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Structural correlates of sensorimotor dysfunction in heavy cannabis users

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Abstract

Sensorimotor dysfunction has been previously reported in persons with cannabis dependence. Such individuals can exhibit increased levels of neurological soft signs (NSS), particularly involving motor coordination and sensorimotor integration. Whether such abnormalities may also apply to non-dependent individuals with heavy cannabis use (HCU) is unknown, as much as the neural correlates underlying such deficits. In this study, we investigated associations between NSS and gray matter volume (GMV) in males with HCU and male controls. Twenty-four persons with HCU and 17 controls were examined using standardized assessment of NSS and structural magnetic resonance imaging (MRI) at 3 T. GMV was calculated using voxel-based morphometry algorithms provided by the Computational Anatomy Toolbox (CAT12). Individuals with HCU showed higher NSS total scores compared to controls. In particular, significant NSS-subdomain effects were found for "motor coordination" (MoCo), "complex motor tasks" (CoMT), and "hard signs" (HS) expression in HCU ($p < 0.05$, Bonferroni-corrected). Compared to controls, persons with HCU showed significant NSS/GMV interactions in putamen and inferior frontal cortex (MoCo), right cerebellum (CoMT) and middle and superior frontal cortices, and bilateral precentral cortex and thalamus (HS). In between-group analyses, individuals with HCU showed lower GMV in the right anterior orbital and precentral gyrus, as well as higher GMV in the right superior frontal gyrus and left supplementary motor cortex compared to controls. The data support the notion of abnormal sensorimotor performance associated with HCU. The data also provide a neuromechanistic understanding of such deficits, particularly with respect to aberrant cortical–thalamic–cerebellar–cortical circuit.

KEYWORDS
cannabis, MRI, neurological soft signs, psychomotor, sensorimotor, VBM

1 | INTRODUCTION

There is increasing and converging evidence that cannabis use is associated with structural alterations of brain morphology and increases the risk for developing manifest schizophrenia (SZ).[1] From a clinical perspective, heavy cannabis users (HCU) are characterized by cognitive,[2–4] psychopathological,[5] and sensorimotor abnormalities.[6] Sensorimotor dysfunction is a transdiagnostic phenomenon and most recent magnetic resonance imaging (MRI) studies in healthy persons with subtle sensorimotor alterations, individuals with schizotypal personality traits, persons at ultra-high risk (UHR) for psychosis, and unaffected first-degree relatives of SZ patients suggest brain mechanisms by which sensorimotor dysfunction reflects vulnerability for the development of manifest SZ (for review see Hirjak et al.[7]). Yet, although both factors imply an increased risk for manifest SZ, the interaction between cannabis use and sensorimotor dysfunction in non-psychotic individuals has been hardly considered by previous studies. As an exception, Derveaux and colleagues[6] examined 45 patients meeting the cannabis dependence Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. This study found a significant association between cannabis dependence and neurological soft signs (NSS) severity, and hence, the authors suggested an interaction between cannabinoids and brain networks underlying NSS. Still, the lack of further data is very surprising since understanding of the interaction between cannabis use, sensorimotor abnormalities, and brain structure prior to overt major psychiatric disorder could foster the identification of neuroimaging biomarkers for UHR individuals.

Given the extant dearth of research, we investigated associations between NSS and gray matter volume (GMV) in HCU compared to control participants. Since previous studies showed that gender modulates cortex morphology,[8] impulsiveness,[9–11] healthy-risk behaviors,[12] patterns of problematic cannabis use,[13] cannabis withdrawal,[14,15] acute effects of cannabis,[16] methamphetamine,[9] and alcohol addiction,[10,17] we sought to examine a homogenous sample and included male subjects only that were carefully selected after detailed diagnostic interviews, including only individuals presenting without cannabis-use disorder or other current and life-time major mental disorders and clinical high risk for psychosis. All participants underwent structured NSS assessment together with and high-resolution structural MRI. We predicted that individuals with HCU will show higher NSS levels compared to controls, particularly in NSS subdomains associated with complex motor and integrative sensorimotor performance. We also expected that NSS differences in HCU will be significantly related to cortical and subcortical areas involved in sensorimotor execution and control.

