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## Gray Matter Volume Differences in Impulse Control and Addictive Disorders—An Evidence From a Sample of Heterosexual Males

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### ABSTRACT

**Backgrounds:** The classification of addictions and impulse control disorders is changing as reflected in the 11th version of International Classification of Disorders (WHO, 2018). However, studies focusing on direct comparison of structural brain differences in behavioral and substance addictions are limited.

**Aim:** Here, we contrast gray matter volumes (GMVs) across groups of individuals with compulsive sexual behavior disorder (CSBD), gambling disorder (GD), and alcohol use disorder (AUD) with those with none of these disorders (healthy controls participants; HCs).

**Methods:** Voxel-based morphometry was used to study brain structure, and severities of addiction symptoms were assessed with questionnaires. To identify brain regions related to severities of addictions, correlations between questionnaire scores and GMVs were computed.

**Main Outcome:** We collected magnetic resonance imaging (GMVs) data from 26 patients with CSBD, 26 patients with GD, 21 patients with AUD, and 25 HC participants (all heterosexual males; age: 24–60; mean = 34.5, standard deviation = 6.48).

**Results:** Affected individuals (CSBD, GD, AUD) compared with HC participants showed smaller GMVs in the left frontal pole, specifically in the orbitofrontal cortex. The most pronounced differences were observed in the GD and AUD groups, and the least in the CSBD group. In addition, a negative correlation was found between GMVs and disorder severity in the CSBD group. Higher severity of CSBD symptoms was correlated with decreased GMVs in the right anterior cingulate gyrus.

**Clinical Implications:** Our findings suggest similarities between CSBD and addictions.

**Strengths and Limitations:** This study is the first showing smaller GMVs in 3 clinical groups of CSBD, GD, and AUD. But the study was limited only to heterosexual men. Longitudinal studies should examine the extent to which ventral prefrontal decrements in volume may represent preexisting vulnerability factors or whether they may develop with disorder progression.

**Conclusions:** Our research extends prior findings in substance use disorders of lower GMVs in prefrontal cortical volumes among 3 clinical groups of patients with specific impulse control (CSBD) and behavioral (GD) and substance (AUD) addictive disorders. The negative correlation between CSBD symptoms and GMV of right anterior cingulate gyrus suggests a link with clinical symptomatology. **Draps M, Sescousse G, Potenza MN, et al. Gray Matter Volume Differences in Impulse Control and Addictive Disorders—An Evidence From a Sample of Heterosexual Males. J Sex Med 2020;XX:XXX–XXX.**

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**Key Words:** Gray Matter Volume; Voxel-Based Morphometry; Compulsive Sexual Behavior Disorder; Gambling Disorder; Alcohol Use Disorder; Addictions; Impulse Control Disorder

## INTRODUCTION

### Compulsive Sexual Behavior Disorder—State of Knowledge

Recently compulsive sexual behavior disorder (CSBD) was included in the 11th version of International Classification of Disorders (ICD-11) and was classified as an impulse control disorder (Code 6C72 in the ICD-11<sup>1</sup>) characterized by “repeated failure to resist an impulse, drive, or urge to perform an act that is rewarding to the person, at least in the short term, despite consequences such as long-term harm either to the individual or to others, marked distress about the behavior pattern, or significant impairment in personal, family, social, educational, occupational, or other important areas of functioning”.<sup>1</sup>

Such characteristics of CSBD resemble features of behavioral (eg, gambling) or substance (eg, alcohol use disorder [AUD]) addictions, raising questions regarding neural similarities.<sup>2</sup>

Addictions are also associated with impaired control and continuing behaviors despite adverse consequences involving substance use (such as alcohol, heroin, or cocaine) or specific behaviors (such as gambling or gaming)<sup>3–7</sup> taking increasing precedence over other life activities and leading to functional impairment in one or more domains of functioning. Historically, the term “addiction” became linked to substance use disorders; in Diagnostic and Statistical Manual of Mental Disorders Third Edition Revised deliberations,<sup>8</sup> addictions were considered as being defined by compulsive drug use.<sup>9</sup> Given data from multiple domains (epidemiological, clinical, neurobiological, and others),<sup>10</sup> gambling disorder (GD) was reclassified in Diagnostic and Statistical Manual of Mental Disorders Fifth Edition as an addictive disorder.<sup>11</sup> During ICD-11 deliberations, GD, gaming disorder, and CSBD were considered.

