



# The relationship of cortical activity induced by pain stimulation with clinical and cognitive features of somatic symptom disorder: A controlled functional near infrared spectroscopy study\*

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## ABSTRACT

**Objective:** The neurobiological correlates of Somatic Symptom Disorder (SSD) introduced in the DSM-5 has been the focus of a limited investigation. We aimed to examine the cortical response to painful stimuli and its relationship to symptom severity as well as cognitive and psychological characteristics in proposed models of somatoform disorders.

**Methods:** We measured hemodynamic responses by 52-channel functional near-infrared spectroscopy. We compared the cortical response to painful stimuli in index patients with SSD ( $N = 21$ ) versus age, and gender matched healthy control subjects ( $N = 21$ ). We used brush stimulation as the control condition. We analyzed the relationship of cortical activity with SSD symptom severity as well as somatosensory amplification (SSA), alexithymia, dysfunctional illness behaviour, worry, and neuroticism.

**Results:** Patients with SSD had higher somatic symptom severity, SSA, alexithymia, neuroticism, illness-related worry, and behaviour. Somatic symptom severity was predicted by a model including SSA and subjective feeling of pain in the index patients. Activity in the left-angular and right-middle temporal gyri was higher in the SSD subjects than the controls during pain stimulation. Positive correlations were detected between mean pain threshold levels and left middle occipital gyrus activity, as well as between SSA-scores and right-angular gyrus activity during pain condition in the index patients with SSD.

**Conclusion:** We present the first evidence that representation of pain in terms of cortical activity is different in subjects with SSD than healthy controls. SSA has functional neuroanatomic correlates and predicts symptom severity in SSD and therefore is involved as a valid intermediate phenotype in SSD pathophysiology.

## 1. Introduction

Medically unexplained symptoms with underlying physical complaints are associated with significant disability and significant health-

related impairments in social and occupational functioning [4]. One third of outpatient visits are associated with medically unexplained somatic problems that have a significant economic impact on healthcare costs with average per-capita expenditure annually of 4700 USD in the

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United States alone [1–3].

The Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM IV-TR) [5] recognized an umbrella category of “somatoform disorders” [6–8]. The most typical of this set of disorders was somatization disorder (SD) with onset prior to 30 years of age over a period of several years [9,10]. The diagnostic threshold of SD was relatively high and many patients with somatic symptoms were unable to meet the full criterion requirement. In the DSM-5 [11], SD has been relabelled as “somatic symptom disorder (SSD)” under the meta-category “somatic symptom and related disorders” [12], with the focus shifting from criterion B symptoms in DSM-IV-TR to criterion A in DSM-5, namely, disproportionate and persistent illness thoughts, high level of anxiety about health or symptoms (i.e., feelings), or excessive time and energy devoted to the symptoms and health concerns (i.e., behaviours) [13]. The validity of the SSD diagnosis has continued to be under discussion [12,14] and future research is needed to elucidate the new SSD construct at different levels of explanation [15].

Studies that focused on neurobiology provide some clues on its underlying pathophysiology. An important hypothesis is the central sensitization (CS) theory that refers to increased neuronal responsiveness through a dual process including disproportionate response to peripheral stimuli at the spinal level, and further augmentation of the response in higher cortical systems leading to continuous state of alertness disrupted by salience attribution, attentional bias, and mismatch-negativity [16–18]. Prefrontal cortex (PFC) is involved in descending pain modulation; it also plays a role in cognitive and emotional processing of pain [19–21].

Boeckle et al. (2016) [22] published a meta-analyses on the neural correlates of somatoform disorders [22] and reported five brain regions that may be indicated in SD pathophysiology: the premotor and supplementary motor cortices; the middle frontal gyrus; the anterior cingulate cortex; insula; and the posterior cingulate cortex. These regions are considered important elements of the neuro-matrix associated with sensation of pain [23–25]. The neuro-matrix does not solely evaluate the pain experience as a physical sensation but also has been shown to comprise three associated components that process sensory, affective, and cognitive features of pain [22]. Since the focus of the new SSD diagnosis has shifted from the amount of physical complaints to cognitive, emotional and behavioural correlates of these symptoms, the neuro-matrix may be informative to test the validity of the new SSD diagnosis as well. The primary aim of this study was to examine cortical activity in elements of the pain neuro-matrix as well as the CS response to painful stimuli in SSD.

We were also interested in the association of previously proposed intermediate phenotypes in SD with cortical response to pain. An important cognitive explanation of somatization is the somatosensory amplification (SSA) [26] which refers to the tendency to experience a somatic sensation as intense, noxious, and disturbing. SSA leads to increased awareness of, and attention to, bodily sensations and may lead to catastrophizing cognitions such as suffering from an undiagnosed illness [27]. Another proposed construct in theory of somatization is alexithymia [28] which is a failure to comprehend and verbalize emotions. Alexithymic individuals fail to differentiate bodily sensations from emotional states. The patients with SD were shown to receive high scores in the Toronto Alexithymia Scale (TAS) [29]. Neurotic character traits (NCT) such as introversion were also found to be associated with somatization [30].

Functional near-infrared spectroscopy (fNIRS) is a recent, non-invasive neuroimaging method capable of measuring cortical activity in a natural sitting position which may be important to measure such activity patterns in psychiatric patients [31,32]. Studies showed that fNIRS is successful at discriminating cortical response to painful stimulus in healthy individuals [33], and that disturbance in fronto-temporo-parietal connectivity as ascertained by fNIRS signals may distinguish subjects with SSD from healthy control subjects [34]. In short, as a new diagnostic category, SSD prioritizes cognitive and emotional aspects of

pain, and its neurobiology needs to be further examined [35]. We here hypothesized that patients with index diagnosis of SSD would have increased activation in cortical areas involved in pain processing. We also hypothesize that SSA, alexithymia, NCTs as well as level of illness related behaviour and worry will be associated with symptom severity as well as cortical activity in subjects with SSD.

## 2. Methods and materials

### 2.1. Participants

The participants were selected from consecutive outpatient among referrals diagnosed with persistent symptoms of DSM-5 SSD with predominant pain at the Ankara University Faculty of Medicine Psychiatry Department between September 2018 to March 2019. Inclusion criteria were: (i) age between 18 and 65 years; (ii) completion of at least eight years of primary education; (iii) absence of concurrent neurological conditions (e.g., stroke, multiple sclerosis), head trauma with loss of consciousness, and physical disability (e.g., vision, hearing, motor deficits) that would interfere with study procedures. A total of 59 subjects with SSD met the inclusion criteria, among whom 6 refused to participate. Those with psychiatric comorbidity including existence of a mood episode ( $N = 19$ ), psychotic disorder ( $N = 2$ ), anxiety disorder ( $N = 4$ ), and previous diagnosis of a personality disorder ( $N = 5$ ) were excluded. The SSD final study group (SSDG) comprised of the remaining 23 subjects. The control group (CG) ( $N = 23$ ) comprised of participants chosen from among healthy volunteers who were frequency matched with the index SSD subjects in terms of gender, chronological age, and educational level. Selection criteria were similar in both groups in terms of age, education and neurological disability. Two participants in each group did not conform with the fNIRS environment leaving 21 SSD index, and 21 CG subjects. The study was approved by the Ankara University Faculty of Medicine Research Ethics Committee (ID:04-240-18) and all participants were enrolled after having signed written informed consent. Sociodemographic characteristics of the two groups are presented in Table 1.