2 | MATERIALS AND METHODS

2.1 | Participants

The study was carried out in the Saarland University Hospital Homburg, Germany. A total of 41 participants met eligibility criteria, as outlined below. Male and right-handed participants aged between 18 and 30 years were enrolled in the study and received MRI scanning and clinical assessment. We specifically included HCU participants using cannabis and nicotine only. To facilitate comparisons with previous research,[18–20] HCU was defined as cannabis use during at least 10 days/month in the past 24 months, and at least 240 days of cannabis use in the past 24 months. Cannabis use criteria for controls was ≤10 joints life-time use and no cannabis use at least 12 months prior to study participation. Current or life-time use of any other illicit substance was an exclusion criterion. Absence of other illicit drugs at the time of testing and MRI was ascertained by urine analyses. Only qualitative drug screenings were used. Participants with a current or life-time mental disorder, as indicated by Structured Clinical Interview for DSM-IV-TR (SCID) interviews, with a history of a neurological disease, significant head trauma or any type of medication were excluded. In particular, alcohol-use disorder according to DSM-IV-TR was an exclusion criterion. Of note, HCU individuals included in this study did not meet diagnostic criteria for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) cannabis-use disorder. In addition, the presence of "attenuated psychosis syndrome," as defined by DSM-5 appendix, was defined as further exclusion criterion.

NSS were examined with the Heidelberg Scale,[21] which consists of five items assessing motor coordination (MoCo, as investigated by Ozeretski's test, diadochokinesia, pronation/supination, finger-to-thumb opposition, speech articulation), three items assessing integrative functions (IF, as investigated by station and gait, tandem walking and two-point discrimination tests), two items assessing complex motor tasks (CoMT: finger-to-nose test, fist-edge-palm test), four items assessing right/left and spatial orientation (RLSpO: right/left orientation, graphesthesia, face–hand test, stereognosis), and two items assessing hard signs (HS: arm holding test, mirror movements). Ratings are given on a 0- to 3-point scale (no vs. marked prevalence). A sufficient internal reliability and test–retest reliability have been established previously.[21,22] NSS assessment was conducted by FW, supervised by RCW.

Additional rating scales in this study included the German ADHD Self Rating Scale (ADHS-SB),[23] Hamilton Depression Rating Scale (HAMD),[24] Alcohol Use Disorder Identification Test (AUDIT)[25] and the Fagerström Test.[26] All HCU participants were evaluated using the Cannabis Use Disorder Identification Test (CUDIT).[27,28] HCU participants were asked for cannabis abstinence for at least 24 h before clinical assessment and MRI. All HCU consented to these study-specific requirements, and none reported craving or other withdrawal symptoms prior to NSS assessment. The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the ethical review board of the Saarland Medical Association, Saarbrücken, Germany. Written informed consent was obtained from all participants after the procedures of the study had been fully explained.

2.2 | MRI data acquisition

High-resolution structural data were acquired using a 3 T Magnetom Skyra (Siemens, Erlangen, Germany) head MRI system. The MRI

parameters of the three-dimensional magnetization-prepared rapid gradient-echo (3D-MPRAGE) sequences were as follows: TE = 3.29 ms; TR = 1900 ms; TI = 1100 ms; FOV = 240 mm; slice plane = axial; slice thickness = 0.9 × 0.9 × 0.9 mm^3; distance factor = 50%; number of slices = 192.

2.3 | Data analysis

Demographic and psychometric differences between the groups were assessed by means of t tests (nominal $p < 0.05$, Bonferroni-corrected for multiple comparisons), as provided by the Statistica software package (vers. 10., https://www.statsoft.de/de/software/statistica) was used.