Owing to the very recent appearance of CSBD in psychiatric classifications, published studies directly comparing CSBD to behavioral and substance addictions have not been published. Therefore, the main aim of this study was to compare brain structures of individuals with CSBD with those of individuals with GD and AUD to examine existence of similar abnormalities in gray matter volumes (GMVs) across these CSBD and conditions classified as behavioral (GD) and substance (AUD) addictions.

Reduced GMV in AUD, GD, CSBD—findings from previous voxel-based morphometry studies

Smaller brain volumes and differences in functioning of reward circuitry and cognitive control pathways have been related to AUD.<sup>11</sup> Neurotoxic effects of alcohol are established,<sup>12–14</sup>

and studies comparing individuals with AUD to healthy controls (HCs) showed lower GMVs among those with AUD in cortical brain regions including the anterior cingulate cortex (ACC) and prefrontal cortex (PFC).<sup>14–23</sup> In AUD, lower GMVs (compared to HCs) have also been reported in other cortical and subcortical brain regions, including the bilateral insula, right amygdala, right putamen, left thalamus,<sup>19,20,23–25</sup> hippocampus<sup>15,25</sup> and caudate.<sup>26</sup>

Lower volumes in prefrontal cortical gray matter, particularly in the ACC, have been also reported in GD.<sup>12,27–30</sup> In addition, lower GMVs have been reported in the bilateral hippocampus, right amygdala, left putamen, right thalamus,<sup>31,32</sup> and right striatum<sup>28</sup> in association with GD. However, results are not entirely consistent, with some studies reporting no volumetric differences in GMVs between individuals with GD and HCs.<sup>20,33</sup> Some authors have compared GMVs in both chemical and behavioral addictions,<sup>20,33</sup> but evidence is limited. The study by Yip et al. compared GMVs between cocaine users and gamblers with HC and revealed decreased PFC GMVs among participants with cocaine-use disorder only.<sup>33</sup> An earlier study from 2012 concerning AUD, GD, and HC participants showed reduction of GMVs only in the AUD group.<sup>20</sup>

Individuals with excessive pornography use without necessarily a diagnosis of CSBD show lower GMVs in the right caudate.<sup>34</sup> Using a region of interest analyses of GMVs focusing on the left and right amygdala, left and right ventral striatum, and ACC, GMV in the left amygdala was found to be increased in patients with CSBD compared with matched HCs.<sup>35</sup> Here, we studied GMVs in individuals with CSBD, AUD, GD, or none of the disorders (HCs). We collected structural brain images from all participants, with self-reported questionnaire data to investigate relationships between addiction symptoms and measures of GMV.

## MATERIALS AND METHODS

### Subjects and Procedure

Subjects were recruited in psychiatric treatment centers in Poland, mostly in Warsaw and Cracow. Age-matched HCs were recruited through internet-based advertisements. All CSBD, AUD, and GD participants were interviewed by psychiatrists and psychologists to confirm diagnoses according to ICD-10. Exclusion criteria for all groups were history of other psychiatric disorders, neurological or medical illness, and any contraindication for magnetic resonance imaging (MRI) procedures. All groups consist of heterosexual men with mean age 34.5 years (standard deviation [SD] = 6.48). There were 26 individuals

**Table 1.** Groups characteristics: symptoms questionnaires, SAST-R and BPS for CSBD, AUDIT for AUD, and SOGS for GD symptoms

	CSBD (N = 26)	HC (N = 25)	P Value
Age, mean (SD)	33.96 (4.285)	34.54 (6.248)	NS
SAST-R <sup>40, 41</sup> , mean (SD)	11.95 (5.545)	2.44 (1.805)	<.001
BPS <sup>42</sup> , mean (SD)	5.93 (2.91)	1.52 (1.917)	<.001
	AUD (N = 21)	HC (N = 25)	P value
Age, mean (SD)	37.67 (7.08)	34.54 (6.248)	NS
AUDIT <sup>37</sup> , mean (SD)	15.69 (11.01)	6.69 (3.925)	<.001
	GD (N = 26)	HC (N = 25)	P value
Age, mean (SD)	33.15 (7.487)	34.54 (6.248)	NS
SOGS <sup>39</sup> , mean (SD)	12.58 (4.768)	0	<.001