### 2.2. Psychometric evaluations

The following instruments were administered in two sessions each lasting approximately 30 min: Somatic symptom severity was measured by the Patient Health Questionnaire-15 (PHQ-15) [36,37], SSA was evaluated by the Somatosensory Amplification Scale (SSAS) [38,39], alexithymia was measured by the Toronto Alexithymia Scale (TAS)

**Table 1**  
Demographics and clinical characteristics of the two groups.

Variables	SSDG ( $N = 21$ )	CG ( $N = 21$ )	
Gender (f/m)	13 / 8	14 / 7	$X^2 = 0.10$ , $p = .50$
Age (years) ( $\bar{x} \pm SD$ )	$44.62 \pm 12.77$	$39.90 \pm 14.01$	$t = 1.14$ , $p = .26$
Education (high school/university)	14 / 7	11 / 10	$X^2 = 0.53$ , $p = .27$
MPT (gf/mm <sup>2</sup> ) ( $\bar{x} \pm SD$ )	$184.76 \pm 22.04$	$189.04 \pm 14.45$	$t = -0.75$ , $p = .46$
VAS scores ( $\bar{x} \pm SD$ )			
VAS-total	$67.14 \pm 19.07$	$62.62 \pm 16.01$	$t = 0.03$ , $p = .96$
VAS-1	$68.81 \pm 20.73$	$72.62 \pm 14.96$	$t = 0.83$ , $p = .41$
VAS-2	$73.57 \pm 21.45$	$73.81 \pm 17.31$	$t = -0.68$ , $p = .50$
VAS-3	$69.84 \pm 18.39$	$69.68 \pm 14.07$	$t = -0.04$ , $p = .97$

Note. SSDG = Somatic symptom disorder group, CG = Control group, SD: standard deviation, VAS: Visual Analog Scale, MPT = Mean pain threshold level, gf = gram force,  $\bar{x}$  = mean, SD = standard deviation.

[40,41], and NCTs were assessed by the Eysenck Personality Questionnaire-Short Form (EPQ-s) [42,43]. Illness related behaviour and worry were quantified using Scale for the Assessment of Illness Behaviour (SAIB) [44,45] and the Whiteley Index (WI) [46,47], respectively.

### 2.3. Experimental design

#### 2.3.1. Assessment of individual mean pain thresholds (MPTs)

We measured pain thresholds of every single participant via a pain stimulation protocol using the Quantitative Sensory Testing (QST) method [48]. We used the Electronic Von Frey (eVF) anesthesiometer (Ugo Basile Co., Varese, Italy) a widely used instrument to measure individual pain thresholds reliably [49,50]. The eVF has a rigid pressure pin and 1–1000 g force/mm<sup>2</sup> can be applied. As described in QST protocols, we applied crescendo pressure stimulus to participants' first interphalangeal joints bilaterally. We asked participants to notify immediately when they felt pain and recorded stimulus intensity. This protocol was applied in five runs with 20 s intervals. In each run, the stimulus was skidded one mm sideward bilaterally to prevent habituation. The MPT was calculated as the average gm force/mm<sup>2</sup> of the five runs (Table 1).

#### 2.3.2. The pain stimulation task

The task is a slightly modified version of a pain stimulation task utilized in assessment of efficacy of transcutaneous electrical nerve stimulation in fibromyalgia patients published by our research group [99]. The difference was that the duration of the pain stimulation condition in the present study was 24 s instead of 20 s. This 24 s duration is consistent with previously published pain stimulation protocols [101–103]. The task consisted of a Pain Condition (PC) and a Control Condition (CC). In the PC, we applied painful stimuli at the exact individual MPT intensity. The stimuli were applied to the right thumbs, 12 times in every 2 s. We used the Visual Analog Scale (VAS) following every stimulation to rate subjective intensity of pain between 0 and 100. Mean VAS-ratings in each group are presented in Table 1. In the CC, we applied a brush stimulus by manually sliding a toothbrush on the right thumb rhythmically for every second for 24 s. We used a block design in which participants were exposed to each two conditions three times. The order of the PC and the CC was pseudo-randomized as illustrated in Fig. 1.

### 2.4. Neuroimaging protocol

Neuroimaging was conducted at the Ankara University Brain Research Center. Hitachi ETG-4000 continuous wave fNIRS system (Hitachi Co., Japan) was used to measure cortical activity. The fNIRS system allows measuring hemodynamic activity changes of oxyhemoglobin ( $\Delta\text{HbO}_2$ ) and deoxyhemoglobin ( $\Delta\text{Hb}$ ) through changes in their concentrations. Near-infrared light for two types of wavelengths (695 and 830 nm) were sent and scattered light were captured via source and detector optodes respectively. Optical wavelength densities were converted into  $\Delta\text{HbO}_2$  and  $\Delta\text{Hb}$  values (in mMmm) using the modified

Beer-Lambert law [51]. Since  $\Delta\text{HbO}_2$  is assumed to reflect cognitive activation due to having higher signal/noise ratio and higher correlation with cerebral blood flow than  $\Delta\text{Hb}$  has [52,53], we focused on  $\Delta\text{HbO}_2$  during the PC and the CC relative to the rest periods in further analyses.

We set the  $3 \times 11$  thermoplastic optode holder over the line of right ear and left ear by calculating two spots: C3 and C4 used in electroencephalography 10–20 electrode positioning system. These two regions were accepted as right and left post-central gyrus which were shown to correspond with right and left primary somatosensory cortex, respectively [54]. The distance between emitter/detector pairs was 3 cm. So, total 180 cm<sup>2</sup> cortical area (6 cm from sagittal axis-pre-Cz and post-Cz- and 30 cm from coronal axis-left and right-tragus) has been investigated. A 3D-digitizer (Polhemus Co., Vermont) was used for determining exact channel positions. Spatial registration was conducted on MNI-template for every participant according probe positions via NIRS-analysis package [55]. The coordinate values of all participants were averaged according to fNIRS spatial registration methods [56] and visualized by BrainNet Viewer Toolbox [57] (Figure-2).