For structural MRI data processing, we used the Statistical Parametric Mapping analysis package (SPM12, http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) together with the Computational Anatomy Toolbox for SPM (CAT12, http://www.neuro.uni-jena.de/cat/) for VBM analysis. VBM included spatial normalization, segmentation and smoothing. In brief, each participant's original T1 image was spatially normalized and segmented into gray and white matter and cerebrospinal fluid (CSF). After data preprocessing, modulated normalized GMV was smoothed using an 8 mm FWHM Gaussian kernel.

NSS differences between the groups and associations between NSS and GMV were investigated as follows: We first determined behavioral differences between the groups using two-sample t tests including total NSS scores and scores on the five NSS subscales (i.e., MoCo, IF, CoMT, RLSpO and HS). A nominal $p < 0.05$ was used, corrected for multiple comparisons using the Bonferroni method. Correlations between NSS and total duration of cannabis use (years), amount (g/week), frequency (days/week) of current cannabis use and CUDIT scores was explored using Pearson correlations (uncorrected $p < 0.05$, Bonferroni-corrected for multiple comparisons).

Next, we considered scores on NSS subscales showing significant between-group differences in SPM-based regression models adjusted for age and total intracranial volume (TIV, sum of gray and white matter and CSF); NSS levels were considered as covariate of interest. In these models, an absolute threshold of 0.1 was used to prevent effects occurring at tissue border regions. Two analysis types were conducted: First, we tested for (negative and positive) associations between GMV and NSS subdomain levels across the entire participant sample, that is, HCU and controls. Second, covariate interactions between GMV and NSS subdomain levels were computed to test for associations that differed in the HCU group compared to controls. For completeness, we also computed between-group comparisons to investigate GMV differences between HCU and controls. In these analyses, age, TIV and NSS were considered as nuisance variables.

In all models, statistical inference was based on a peak-level threshold of $p < 0.001$ (uncorrected at the voxel level), in conjunction with an empirically determined extent threshold *k* (i.e., expected voxels per cluster and contrast) based on SPM resolution elements. Stereotaxic coordinates of significant between-group differences or associations with distinct NSS subscales are reported from maxima

TABLE 1 Demographics and clinical scores for controls and HCU

	Controls (n = 17)		HCU (n = 24)		
	Mean	SD	Mean	SD	p value*
Age (years)	24.8	3.4	23.1	3.0	0.11
Education years	16.1	3.0	14.1	2.9	0.04
HAMD	0.4	0.8	1.3	1.9	0.07
ADHD-SB	7.8	8.8	11.5	5.9	0.11
sCUDIT			17.0	8.6	
Duration of cannabis use (years)			2.8	1.8	
Onset of cannabis use (age)			19.5	2.2	
Current cannabis use (days/week)			4.3	1.1	
Current cannabis use (g/week)			1.9	0.9	
NSS total score	4.9	4.3	12.9	5.7	**<0.001**
NSS motor coordination (MoCo)	1.1	1.2	4.1	2.8	**<0.001**
NSS integrative functions (IF)	1.0	1.1	1.4	0.9	0.24
NSS complex motor tasks (CoMT)	0.8	1.4	2.9	2.2	**0.002**
NSS right/left & spatial orientation (RLSpO)	1.1	1.4	2.3	1.9	0.03
NSS hard signs (HS)	0.9	1.1	2.3	1.3	**0.001**

Note: Data are given as means/standard deviation (sd). Results surviving Bonferroni correction are marked in bold (threshold 0.05/6 NSS scores, p = 0.008).
Abbreviations: ADHD-SB, Self Rating Scale for Attention-Deficit/Hyperactivity Disorder; CUDIT, Cannabis Use Disorder Identification Test; HAMD, Hamilton Depression Rating Scale; HCU, heavy cannabis users.
*Uncorrected $p < 0.05$.

within a given cluster according to the Montreal Neurological Institute (MNI) template. Following peak voxel values, distinct anatomical regions emerging from the between-group comparisons were labeled according to the Neuromorphometrics atlas, as implemented in SPM12.