AUD = alcohol use disorder; AUDIT = Alcohol Use Disorders Identification Test; BPS = Brief Pornography Screening Test; CSBD = compulsive sexual behavior disorder; GD = gambling disorder; NS = not significant; SAST-R = Sex Addiction Screening Test-Revised; SD = standard deviation; SOGS = South Oaks Gambling Screen.

with CSBD (mean age = 33.96 years [SD = 4.285]), 21 individuals with AUD (mean age = 37.67 years [SD = 7.08]), 26 individuals with GD (mean age = 33.15 years [SD = 7.487]), and 25 HCs (mean age = 34.54 [SD = 6.248]). All participants were free of any drugs that could interfere with the MRI results (eg, they were not currently on antidepressants).

All subjects provided written informed consent and were screened for sexual orientation (using the Polish version of Kinsey Scale<sup>36</sup>), alcohol abuse (using the Alcohol Use Disorders Identification Test [AUDIT]<sup>37</sup>), GD (using the South Oaks Gambling Screen [SOGS]<sup>38,39</sup>), and CSBD (using the Sex Addiction Screening Test-Revised [SAST-R]<sup>40,41</sup> and Brief Pornography Screening Test [BPS]<sup>42</sup>). Participants further completed the Obsessive Compulsive Inventory,<sup>43</sup> UPPS-P Impulsive Behavior Scale,<sup>44,45</sup> and Monetary Choice Questionnaire.<sup>46</sup> Several subjects had missing data for the impulsivity and compulsivity scales (see detail information in questionnaires results). The study was approved by the Institute of Psychology, Polish Academy of Sciences Ethics Committee.

## Data Acquisition and Preprocessing

MRI data acquisition took place at the Laboratory of Brain Imaging, Nencki Institute of Experimental Biology using a 3-Tesla MR scanner (Siemens Magnetom Trio TIM, Erlangen, Germany) equipped with a 12-channel phased array head coil. Head movements were minimized with cushions placed around the participants' heads. A set of high-resolution T1-weighted images was acquired using the following acquisition parameters: repetition time, 2,530 ms; echo time, 3.32 ms; flip angle, 7°. One data set consisted of 176 sagittal images with an in-plane resolution of 1 mm<sup>3</sup>, field of view 256 mm; and slice thickness 1 mm.

Statistical Parametric Mapping (SPM12 (<http://www.fil.ion.ucl.ac.uk/spm>); Wellcome Trust Centre for Neuroimaging, London, UK<sup>47</sup>) running on MATLAB was used for data processing and statistical analyses. First, T1-weighted structural images from single subjects were visually inspected and manually reoriented to set the origin at the ACC according to Ashburner's<sup>48</sup> manual. Images were automatically classified into gray matter, white matter, and cerebrospinal fluid using the "New Segmentation" tool based on a mixture of Gaussian models and tissue probability maps.<sup>49</sup> The quality of segmented images was visually inspected. High-dimensional Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra<sup>50</sup> was used to create a study-specific template. Finally, images were normalized, modulated, and smoothed with an isotropic Gaussian kernel of 4 mm of full-width half maximum. Smoothed modulated normalized images were entered into a design matrix with age and total intracranial volumes as separate regressors.