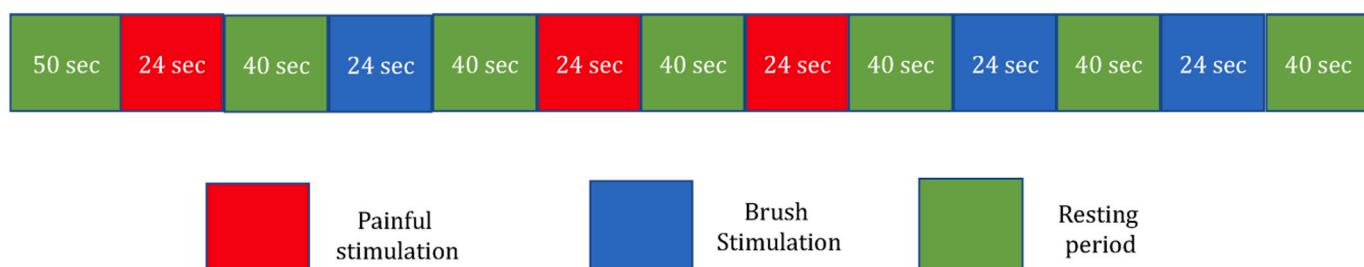
### 2.5. Data pre-processing

Pre-processing steps of  $\Delta\text{HbO}_2$  and  $\Delta\text{Hb}$  signals were conducted using MATLAB (MathWorks, Inc., Natick, Massachusetts). Pre-processing steps were: baseline correction; detrending to eliminate low-frequency drift; exclusion of highly contaminated channels due to motion artefacts; filtering for systematic artefacts such as heartbeat and respiration; smoothing; and averaging of condition blocks. Data during the rest periods was used as the baseline activity. The task activity reflects changes in HbO<sub>2</sub> concentrations according to those baseline periods. There were two baselines. The pre-task baseline period was the mean of 9 s rest period preceding the task (PC or CC). The post-task baseline was the mean of the last 7 s of the post task rest period. We used band-pass filter with a 0.01–0.5 Hz cut-off frequency and moving average (MA-window: 5 s.). The fNIRS device marks sharp signal changes (over 0.4 mMmm in over two seconds) as body movement artefacts (BMAs). BMAs were re-examined and confirmed by a researcher blind to the study groups. Data with BMAs were removed from further analyses.

### 2.6. Statistical analyses

Chi-Square tests were conducted to compare gender and educational differences between groups. Independent samples-t-test was performed for age and comparison of MPT's and VAS-mean ratings. SSAS, TAS, WI, EPQ-s and SAIB scores were compared with independent samples-t-tests or Mann-Whitney U tests where appropriate. We also performed a stepwise linear regression analysis to explore whether a model consisting of SSAS, TAS, WI, EPQ-neuroticism and VAS-mean ratings as independent variables explain the severity of somatic symptoms as ascertained by the PHQ-15 score as the dependent variable in the SSDG.

Neuroimaging data was analyzed by 2 'Group' (SSDG vs. CG)  $\times$  'Condition' (PC and CC)  $\times$  'Channel' (52 measurement channels) mixed-ANOVA design. Greenhouse-Geisser correction was used for



**Fig. 1.** Illustration of the experimental design.

Type-1 errors that may be associated with sphericity violations and Bonferroni correction was employed in post-hoc comparisons to prevent Type-1 errors related to multiple comparisons. Spearman correlation coefficients were calculated between mean channel activity projecting to cortical regions (Fig. 2) during the two conditions and psychological test scores. In these correlation analyses, False Discovery Rate (FDR) method [58] was used to prevent possible Type-1 errors that may stem from multiple testing.

### 3. Results

Age, gender and education level were comparable in both groups (Table 1).

The individual MPTs [ $t(40) = -0.75, p = .46$ ] and VAS-ratings were comparable among the two groups [Total-VAS:  $t(40) = 0.03, p = .98$ ; VAS-1:  $t(40) = 0.83, p = .41$ ; VAS-2:  $t(40) = -0.68, p = .50$ ; VAS-3:  $t(40) = -0.04, p = .97$ ] (Table 1).

Psychological variables indicated significant differences between the two groups (Table 2). Expectedly SSDG scored higher than the CG in PHQ-15 [ $t(40) = 7.51, p < .001$ ], SSAS [ $t(39) = 4.80, p < .001$ ], and TAS [ $t(37) = 3.01, p = .005$ ] and lower than the CG in inversely-scored SAIB [ $t(39) = -4.71, p < .001$ ], and the WI [ $Z = -5.20, p < .001$ ] (Table 2). In terms of character features, only difference between the two groups was found in the EPQ-neuroticism dimension where the SSDG took higher scores than the CG ( $Z = -3.73, p < .001$ ) (Table 2).

The regression analysis revealed that a model consisting of VAS-mean ( $\beta = 0.45, t = 2.44, p = .03$ ) and SSAS-scores ( $\beta = 0.43, t = 2.35, p = .03$ ) explains the 42% of variance in the PHQ-15 score in the SSDG [ $F(2) = 7.44$ , adjusted  $R^2 = 0.42, p = .005$ ]. WI, TAS and EPQ-neuroticism scores were excluded from the model.

ANOVA revealed that 'Group' main-effect was not significant. However, the 'Condition' main-effect was significant [ $F(1,49) = 12.26$ ,

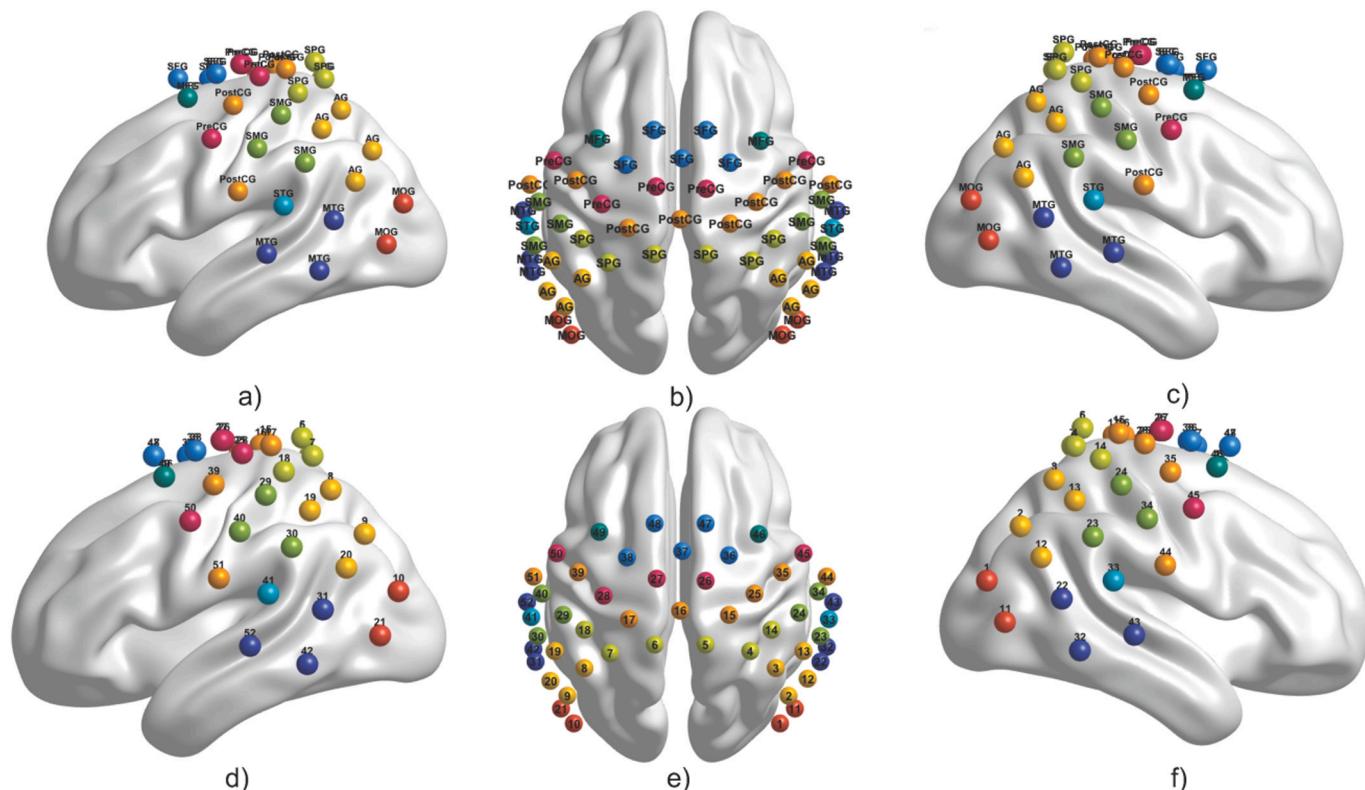
**Table 2**  
Comparison of the two groups in psychological measures.