3 | RESULTS

3.1 | Demographic and psychometric variables

The two groups did not differ in terms of age, HAMD and ADHD-SB scores; see also Table 1. Controls had more education years compared to HCU (uncorrected $p < 0.04$), but this difference was no longer significant after Bonferroni correction.

3.2 | NSS

Individuals with HCU showed significantly higher NSS total scores when compared to controls ($p < 0.001$; Bonferroni corr.). Scores on the NSS subscales MoCo, CoMT and HS were significantly higher in HCU compared to controls ($p < 0.001$, $p = 0.002$ and $p = 0.001$; Bonferroni correction). IF and RLSpO differences between the groups were not significant after Bonferroni correction (uncorrected $p = 0.24$ and 0.03, respectively); see also Table 1 for more details. Significant associations between NSS (total score and subdomain scores) and CUDIT, duration of cannabis use, amount and frequency of current weekly cannabis use were not found (all $p > 0.05$); detailed statistics available upon request.

3.3 | MRI analyses

Across the entire sample, distinct associations were found between GMV and MoCo, CoMT and HS, respectively; see also Supporting Information Table S1 anatomical denominations and stereotaxic coordinates. In brief, significant positive associations between MoCo and GMV were found in the bilateral striatum, left brainstem, and in regions of the temporal lobe. Negative associations were found in the right central operculum. A positive association between CoMT and GMV was found in the right inferior temporal gyrus, whereas negative associations were detected in the right middle and medial orbital and superior frontal gyri and bilateral postcentral cortex. Positive associations between HS and GMV were detected in the right middle frontal gyrus, right cerebellum, and right pallidum.

For completeness, associations between GMV and total NSS scores were also calculated (detailed anatomical denominations and stereotaxic coordinates are available upon request). Briefly, across the entire sample, significant positive associations were found in the right inferior temporal, right middle frontal, left inferior occipital, right middle occipital gyri, and left supramarginal gyri, as well as in the right