## Statistical Analysis

For group comparisons, modulated, normalized, and smoothed images were used to conduct the statistical analysis. GMVs for all subjects were entered into a general linear model with age as a

**Table 2.** Groups characteristics: compulsivity (OCI-R) and impulsivity (UPPS-P and MCQ) scales (results from ANOVAs)

	CSBD (N = 26)	AUD (N = 21)	GD (N = 26)	HC (N = 25)	P Value
Age, mean (SD)	33.96 (4.285)	37.67 (7.08)	33.15 (7.487)	34.54 (6.248)	NS
OCI-R, <sup>43</sup> mean (SD)	17.37 (11.476)	9.9 (4.253)	20.15 (11.478)	12.48 (7.959)	<.001
UPPS-P Impulsive Behaviour Scale <sup>44,45</sup>					
UPPS-P Negative Urgency Scale, mean (SD)	27.17 (3.198)	27.58 (5.401)	31.08 (7.138)	27.67 (7.176)	NS
UPPS-P Premeditation Scale, mean (SD)	20 (3.795)	23.58 (4.963)	24.19 (5.426)	23.89 (3.296)	NS
UPPS-P Perseverance Scale, mean (SD)	21.5 (3.082)	19.5 (4.945)	21.38 (3.645)	23.56 (4.035)	NS
UPPS-P Sensation Seeking Scale, mean (SD)	33.5 (7.918)	34.42 (6.417)	33.62 (6.694)	27.44 (6.483)	NS
UPPS-P Positive Urgency Scale, mean (SD)	25.67 (5.715)	28 (8.643)	32.12 (10.109)	26.78 (6.553)	NS
MCQ <sup>46</sup>					
MCQ overall k value, mean (SD)	0.0193 (0.03)	0.0313 (0.06)	0.0319 (0.05)	0.0295 (0.05)	NS
MCQ small k value, mean (SD)	0.0326 (0.04)	0.0438 (0.07)	0.0597 (0.07)	0.0405 (0.06)	NS
MCQ medium k value, mean (SD)	0.0152 (0.02)	0.0231 (0.04)	0.0318 (0.05)	0.0270 (0.04)	NS
MCQ large k value, mean (SD)	0.0198 (0.04)	0.0226 (0.05)	0.0217 (0.05)	0.0204 (0.04)	NS

ANOVA = analysis of variance; AUD = alcohol use disorder; CSBD = compulsive sexual behavior disorder; GD = gambling disorder; MCQ = Monetary Choice Questionnaire; NS = not significant; OCI-R = Obsessive Compulsive Inventory-Revised; SD = standard deviation.

covariate, more specific in analysis of variance model with separate cells for 4 groups. Data were corrected for participants' total intracranial volume by using proportional normalization and were masked with a 0.2 masking threshold. We used 2 sample *t*-tests comparing patients with HC. In each comparison, we calculated 2 contrasts: (HCs > one of the defected group) contrast and inverse contrast. Those contrasts were calculated to all the groups separately. To identify brain regions significantly correlated with symptoms, we separately ran a correlation analysis using the appropriate questionnaires (SAST-R, BPS AUDIT, SOGS) as covariates. These analyses were conducted separately for each specific clinical subgroup: in AUD with AUDIT scores, in GD with SOGS scores, and in CSBD subgroup with SAST-R and BPS scores. All whole-brain results were identified using a voxel-wise uncorrected threshold of  $P < .001$  associated with a cluster-wise Family Wise Error (FWE) correction threshold of  $P < .05$ .

## RESULTS

### Group Characteristics—Questionnaire Results

CSBD subjects had higher SAST-R and BPS ( $P < .001$ ) scores than HCs, AUD subjects had higher AUDIT ( $P < .001$ ) scores than HCs, and GD subjects had higher SOGS ( $P < .001$ ) scores than HCs (Table 1). There were between-group differences in Obsessive Compulsive Inventory scores (In post-hoc tests, there were significant differences between GD vs AUD and GD vs HC participants,  $P = .05$ ). We did not find any differences in UPPS and Monetary Choice Questionnaire scores (Table 2).