Variables	SSDG	CG	
PHQ-15 ( $\bar{x} \pm SD$ )	$13.71 \pm 4.68$	$4.52 \pm 3.09$	$t = 7.52, p < .001^*$
SAIB <sup>a</sup> ( $\bar{x} \pm SD$ )	$29.95 \pm 13.70$	$51.52 \pm 15.49$	$t = -4.71, p < .001^*$
SSAS ( $\bar{x} \pm SD$ )	$34.00 \pm 7.49$	$22.65 \pm 7.65$	$t = 4.80, p < .001^*$
TAS ( $\bar{x} \pm SD$ )	$48.21 \pm 11.62$	$37.10 \pm 11.44$	$t = 3.01, p = .005^*$
WI [ $\bar{x}$ (min-max)]	8 (7-13)	14 (9-14)	$Z = -5.20, p < .001^*$
EPQ [ $\bar{x}$ (min-max)]			
Extraversion	3 (0-6)	3 (0-6)	$Z = -0.29, p = .77$
Psychoticism	1 (0-4)	2 (0-3)	$Z = -1.55, p = .12$
Neuroticism	5 (3-6)	2 (0-5)	$Z = -3.73, p < .001^*$
Falsification	5 (2-6)	5 (1-6)	$Z = -0.35, p = .73$

Note. SSDG = patients with SSD, CG = health control subjects, PHQ-15 = Patients Health Questionnaire-15, SAIB = Scale for the Assessment of Illness Behaviour SSAS = Somatosensory Amplification Scale, WI = Whiteley Index, TAS = Toronto Alexithymia Scale, EPQ-s = Eysenck Personality Questionnaire-Short Form,  $\bar{x}$  = mean,  $\tilde{x}$  = median, min = minimum, max = maximum, SD = standard deviation \* = Statistically significant.

$p = .001, p_{\text{H}}^2 = 0.24$ . The post-hoc analyses revealed that this significance stemmed from higher activity during the PC relative to the CC (MD: 0.027, SE: 0.008,  $p = .001$ , 95%CI: 0.011–0.042).

The 'Channel' main-effect [ $F(51,461) = 2.61, p < .001, p_{\text{H}}^2 = 0.06$ ] and the 'Group'  $\times$  'Condition'  $\times$  'Channel' interaction [ $F(9,356) = 2.1, p < .03, p_{\text{H}}^2 = 0.05$ ] were significant. Cortical activity in the two groups during PC and CC in all measurement channels is presented in Fig. 3 and in Supplementary Table 1. The activity maps in the two groups during the two conditions are presented in Fig. 4. Post-hoc analyses from the 'Group' perspective showed that triple interaction stems from higher activity among the SSDG than the CG in Channels 19 and 32 which project to left-AG and to right-MTG respectively during the PC, while activity in right-MTG was higher among the CG than the SSDG during



**Fig. 2.** Projection of measurement channels and ROI's on the cortex.

Presentation of measurement channels: a) left-sided view; b) top-view; c) right-sided view. Presentation of ROI's: d) left-sided view; e) top-view; f) right-sided view. SFG: Superior Frontal Gyrus, MFG: Middle Frontal Gyrus, Pre CG: Pre central Gyrus, Post CG: Post central Gyrus, SMG: Supramarginal Gyrus, STG: Superior Temporal Gyrus, MTG: Middle Temporal Gyrus, AG: Angular Gyrus, SPG: Superior Parietal Gyrus, MOG: Middle Occipital Gyrus.

the CC (Table 3). Post-hoc analyses from the 'Condition' perspective revealed that activity in several cortical regions in both groups were higher during the PC than the CC (Table 4).

### 3.1. Correlations between brain activity and psychological features

Although we observed several correlations between the cortical activity and behavioural ratings (Table 5), only a few survived after the FDR correction. Among the SSDG, MPT values were positively correlated with activity in the left-MOG ( $r = 0.56, p = .008$ ), SSAS-score was positively correlated with the right-AG activity ( $r = 0.75, p < .001$ ) during the PC. The correlation heat map between the SSAS-scores and cortical activity is presented in Fig. 5. Among the CG, TAS-score was negatively correlated with left-SPG activity during the CC ( $r = -0.76, p < .001$ ).

## 4. Discussion

The study findings provide important validation of the new DSM-5 SSD diagnosis concerning differences in representation of pain in terms of cortical hemodynamic activity between subjects with SSD and healthy controls. The study also underscores that somatosensory amplification (SSA) is an important predictor of symptom severity in DSM-5 SSD with its own functional cortical correlates identified by means of fNIRS.

First, as anticipated, the SSDG had higher scores than the CG in PHQ-

15, SSAS, TAS, EPQ-neuroticism and lower scores for the inversely scored WI the SAIB; however, the two groups were comparable in terms of MPTs and VAS ratings. Second, the somatic symptom severity was predicted by a model including VAS-mean and SSAS-scores in the SSDG. Third, pain compared to brush stimulation was associated with higher activity in several areas in both groups. Fourth, the activity in the left-AG and the right-MTG were higher in the SSDG than the CG during PC. Finally, the positive correlations were detected between MPTs and left-MOG activity and between SSAS-score and right-AG activity during PC in the SSDG.

Although previous studies have assessed the role of psychological features related to the DSM-IV SD diagnosis [59–64], to our knowledge, the current study is the first to demonstrate that the new DSM-5 SSD diagnosis is also associated with SSA, alexithymia, neuroticism, worries as well as behaviours associated with somatic symptoms. Given that the shifting emphasis of the DSM-5 diagnostic criteria to cognitive and behavioural consequences of somatic symptoms, this is an expected finding and underscores the importance of these characteristics in SSD pathophysiology. On the other hand, it was rather unexpected that the MPTs were not different between the groups.