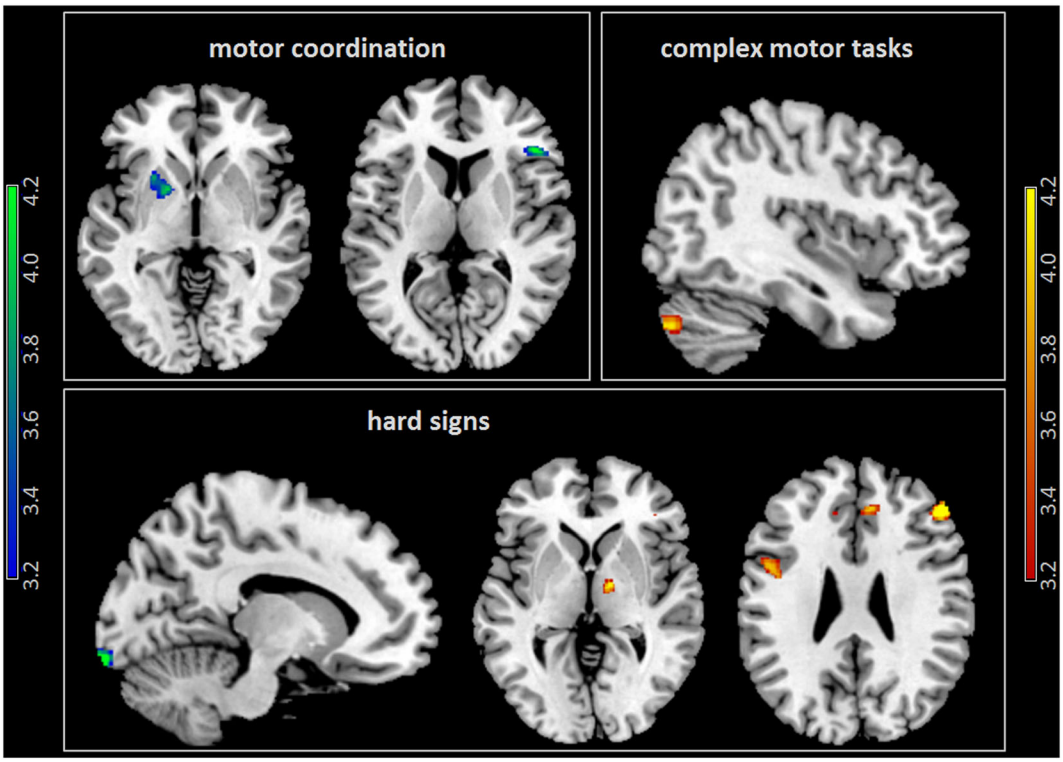

FIGURE 1 Interactions between NSS × GM in HCU versus controls. Results of between-group regression analyses adjusted for age and TIV, $p < 0.001$, uncorrected, spatial extent correction $k > 74$ voxels (k = expected voxels per cluster). The color bar represents T values (blue/green: negative NSS × GMV interaction HCU versus controls; red/yellow: positive NSS × GMV interaction HCU versus controls

putamen and cerebellar vermal lobules VI and VII. Negative associations were found in the right central operculum and right middle frontal gyri. Interaction analyses revealed stronger associations in HCU versus controls in the left precentral gyrus, left supplementary motor cortex, and right middle frontal gyrus.

Interaction analyses revealed the following domain-specific findings (see also Figure 1 and Table 2): *MoCo* × *GMV*: Compared to controls, individuals with HCU showed weaker associations in the right inferior frontal gyrus (IFG) and left putamen. Stronger associations were found in the right central operculum. *CoMT* × *GMV*: Compared to controls, individuals with HCU showed stronger associations in the right cerebellum. *HS* × *GMV*: Compared to controls, individuals with HCU showed weaker associations in the left occipital pole. Stronger associations were found in the right middle and superior frontal gyrus (SFG), bilateral precentral gyrus, left precuneus, and right thalamus.

In *between-group analyses*, individuals with HCU showed lower GMV in the right anterior orbital gyrus (x/y/z = 27 41–14, Z = 3.71, k = 85 voxels) and right central operculum and precentral gyrus (x/y/z = 59/18/14, Z = 3.47 and x/y/z = 57/12/21, Z = 3.29, k = 102 voxels) compared to controls. In addition, individuals with HCU showed higher GMV compared to controls in the right SFG, medial segment (x/y/z = 12/54/23, Z = 3.76, k = 84 voxels), and left supplementary motor cortex (x/y/z = −14/15/47, Z = 3.80, k = 154 voxels); figures are available upon request.

4 | DISCUSSION

We investigated associations between NSS and brain structure in HCU compared to non-consuming healthy controls. Three main findings emerged: First, compared to controls, HCU showed significantly higher scores on NSS subscales MoCo, CoMT and HS. Second, NSS severity in HCU was not significantly related to user-dependent variables. Third, group-specific interaction analyses revealed significant associations between these deficits and cortical–thalamic–cerebellar–cortical circuit (CCTCC) GMV.

In line with our predictions, HCU showed higher NSS levels in predominantly motor NSS subscales when compared to controls. Of note, NSS expression in HCU was not significantly related to user-dependent variables, such as duration of cannabis use, amount or frequency of current cannabis use or CUDIT scores. These findings are interesting for several reasons: Cannabinoid substances influence sensorimotor (e.g., catalepsy, decreased motor activity, hyperactivity or stereotypy) and cognitive performances in both humans[29,30] and rats (for review see[31]). From an anatomical point of view, cannabinoid receptors (e.g., CB_1 receptor) are highly expressed in typical sensorimotor regions such as the basal ganglia (e.g., striatum), cerebellum and neocortex.[32] Regular cannabis use can stimulate CB_1 receptors and influence the functioning of individual sensorimotor regions. Furthermore, Δ^9-tetrahydrocannabinol (Δ^9-THC) modulates dopamine transmission in the limbic striatum[33] and might differentially affect limbic/associative and sensorimotor cortical circuits.[34,35] Furthermore, stimulation of cannabinoid receptors (e.g., CB_1 receptor) modulates cortical information transmission through the sensorimotor and medial prefrontal circuits of the basal ganglia.[35] This is also in line with recent animal studies that have shown a relationship between Δ^9-THC use and sensorimotor abnormalities (i.e., prepulse inhibition of the startle response) during adolescence.[34] In a more recent study in humans,[36] regular cannabis users showed an increased postural sway, possibly reflecting disrupted cerebellar processing of incoming peripheral nervous system information.[36] Eventually, cannabinoids might also have a positive influence on sensorimotor functioning in Tourette's syndrome patients with psychiatric comorbidities such as ADHD, anxiety, depression, and rage attacks, respectively.[29,30]