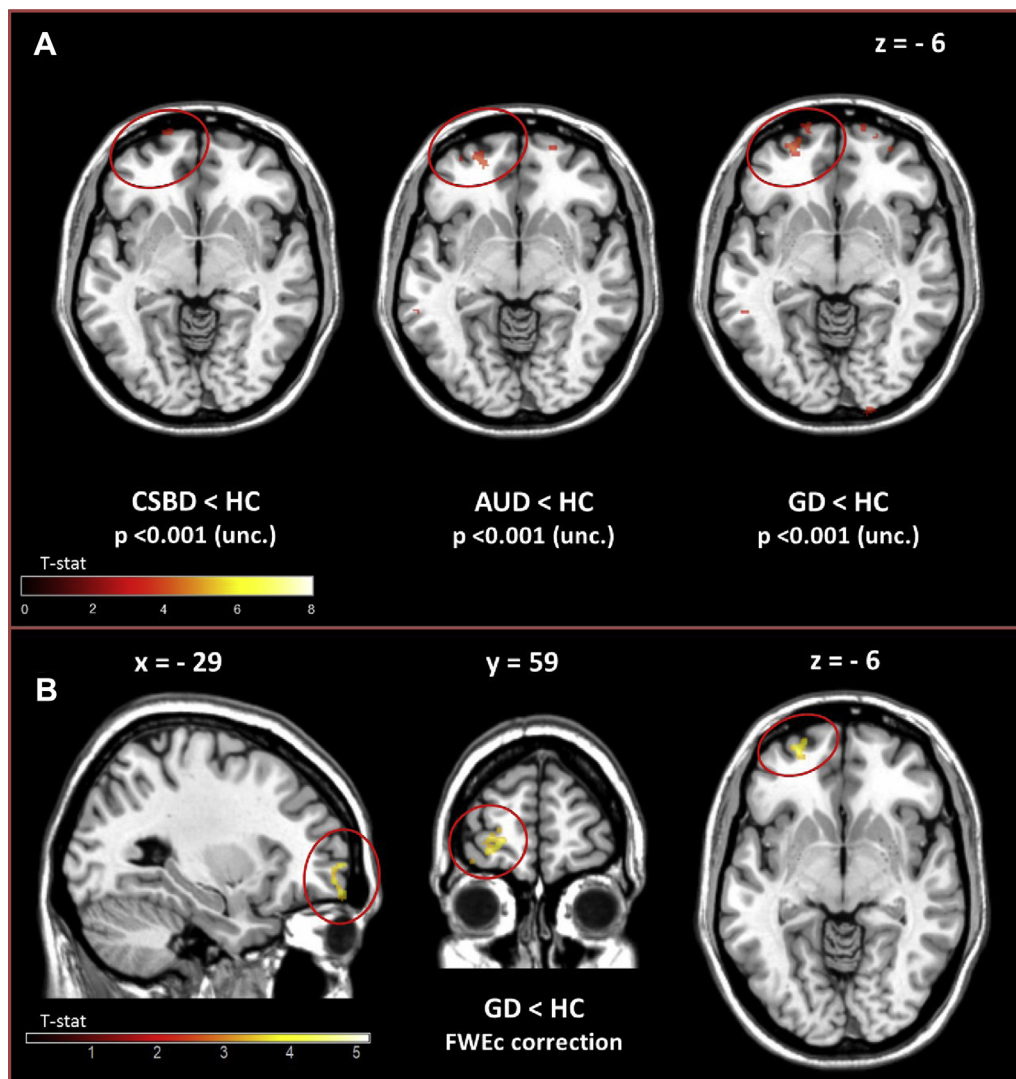
### Voxel-based Morphometry Results in Whole-Brain Analyses

We observed that compared with healthy subjects, affected individuals (those with CSBD, GD, or AUD examined separately in *t*-tests) showed less GMVs in the same brain area: left frontal pole, more precisely in the left orbitofrontal cortex (Figure 1A). The most pronounced results were observed in GD (T-stat = 5.20, peak coordinates:  $x = -32$ ,  $y = 65$ ,  $z = -14$ ) and AUD groups (T-stat = 4.43, peak coordinates:  $x = -27$ ,  $y = 60$ ,  $z = -11$ ), and the least pronounced in the CSBD group (T-stat = 3.8, peak coordinates:  $x = -20$ ,  $y = 71$ ,  $z = -9$ ). Only results from the GD group survived FWE correction at a cluster level ( $k = 282$  voxels) in subsequent pair-wise comparisons, see GD group results in Figure 1B.

### Correlation Analyses

In the CSBD group, scores on the SAST-R were negatively correlated with GMVs in the anterior cingulate gyrus (T-stat = 6.56, peak coordinates:  $x = 14$ ,  $y = 39$ ,  $z = 32$ ), with results surviving FWE correction at a cluster level of  $k = 253$  voxels (Figure 2A). No other correlations were significant. In Figure 2B a scatterplot of GMVs of anterior cingulate gyrus and SAST-R scores in CSBD group is presented.





