS remains on a condition-by-condition basis. In this study, CSS diagnoses were self-reported and not independently verified. It is possible that participants may have indicated conditions that were not formally clinically diagnosed. Future studies recruiting via health services or incorporating additional questions are needed to confirm these findings. Finally, as a cross-sectional study, this research is limited when exploring cause and effect, such as through the path analyses, and any inferences drawn need to be treated with caution. Longitudinal studies may be able to shed more light on how and why autism and CSS might be related.

Conclusions

In conclusion, in a large sample of autistic adults, 21% had a diagnosis of at least one CSS included in this study, and the majority experienced symptoms of CSS, with 60% scoring at or above the clinical cut-off for a likely CSS on a widely used screening measure.

The results suggest that clinicians need to be aware of a possible association between CSS and autism and mindful of the potential risk of misdiagnosis or diagnostic overshadowing. This is particularly true for females, in whom autism is underdiagnosed [36]. Future research could consider whether autism screening in the diagnostic CSS diagnostic process might be appropriate, for example, and consider whether physical symptoms in autism may warrant evaluation for a CSS bearing in mind the high percentage of autistic adults in this sample that experienced CSS symptoms but did not have a CSS diagnosis.

Most importantly, practitioners should recognise that physical health symptoms and co-occurring conditions are common in autistic people, and that these symptoms can be treated to improve overall quality of life.

Abbreviations

AQ: Autism Spectrum Quotient; CSI: Central Sensitization Inventory; CSS: Central Sensitivity Syndromes; FMS: Fibromyalgia Syndrome; HADS: Hospital Anxiety and Depression Scale; IBS: Irritable Bowel Syndrome; ME/CFS: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; NAR: Netherlands Autism Register; PTSD: Post-Traumatic Stress Disorder; SPQ: Sensory Perception Quotient; TMJD: Temporomandibular Joint Disorder

Declarations

Ethics approval and consent to participate

The protocol of this study was approved by the ethics committee of the VU University Medical Center (approval number 2013/45) and all participants provided written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are available in the Netherlands Autism Register, www.nederland-sautismeregister.nl/english/.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SG proposed the research question and developed the initial research design. SB, AS and RW prepared and administered the NAR questionnaires, and the corresponding data. SG analysed and interpreted the data with support from RAH and SN and wrote the first draft of the manuscript. All authors read, contributed to, and approved the final manuscript.

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Figures

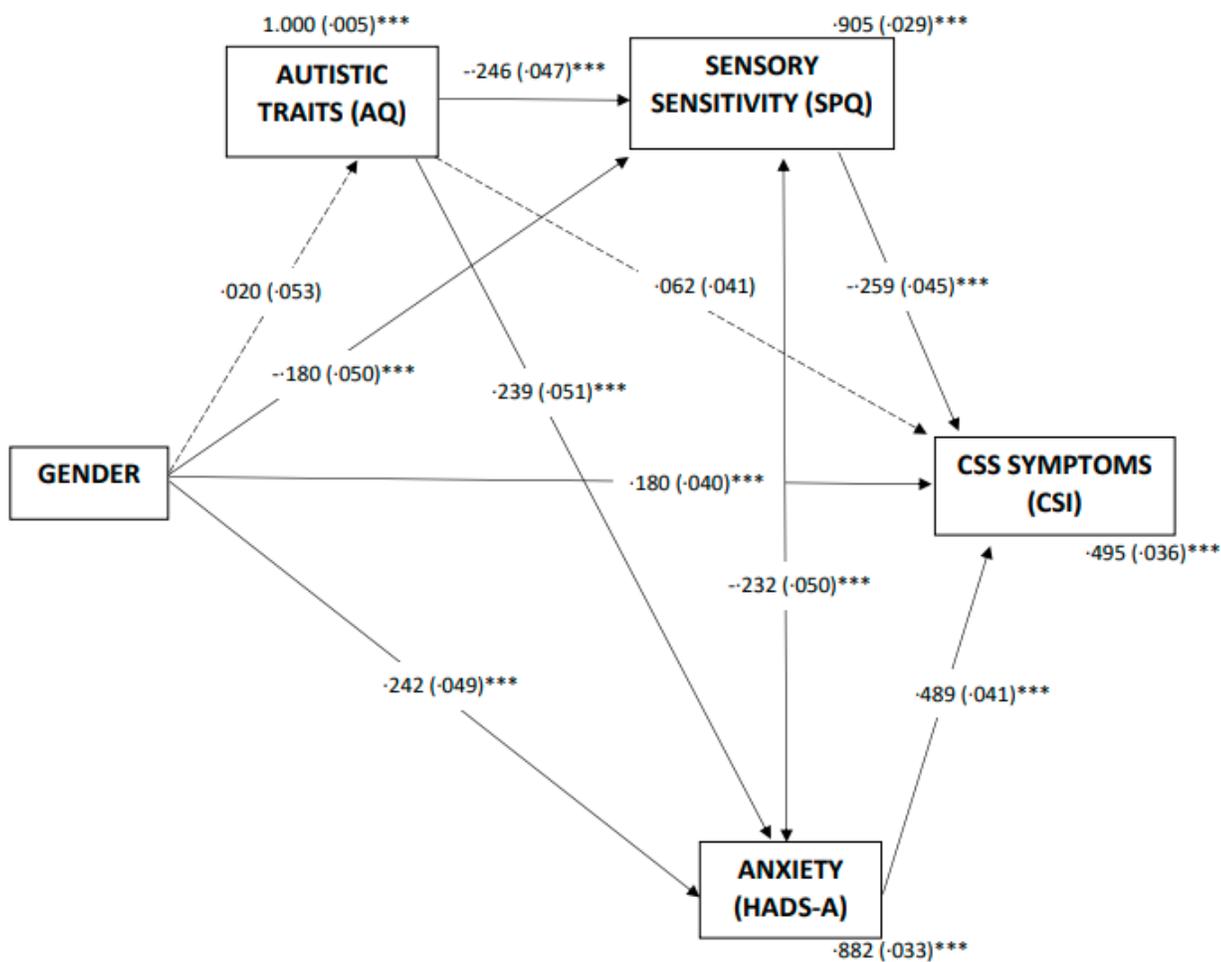


Figure 1

Path model for the effect of Sex on CSI scores Path model of CSS symptoms in autistic adults – standardized path coefficients (S.E), covariates and residual variance shown. * $p < .05$; ** $p < .01$; *** $p < .001$

Supplementary Files

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