In line with our hypotheses and consistent with previous reports, the associations between distinct NSS subscales and GMV enhance a transnosologic understanding of neuromechanisms underlying

TABLE 2 Differential correlation strength between NSS/GMV in HCU versus controls

NSS subdomain		Anatomical region	x	y	z	Z	k
Motor coordination (MoCo)	*controls>HCU*	Right inferior frontal gyrus	47	29	9	4.99	175
		Left putamen	−18	6	0	3.67	304
	HCU>controls	Right central operculum	46	−14	12	3.67	167
Complex motor tasks (CoMT)	*HCU > controls*	Right cerebellum	42	−81	−38	3.71	126
Hard signs (HS)	*controls>HCU*	Left occipital pole	−12	−102	−15	4.14	134
	HCU > controls	Right middle frontal gyrus	51	36	29	4.42	207
		Right superior frontal gyrus (medial segment)	9	36	29	3.99	114
		Right precentral gyrus	12	−24	60	3.97	138
		Left precentral gyrus	−47	3	30	3.94	381
		Left precuneus	−17	−39	44	3.89	131
		Right thalamus	12	−8	2	3.75	85
		Right middle frontal gyrus	51	18	36	3.57	110

Note: Results from second-level multiple regression, peak-level threshold $p < 0.001$, corrected for spatial extent using an empirically determined threshold $k > 74$ voxels (no. of expected voxels/cluster based on SPM resolution elements).

sensorimotor abnormalities in HCU. In the participant sample under study, these findings are relevant for a number of reasons: First, we found an association between MoCo and GMV in the right IFG and left putamen. The IFG is crucial for cognitive and motor inhibition, as well as for careful thinking and planning.[37–39] The putamen, together with the caudate nucleus, is interconnected with the primary motor cortex (precentral gyrus, M1) and the supplementary motor area, and hence it has a fundamental role in sensorimotor control.[40] This finding nicely corresponds with behavioral requirement on the MoCo subscale items, which includes finger-to-thumb opposition and speech, and points towards an aberrant interaction between cortico-cortical structures leading to sensorimotor and language abnormalities.[41] Although the cerebellum is clearly associated with NSS levels in patients with SZ,[42–45] the second finding shows that cerebellum is involved in the pathogenesis of NSS in HCU as well. While the cerebellum is involved in fine motor and visuomotor adaptation skills, cerebellar alterations essentially apply to sensorimotor abnormalities assessed by the COMT subscale which comprises the finger-to-nose and fist-edge-palm test.[46] Third, another cluster of pronounced association between NSS subscale HS (arm holding test and mirror movements) and GMV was identified in the SFG, bilateral M1, left precuneus and right thalamus. Supported by previous MRI studies, SFG is involved in CoMT.[47,48] M1 is responsible for execution of voluntary movements and the control of response inhibition.[39] Furthermore, the involvement of M1 in the pathogenesis of NSS in SZ is well-documented.[49,50] The precuneus plays a crucial role in sensorimotor tasks requiring somatosensory control and has its major connections to the prefrontal and cingulate cortex.[51,52] GMV reduction in the right central operculum and M1 illustrates aberrant inhibition of bodily movements and disturbed integration of visuospatial stimuli and might lead to subtle sensorimotor impairments such as disrupted arm holding test and mirror movements in HCU. Finally, these associations suit previous postulations that NSS-related reduced GMV might represent a useful cytoarchitectural measure to assess morphological patterns underlying early sensorimotor abnormalities and vulnerability to SZ. In summary, it appears plausible that not just one but a number of different factors (cannabis use, brain CB_1 receptor availability and brain morphology) can improve our understanding of the neurobiological underpinnings of NSS in populations at high risk for SZ. Taken together, our findings are largely consistent with the literature on NSS-related structural brain changes in healthy individuals without cannabis use,[48,53,54] UHR populations[55–57] and patients with manifest SZ.[41,58–62]