**Figure 1.** Results from the study. Panel A shows GMV comparisons in affected (CSBD, AUD, GD) versus HC groups. Panel B shows GMV comparisons in GD vs HC groups at FWE correction on cluster level. AUD = alcohol use disorder; CSBD = compulsive sexual behavior disorder; FWEc = Family Wise Error; GD = gambling disorder; GMV = gray matter volume. Figure 1 is available in color online at [www.jsm.jsexmed.org](http://www.jsm.jsexmed.org).

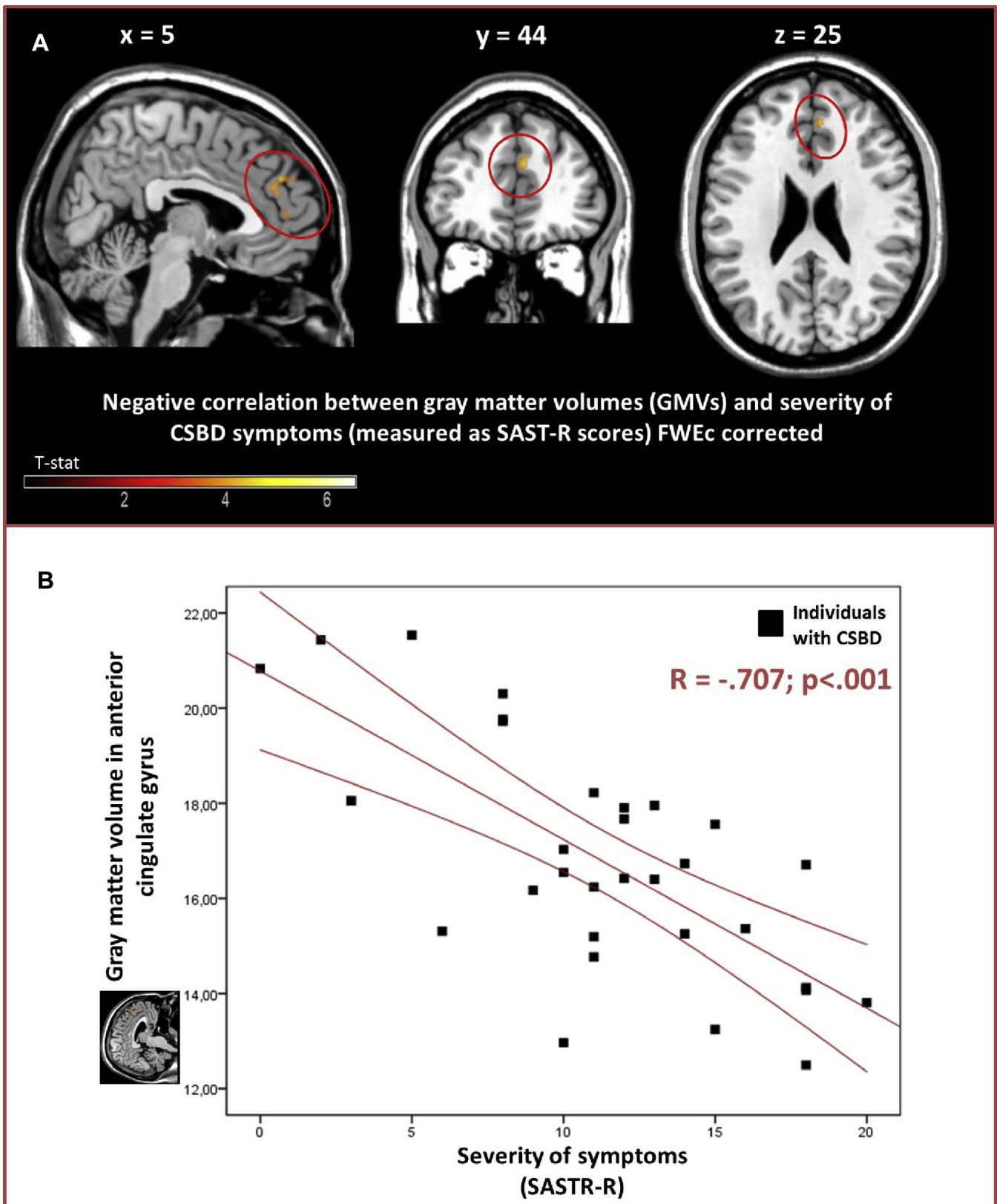
## DISCUSSION

According to our knowledge, this is the first study aiming to identify common brain structural abnormalities between individuals with CSBD and those diagnosed with behavioral (GD) and substance (AUD) addictions. We also examined correlations between clinical symptoms of CSBD and GMVs. We observed similar decreased GMV in the left frontal pole among all 3 groups (CSBD, GD, and AUD) when compared with HCs. However, this difference remained significant after FWE correction only in participants with GD. In case of patients with CSBD, we have found a negative correlation between severity of CSBD symptoms (measured with SAST-R) and GMVs in the right anterior cingulate gyrus. Implications are discussed in the following section.

## CONCLUSION

Our results suggest that a common feature of CSBD and behavioral (GD) and substance (AUD) addictions is that they lower GMV in frontal pole—a subregion of PFC implicated in cognitive control,<sup>35,51,52</sup> and cognitive processing.<sup>53–55</sup> Reduction of GMVs in the frontopolar cortex was previously found in AUD and GD.<sup>15,18,21,27</sup> Our results suggest that CSBD resembles GD and AUD from the perspective of GMV reduction in the frontopolar cortex. However, our results need to be replicated on a larger sample and pass FWE correction.

The ACC has been implicated functionally in cognitive control, processing negative stimuli,<sup>56,57</sup> error prediction processing, reward learning,<sup>58,59</sup> and cue-reactivity.<sup>34,60</sup> With respect to CSBD, ACC activity in response to sexually explicit cues was