Some studies reported that patients with former diagnosis of SD [65], fibromyalgia [66] as well as somatoform pain disorder (somatoform-PD) [67] have lower pain thresholds and perceive higher subjective pain than healthy control subjects [68,69]. The discrepancy between these results may stem from methodological differences. In a number of previous studies with positive results, painful stimuli were applied to thenar

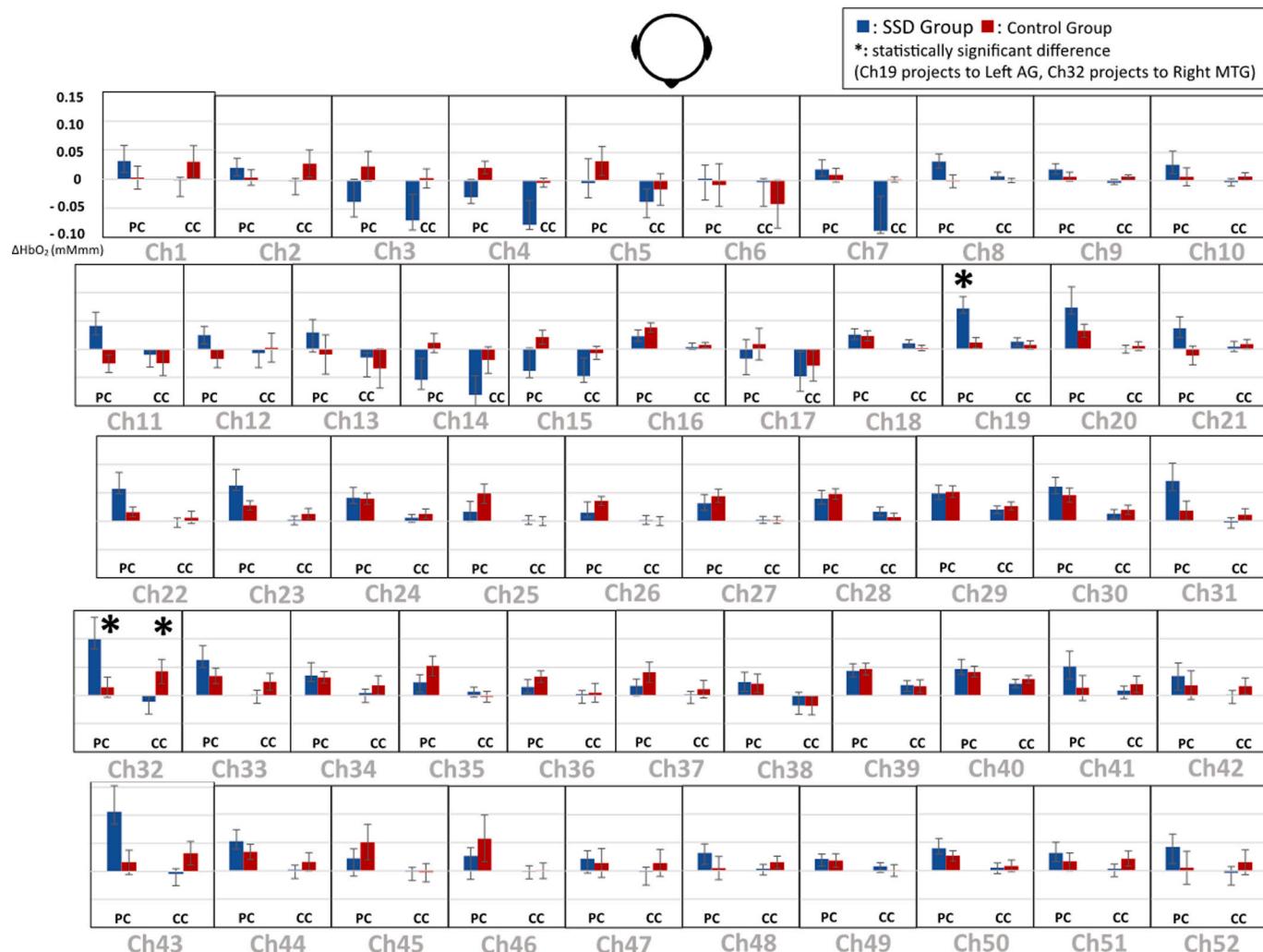
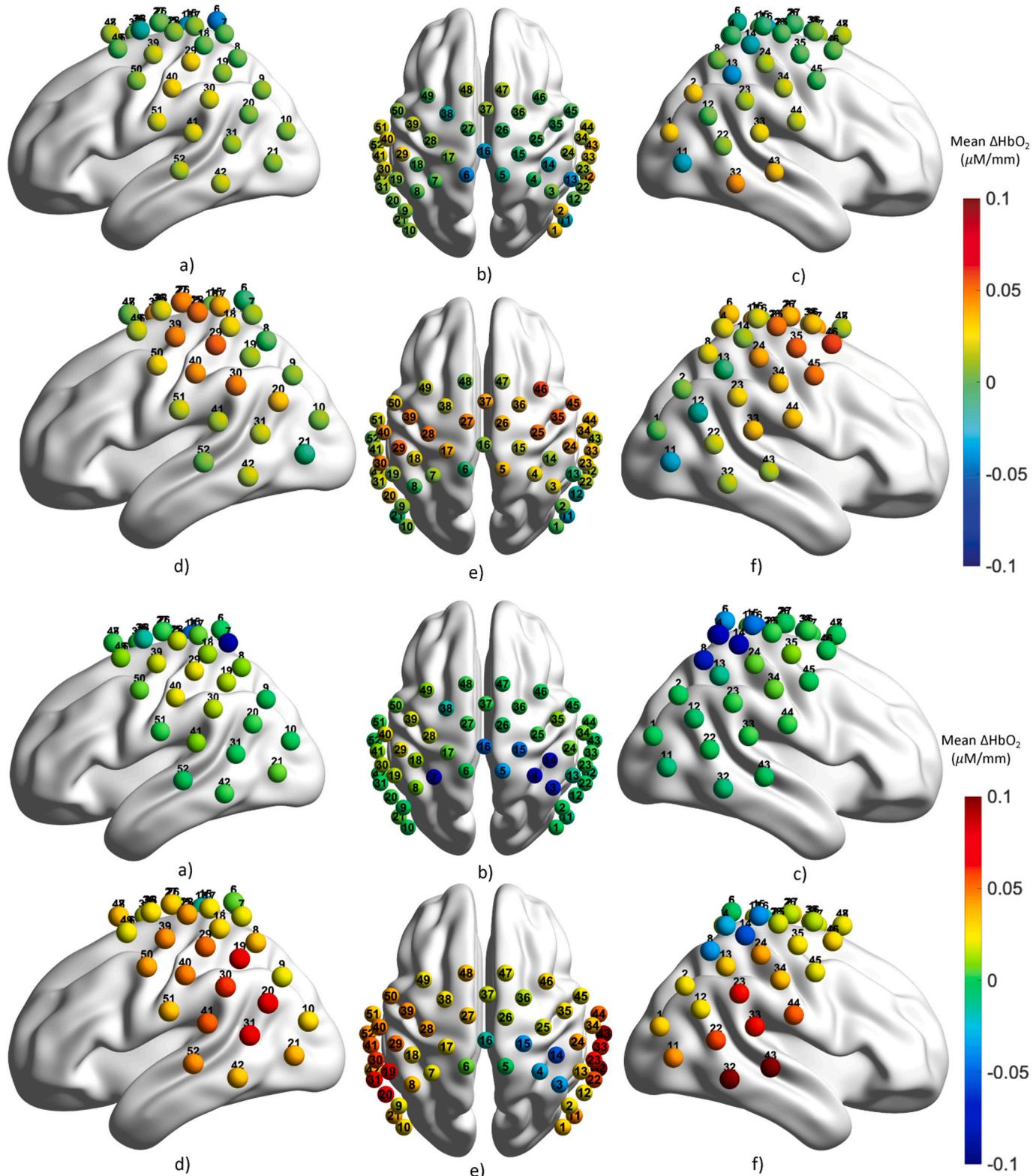


Fig. 3. Cortical activity in the two study groups during the pain and the control conditions.