Interestingly, previous MRI studies[48,53] found no association between basal ganglia and NSS in healthy persons without cannabis use. Therefore, from a pathophysiological point of view and in line with the findings of this study, it can be speculated that cannabinoids modulate the anatomical structure as reflected by GMV variations and the functional organization of the CCTCC (through dopaminergic transmission and anandamide in the striatum) and hence, both factors might lead to impaired synchrony of movements[63,64] and the so-called "motor dysmetria". Furthermore, the present findings are also in line with a recent study that combined activation likelihood estimate (ALE) meta-analysis with meta-analytic functional connectivity modeling.[65] That study confirmed aberrant ventral striatal activation in SZ; yet, even more important, connectivity modeling revealed interconnections between ventral striatum and sensorimotor regions, particularly pre-supplementary area, midbrain and cerebellum. Aberrant ventral striatal and sensorimotor brain function in SZ were highlighted. The meta-analytical evidence, in conjunction with findings of this study, suggests that reward and sensorimotor systems are intricately linked in the pathophysiology of both psychotic disorders and psychotropic substance-use. Clearly, further research is needed to parse out putative connections between sensorimotor system dysfunction and impaired reward processing in the context of substance-use disorders with and without comorbid psychosis.

Strengths of this study include standardized NSS assessment in conjunction with structural MRI data analysis, as well as the homogenous, clinically well-characterized sample of male participants with HCU presenting without major mental disorders and without current or a history of attenuated psychotic symptoms. Nevertheless, this study has several potential limitations which need to be considered. Besides the relatively modest sample size, we infer from cross-sectional data, so that we cannot make any claims about the changes of cognitive dysfunction or brain structure over time. Further, we did not investigate putative changes in neural activity, which have been frequently detected in HCU in previous studies[20,66–68] and may essentially modulate NSS expression. To reduce gender bias, we deliberately investigated an exclusively male population. Thus, the present findings may not necessarily apply to female HCU. Keeping such limitations in mind, this study provides a first neuromechanistic understanding of such deficits, particularly with respect to aberrant CCTCC, and a first starting point for future research that has to elucidate gender differences in more detail.

4.1 | Conclusion

Cannabis does not contribute directly (through cannabis intoxication) to the development of NSS but rather by modulating the endocannabinoid system, which regulates the mesolimbic dopamine release, and inducing a sensorimotor dysfunction within the CCTCC. Future research requires carefully designed longitudinal MRI studies, preferably combining information from positron-emission-tomography (e.g., [^{18}F]FMPEP-d2 or [^{11}C]MePPEP PET tracers,[69] as much as careful consideration of further demographic and clinical characteristics; e.g., persons at high clinical risk for psychosis and individuals with first-episode psychosis with comorbid cannabis use) to elucidate the full spectrum of sensorimotor dysfunction of HCU in more detail.

AUTHOR CONTRIBUTIONS

RCW, FW, and WR were responsible for the study concept and design. RCW, FW, MW, and WR contributed to the acquisition of clinical and neuroimaging data. RCW performed the neuroimaging and statistical analyses. MMS, NDW, and KMK assisted with data analysis and interpretation of findings. RCW and DH drafted the manuscript.

RCW, KMK, and DH provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved final version for publication.

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ETHIC STATEMENT

The study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. All participants gave written informed consent as approved by the ethical review board of the Saarland Medical Association, Saarbrücken, Germany.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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