**Figure 2.** Results from correlation analysis. Panel A shows negative correlation between gray matter volumes and severity of CSBD symptoms (measured with SAST-R) in patients with CSBD at FWE correction on cluster level. Panel B shows a scatterplot of gray matter volumes in anterior cingulate gyrus and SAST-R scores in patients with CSBD. CSBD = compulsive sexual behavior disorder; FWEc = Family Wise Error; SAST-R = Sex Addiction Screening Test-Revised. Figure 2 is available in color online at [www.jsm.jsexmed.org](http://www.jsm.jsexmed.org).

linked to sexual desire in men with CSBD.<sup>61</sup> Men with CSBD also displayed an enhanced preference for sexual novelty, which was related to ACC habituation.<sup>62</sup> As such, the current findings extend prior functional studies by suggesting that ACC volume relates importantly to CSBD symptomatology in men. As animal models investigating functional lateralization suggest, right ACC and interconnected left cortical regions may be particularly involved in observational fear learning.<sup>63</sup> So far, there is no strong replication of these findings in humans<sup>64,65</sup>; however, similar to our study, others have found lateralized CSBD symptoms correlating inversely with GMVs in the left superior temporal gyrus.<sup>66</sup> Therefore, further studies using a larger sample are needed to investigate structural differences in CSBD, their lateralization, and their relationship to clinically relevant phenomena. One of potentially interesting targets to assess in future studies on CSBD could be observational fear learning.

### Limitations

Our study delivers new data on gray matter differences in individuals with impulse control and addictive disorders, but it remains unknown if the observed differences are preexisting factors relating to vulnerability, a result of the disorders or some other possibility. This limitation is common to cross-sectional studies assessing structural brain differences.<sup>67</sup> A longitudinal design is needed to evaluate the role of GMVs as they relate to the development and progression of symptoms of addictive behaviors. Also, there is a limitation connected to the fact that it is impossible to compare or equate severity across all studied disorders per se, so the results are more likely to be the function of degree than categorical differences. Another limitation of the study is the relatively small sample size that may have precluded some findings surviving FWE correction. Additional studies involving larger samples are warranted. Also, the limitations are connected to the fact that the study involved solely heterosexual males with a limited age range from only the Polish population; in the future studies, diversity is needed.

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