**Fig. 4.** Activity heat maps during the two conditions in the two groups.

eminence of hands [70], middle fingers [67] or non-dominant hands [69]. We applied pain to the right thumb in right-handed participants, but a previous study found that pain sensitivity to contralateral body side may be higher [71]. It needs to be noted that, somatosensory cortical representation (homunculus) is bigger than the other part of extremities in dominant-hand thumb that could interfere with the

results. Furthermore, presence of a mood episode at the time of assessment was an exclusion criterion in this study and depression may interfere in pain perception [72,73]. However, VAS-ratings were also not different among the two groups suggesting that similarity between them in physical and subjective measures of pain may be a valid finding associated with the nature of the SSD diagnosis.

**Table 3**

'Channel × Condition × Group' Interaction from the Perspective of 'Group' Comparisons at each level of 'Channel' and 'Condition'.

Ch	Hemisphere-BA, (Percent overlap)	Corresponding cortical structure	MNI			Condition	Group	MD	SE	P
			X	Y	Z					
19	L-BA39, (0.66)	Angular Gyrus	-58	-49	51	PC	SSDG>CG	0.061	0.022	0.01
32	R-BA 21, (0.77)	Middle Temporal Gyrus	70	-47	-7	PC	SSDG>CG	0.085	0.042	0.048
32	R-BA 21, (0.77)	Middle Temporal Gyrus	70	-47	-7	CC	CG > SSDG	0.053	0.023	0.03

Note. Ch: Channel, L: Left, R: Right, BA: Brodmann Area, MNI: Montreal Neurological Institute, SSDG: Somatic Symptom Disorder Group, CG: Control Group, PC: Pain Condition, CC: Control Condition, MD: Mean difference, SE: Standard error, Results are presented as mMm. Bonferroni correction was applied for all comparisons. Channel numbers and average coordinate positions with corresponding cortical structures registered onto MNI space after using LONI probabilistic cortical atlas (LPBA) [100].

**Table 4**

'Channel × Group × Condition' Interaction from the Perspective of 'Condition' Comparisons at each level of 'Channel' and 'Group'.

Group	Ch	Hemisphere- BA, (Percent overlap)	Corresponding cortical structure	MNI			Condition	MD	SE	P
				X	Y	Z				
SSDG	7	R-BA5,(0.92)	Sup. parietal gyrus	-32	-50	72	PC > CC	0.108	0.044	0.02
	8	R-BA39,(0.71)	Angular gyrus	-44	-57	72	PC > CC	0.025	0.011	0.03
	9	L-BA39,(0.96)	Angular gyrus	-52	-70	42	PC > CC	0.023	0.009	0.02
	13	R-BA39,(0.86)	Angular gyrus	59	-49	51	PC > CC	0.044	0.018	0.02
	17	L-BA1,(0.56)	Postcentral gyrus	-23	-34	76	PC > CC	0.019	0.008	0.02
	19	L-BA39,(0.66)	Angular gyrus	-58	-49	51	PC > CC	0.059	0.015	< 0.001
	20	L-BA39,(0.96)	Angular gyrus	-60	-63	29	PC > CC	0.073	0.027	0.01
	22	R-BA21,(0.72)	Mid. temporal gyrus	67	-54	13	PC > CC	0.057	0.023	0.02
	23	R-BA40,(0.56)	Supramarginal gyrus	-60	-63	29	PC > CC	0.060	0.021	0.007
	24	R-BA40,(0.96)	Supramarginal gyrus	57	-31	57	PC > CC	0.035	0.014	0.02
	27	L-BA4,(0.63)	Precentral gyrus	-10	-15	78	PC > CC	0.029	0.011	0.01
	28	L-BA1,(0.59)	Postcentral gyrus	-35	-23	73	PC > CC	0.023	0.011	0.01
	29	L-BA40,(0.65)	Supramarginal gyrus	-54	-32	57	PC > CC	0.028	0.012	0.02
	30	L-BA40,(0.88)	Supramarginal gyrus	-66	-42	37	PC > CC	0.047	0.016	0.005
	31	L-BA21,(0.53)	Mid. temporal gyrus	-67	-54	13	PC > CC	0.073	0.026	0.008
	32	R-BA21,(0.77)	Mid. temporal gyrus	70	-47	-7	PC > CC	0.111	0.035	0.003
	33	R-BA22,(0.62)	Sup. temporal gyrus	71	-34	20	PC > CC	0.062	0.023	0.01
	38	L-BA8,(0.72)	Sup. frontal gyrus	-24	-5	74	PC > CC	0.041	0.013	< 0.001
	39	L-BA1,(0.56)	Postcentral gyrus	-47	-12	61	PC > CC	0.025	0.010	0.02
	43	R-BA21,(0.66)	Mid. temporal gyrus	73	-26	-1	PC > CC	0.111	0.040	0.009
	44	R-BA1,(0.55)	Postcentral gyrus	70	-14	26	PC > CC	0.050	0.021	0.02
	50	L-BA4,(0.77)	Precentral gyrus	-57	-3	47	PC > CC	0.034	0.014	0.02
	14	R-BA5,(0.98)	Sup. parietal gyrus	44	-39	67	PC > CC	0.030	0.014	0.04
	16	R-BA1,(0.86)	Postcentral gyrus	1	-30	76	PC > CC	0.038	0.016	0.02
	17	L-BA1,(0.56)	Postcentral gyrus	-23	-34	76	PC > CC	0.031	0.008	< 0.001
	18	L-BA5,(0.65)	Sup. parietal gyrus	-44	-39	66	PC > CC	0.021	0.009	0.02
CG	25	R-BA1,(0.55)	Postcentral gyrus	36	-22	73	PC > CC	0.048	0.014	0.002
	26	R-BA4,(0.70)	Precentral gyrus	13	-16	78	PC > CC	0.040	0.012	0.002
	27	L-BA1,(0.63)	Precentral gyrus	-10	-15	78	PC > CC	0.042	0.011	< 0.001
	28	L-BA1,(0.59)	Postcentral gyrus	-35	-23	73	PC > CC	0.041	0.011	0.001
	29	L-BA40,(0.65)	Supramarginal gyrus	-54	-32	57	PC > CC	0.025	0.012	0.04
	35	R-BA1,(0.85)	Postcentral gyrus	49	-12	62	PC > CC	0.054	0.014	< 0.001
	38	L-BA8,(0.72)	Sup. frontal gyrus	-24	-5	74	PC > CC	0.039	0.012	0.003
	39	L-BA1,(0.56)	Postcentral gyrus	-47	-12	61	PC > CC	0.030	0.010	0.005
	45	R-BA4,(0.52)	Precentral gyrus	59	-3	48	PC > CC	0.054	0.021	0.01
	46	R-BA8,(0.62)	Mid. frontal gyrus	38	6	64	PC > CC	0.057	0.024	0.03

Note. SSDG: Somatic Symptom Disorder Group, CG: Control Group, Ch: Channel, BA = Brodmann Area, MNI: Montreal Neurological Institute, L: Left, R: Right, Sup: Superior, Mid: Middle, PC: Pain Condition, CC: Control Condition, MD: Mean difference, SE: Standard error, Results are presented as mMm. Bonferroni correction was applied for all comparisons. Channel numbers and average coordinate positions with corresponding cortical structures registered onto MNI space after using LONI probabilistic cortical atlas (LPBA) [100].

The major change from SD in the DSM-IV to SSD in the DSM-5 was that the former iteration required specific number of somatic complaints; the SSD diagnosis no longer has such a requirement. However, for SSD to be endorsed, the somatic symptoms must be significantly distressing or disruptive to daily life and must be accompanied by excessive thoughts, feelings, or behaviours [11]. In other words, the focus of the diagnosis has shifted from severity of physical/somatic symptoms to cognitive, emotional and behavioural consequences of these symptoms which may partly explain the lack of difference in MPTs and VAS-scores despite significant difference in cognitive, emotional and behavioural measures.

Previous studies carried out in patients with SD showed that SSA [62], alexithymia [74,75], illness related worries [76] are associated

with severity of somatic symptoms. However, the current study found considerable variance (42%) in somatic symptom severity predicted only by a model including VAS-mean and SSAS-scores, with WI, TAS and EPQ-neuroticism scores excluded from the predictive model. This suggests that SSA and subjective feeling of pain continue to be involved as important elements in the new SSD diagnosis and predict symptom severity at a greater extent than alexithymia, illness related worries or personality. Our results suggest that individuals with the new SSD diagnosis do have marked cognitive, emotional and behavioural alterations, with the severity of physical symptoms predicted mostly by SSA and subjective feeling of pain. Nevertheless, it must be noted that some psychological features such as cognitive dysfunction [77] or number of emergency service admissions [78] were not investigated in this study.

**Table 5**

Significant correlations between ROI activity and psychological ratings in the two groups.

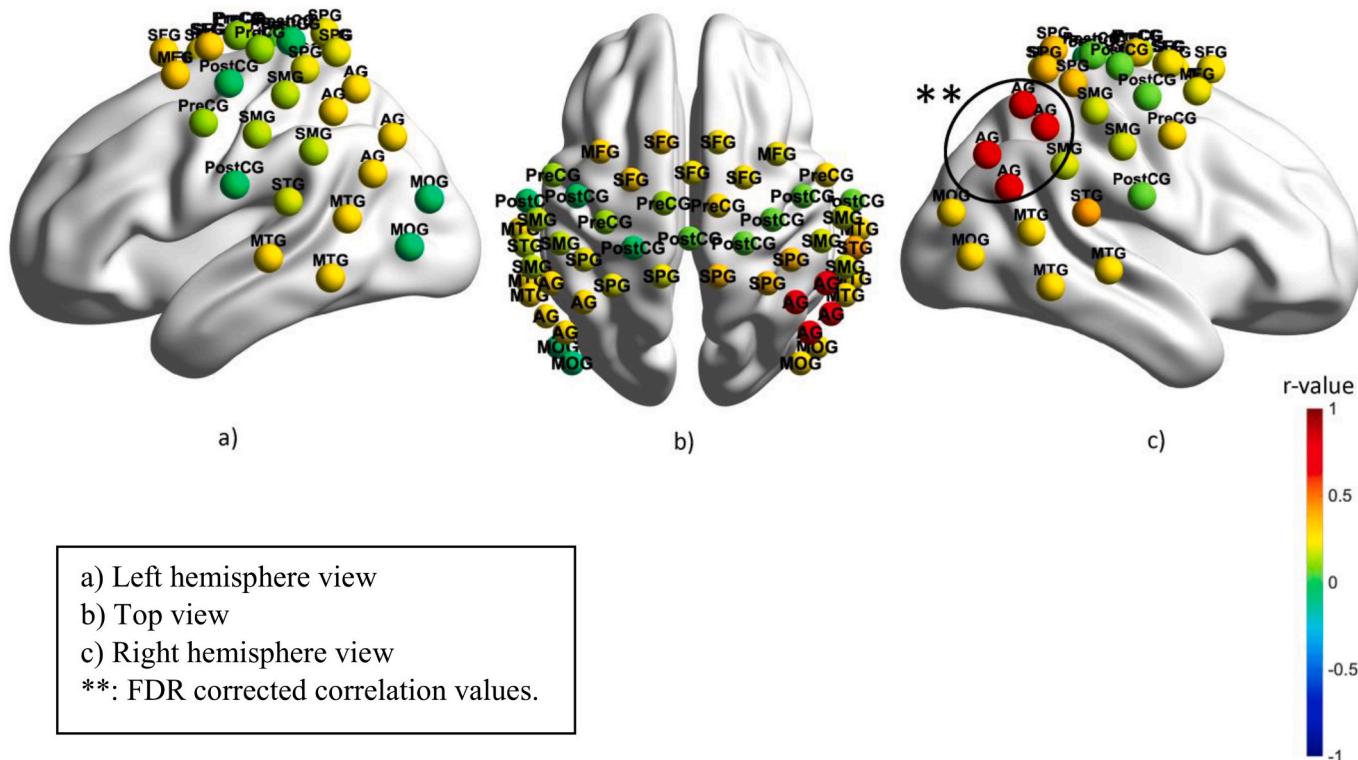
Group	Rating	Condition	ROI	
SSDG	MPT level	PC	L-Mid occipital gyrus	$r = 0.56, p = .008^*$
		PC	L-Mid temporal gyrus	$r = 0.45, p = .04$
	PHQ-15-score	PC	R-Angular gyrus	$r = 0.45, p = .04$
		CC	L-Sup temporal gyrus	$r = 0.46, p = .04$
		CC	L-Mid occipital gyrus	$r = 0.45, p = .04$
	SSAS-score	PC	R-Angular gyrus	$r = 0.74, p < .001^*$
		CC	L-Sup temporal gyrus	$r = 0.47, p = .03$
	WI-score	CC	R-Precentral gyrus	$r = -0.52, p = .02$
		CC	R-Sup temporal gyrus	$r = -0.48, p = .03$
	CG	CC	L-Mid occipital gyrus	$r = -0.49, p = .03$
		CC	L-Mid occipital gyrus	$r = 0.53, p = .02$
		CC	L-Sup parietal gyrus	$r = -0.76, p < .001^*$
		CC	L-Mid occipital gyrus	$r = 0.53, p = .02$

Note. SSDG: Somatic Symptom Disorder Group, CG: Control Group, ROI: Region of interest, MPT = Mean pain threshold level, PHQ-15: Patient Health Questionnaire, SSAS: Somatosensory Amplification Scale, WI: Whiteley Index, TAS: Toronto Alexithymia Scale, PC: Pain Condition, CC: Control Condition, L: Left, R: Right, Sup: Superior, Mid: Middle, \*: Significant after the FDR correction.

The significant ‘Condition’ main-effect is an expected finding and suggests that pain presumably associated with higher cortical load than brush is associated with higher cortical activity in both groups. Furthermore, in both groups the pain was associated with higher activity than brush stimulation in channels which project to superior parietal, superior frontal, pre-central, post-central and supramarginal gyri

(Table 3). This is not surprising as these areas were previously shown to respond to painful stimuli [79,80]. Post-hoc analysis from the ‘Condition’ perspective showed that only in the SSDG, the pain vs. brush contrast was evident in AG, MTG and STG. Furthermore, post-hoc analysis from the ‘Group’ perspective demonstrated that SSDG showed higher activity than the CG in the left-AG and to right-MTG respectively during the PC. The AG lies in the posterior of the inferior parietal lobule and is greatly expanded in humans compared with other primates [81]. Seghier (2013) performed a review of the functions and networks of the AG and reported that this region serves as a cross-modal hub where converging multisensory information is combined and integrated to comprehend events, manipulate mental representations, and re-orient attention to relevant information [82]. Activity in AG was shown to increase particularly during cognitive evaluation of pain [83]. A further study showed activation of the left-AG in healthy participants related to general evaluation of somatosensory data [84], suggesting that the left-AG may not be specific to pain perception but evaluation of it. Additionally, in one study, it was shown that AG plays a central role in pain reduction when fibromyalgia patients listen to music [85]. Li et al. (2018) reported increased gray matter volume in left-AG in drug-naïve SD patients [86]. Therefore, increased activity in AG in SSDG compared to CG may indicate that pathophysiology in SSD may involve an anomaly, represented by altered activity in the left-AG, in holistic processing (e.g., comprehension, cognitive evaluation, meaning attribution) rather than physical sensation of pain.

The MTG is primarily responsible for semantic memory and sensory processing [87] and structural and functional anomalies in this region were reported in somatoform disorders. For example, MTG gray matter volume was found to be increased in SD [86]. MTG hyperactivity was detected during resting state in somatoform-PD [88]. Besides, increased activity in right-STG and bilateral MTG was observed in somatoform-PD under pain stimulation particularly during negative emotional experience [89]. Furthermore, MTG activation was observed in response to negative emotions, without any noxious stimulation in patients with somatoform-PD [89]. Increased activity as noted in the current study in



**Fig. 5.** Correlation heat map between SSAS-score and mean  $\Delta\text{HbO}_2$  values during the pain condition among subjects in the SSDG.

this area during painful stimuli among participants in the SSDG relative to the CG may therefore suggest anomalies in emotional and/or memory-related aspects of pain processing such as anticipation, and/or exaggerated memory retrieval about negative experiences of somatic sensations in SSD. Another finding in the current study, more difficult to interpret, is the higher activity in the right-MTG in CG than SSDG during brush stimulation. Besides playing a role in memory and cognitive processes, previous research suggests that the right-MTG is involved in the emotional processing of sensations and responsive to music and rhythm [90]. Particularly, the right-MTG may respond to positive vs. negative emotional faces [91]. In the present study brush stimuli was applied in a rhythmic way, and although we did not perform a structured rating of subjective feelings during the CC, most participants reported that they found brush stimulation relaxing. It is therefore speculated that the right-MTG may show activity contrasts in response to emotional state accompanying physical stimulation in healthy individuals.

The present study found significant correlations between behavioural measures and neuroimaging data some of which remained so after FDR-correction (Table 5). The first is the positive correlation between MPTs and left-MOG activity during PC in the SSDG. This may not be surprising given that the MOG is sensitive to intensity of the pain, that is, shows higher activity during high vs. low pain conditions [79]. The other positive correlation was between the SSAS-score and right-AG activity during PC. The SSA as proposed by Barsky and colleagues (1990) as a multifaceted construct that involves an attention bias to somatic sensations together with cognitive and affective biases in processing of these sensations. With its location at the junction between the occipital, temporal, and parietal lobes, the AG is considered an important interface that conveys and integrates information between different modalities [82]. The right-AG is involved in visuospatial attention [92], shifting attention toward particular stimuli with high salience [93] such as painful stimuli in this study, and resolution of cognitive [94] and emotional [95] conflicts. In one study using evoked potentials in electroencephalography, SSA was associated with late evoked potentials that seems to be more closely related to the processing of sensory input at the higher levels of central nervous system [96]. To our knowledge, the present study is therefore the second to report an association between brain activity and SSA, and suggest that activity in the right-AG may be the neurobiological correlate of the degree of SSA in SSD. This finding underscores the importance of SSA as a putative valid intermediate phenotype in emergence of SSD.

In contrast, for the CG the study found a negative correlation between the TAS-score and activity in the left-SPG during brush simulation. Alexithymia is a trait characterized by disturbance in identification of emotions as well as external oriented cognitive style. In parallel, SPG may be involved in processing of negative emotions [97]. Moreover, lesions in the left-SPG were associated with self-disturbance in the sense of one's own body part localisations. Therefore, lower activity in the left-SPG may be representative of higher alexithymia.

Results of the present study must be evaluated with consideration of two important limitations. First, the SSDG consisted of patients followed at a university hospital. Subjects with comorbid mood episode or anxiety disorder were excluded. This was done in order to increase the internal validity of the design but inevitably may lead to less generalizable results. Second, fNIRS is capable of measuring only cortical activity. The pain network involves many sub-cortical areas such as the amygdala, brain-stem and the parabrachial nucleus [98]. The activity difference between the two groups may therefore be higher in these areas. Nevertheless, the study is the first attempt for assessing cortical reaction to pain in participants with a DSM-5 SSD diagnosis. We used the eVF as a reliable method to standardize painful stimuli and the ecological validity of the neuroimaging technique was high. The findings support the validity of the new DSM-5 SSD diagnosis and that pain stimulation in terms of cortical activity can discriminate healthy controls from index subjects with SSD, and that the SSA is an important predictor of symptom severity in SSD with its own functional neuroanatomical correlates.

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## Contributors' statement

Bora Baskak and Burçin Çolak designed the study, wrote the protocol, performed the statistical analyses and made the major contribution to the writing of the manuscript. Aykut Eken performed the pre-processing of the fNIRS data, contributed to study design as well as writing of the manuscript. Selma Çilem Uygur, Adnan Kusman, Neşe Burcu Bal, Damla Sayar and Batuhan Çakmak completed the literature search and contributed to neuroimaging analyses. Kerim Munir and Özgür Öner contributed to writing of the manuscript. All authors have seen and agree with the content of the manuscript and guarantee the accuracy of the references.

## Declaration of Competing Interest

The authors declare that they have no conflict of interest. Funding for this study; design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication was provided by the authors.

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