Cortical Thickness and Subcortical Volumes in Adolescent Synthetic Cannabinoid Users with or Without ADHD: a Preliminary Study

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ABSTRACT

Introduction: Synthetic cannabinoids (SCs) have become increasingly popular in the last few years, especially among adolescents. Given Attention deficit/hyperactivity disorder (ADHD) is over represented in patients with substance use across adolescents compared to the general population, the current study aims were two-fold: i) examine cortical thickness, surface area and subcortical volumes in SC users compared to controls, ii) examine the influence of ADHD on cortical thickness, surface area and subcortical volumes in SC users.

Methods: Structural magnetic resonance imaging scans were acquired from 28 SC users (15 without ADHD and 13 with ADHD combined type) and 13 controls.

Results: We found that SC users both with and without ADHD groups

have significantly reduced cortical thickness compared to controls in areas of the left caudal middle frontal and left superior frontal. In addition, SC users with ADHD also showed reduced cortical thickness in the right precentral and postcentral gyri. We also found increased right nucleus accumbens volume in SC users without ADHD, but not with ADHD, compared to controls.

Conclusion: These results suggest that similar to cannabis use, SC use has also negative effects on brain morphology and comorbidity of ADHD and substance dependence may show different cortical thickness and subcortical volume alterations than substance use alone.

Keywords: Synthetic cannabinoids; ADHD; structural imaging; cortical thickness; subcortical volume

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INTRODUCTION

Synthetic cannabinoids (SCs) are a group of compounds that imitate the effects of Δ -9-tetrahydrocannabinol (THC) on cannabinoid receptors. THC is the main psychoactive part of natural cannabis, which is a partial agonist of cannabinoid receptors 1 and cannabinoid receptors 2. However, SCs are full agonists of cannabinoid receptors that make them more potent compared to cannabis (1). Furthermore, in contrast to natural cannabis, SCs do not contain cannabidiol thought to play a protective role (2). SCs are marketed under various names such as "Spice", "Bonzei", "K2", "Aroma" or "Kronic". These substances are also known as "designer drugs"- "herbal highs" and can be found via the internet or herbal markets. There are three major groups of SCs based on their chemical structure, including JWH series, HU series and CP series (3). Although screening tests have been developed, it is still difficult to determine these products because of the chemical variety. SCs have become increasingly popular in the last few years, especially among adolescents and young adults in both Europe (4) and USA (5) and are associated with serious negative psychiatric effects such as acute psychosis and suicidal ideation (6).

As mentioned above, SCs contain chemicals that are more potent than THC but do not contain cannabidiol and may thus represent a greater risk for harms on brain morphometry than natural cannabis. However, to date, no study investigated the effects of SC use on cortical thickness or surface area. Interestingly, only few previous studies investigated the association between cortical thickness and cannabis use in adolescents or young adults. Lopez-Larson et al. (7) had shown both increased (bilateral lingual, right superior temporal, right inferior parietal and left paracentral) and decreased (bilateral superior frontal, bilateral insula and right caudal middle frontal) cortical thickness in adolescents with a history of heavy cannabis use compared to controls. Another two previous studies found thinner bilateral superior frontal sulcus, right anterior and posterior cingulate, and left precentral gyrus (8) and thinner right fusiform gyrus (9) in young adults with cannabis use compared to controls.

SC use might also affect subcortical volumes given the subcortical structures are rich in endocannabinoid receptors (10). Only one

previous whole-brain voxel-based morphometry (VBM) study found reduced thalamic volumes in young adult SC users compared to controls (11). Although previous studies in cannabis users have demonstrated alterations in volumes of subcortical structures, studies have been mixed. For example, studies have reported volume reductions in hippocampus (12) and amygdala (12), increases in nucleus accumbens (13) or no differences (14) in subcortical volumes in cannabis users compared to controls. Inconsistencies between the studies may relate to the differences in the imaging analyses or clinical characteristics of the samples such as stage of illness, brain maturational stage, diagnostic comorbidity and medication.

Attention deficit/hyperactivity disorder (ADHD) is more prevalent among patients with substance use in both adolescents and adults compared to the general population (15) and cortical thickness abnormalities were observed in multiple brain regions including frontal, parietal and temporal areas in the ADHD patients (16). Despite the high rates of comorbidity, to date, no studies investigated the effects of this comorbidity on the cortical thickness in the adolescents. Only one previous study in young adults reported thinner bilateral superior frontal sulcus, right anterior and posterior cingulate, and left precentral gyrus in the cannabis users after controlling for ADHD diagnosis (8). They also found thinner left precentral and postcentral cortical thickness in young adults who had persistent ADHD after controlling for cannabis use. Therefore, ADHD might be a confounding factor in studies investigating cortical thickness in substance users. Thus, in this study, we explored SC users with and without ADHD compared to controls to investigate the possible effects of comorbidity on cortical thickness and surface area.

The first aim of the study was to examine cortical thickness, surface area and subcortical volumes in SC users compared to healthy controls. The second aim of the current study was to examine the influence of ADHD on cortical thickness, surface area and subcortical volumes in SC users. To do this, we compared three demographically well-matched groups: adolescent SC users with and without ADHD and healthy controls.

METHODS

Participants

28 SC users (15 without ADHD and 13 with ADHD combined type), with a history of using SC more than three times a week for at least 6 months prior to study enrollment were enrolled in the study along with 13 typically developing controls. All participants were between age 14 and 18. Users and controls were right-handed. All of the patients were recruited from Child and Adolescent Psychiatry addiction unit at Ege University Hospital in Izmir, Turkey. Adolescent controls were recruited from local schools. The groups were matched for age and duration of education. Both SC users and controls were male and active smokers.

Exclusion criteria for SC users were: illicit drugs consumed on more than 15 occasions in the past year or more than 12 alcoholic beverages consumed per week; history of any diagnosed psychiatric illness; use of psychoactive medications in the last two months; loss of consciousness for more than 10 minutes; hepatic, endocrine or renal disease; history or presence of a neurological disorder; and contraindications for MRI. Controls met the same criteria as patients, except for a history of SC use and ADHD. Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL) (17) as used to assess the presence of ADHD with combined type and other psychiatric diagnoses.

All subjects/parents gave written informed consent to participate in the study. The study was approved by Ege University Ethics Committee.

MRI Acquisition

All MRI scans were performed using 3T MR system (Siemens, Verio, Erlangen, Germany) with a standard quadrature head coil. 3D-T1-weighted MP-RAGE images scanned to get structural images. In these sequences TR/TE/TI=1900/2.21/900 ms, voxel size=1 mmx1 mmx1 mm, slice thickness=1 mm, FoV=224x256 mm, slice number=176, FA=9°, matrix=224x256, scanning time=6 minutes.

Cortical Thickness and Surface Area Analysis

We analyzed T1 images by using the FreeSurfer software package (version 5.3.0, <http://surfer.nmr.mgh.harvard.edu>), which is available freely online. Imaging processing procedures were based on previous reports (18, 19). Processing steps included motion correction, removal of non-brain tissue, transformation to Talairach-like space, segmentation of subcortical gray/white matter tissue, intensity normalization, tessellation of the gray matter-white matter boundary, automated topology correction, and surface deformation. Cortical thickness was measured by averaging the distance between the pial surface and grey-white surface (20).

All images were visually inspected to assess reconstruction errors, including skull-strip errors, gross segmentation errors and white matter and pial surface inaccuracies. Surface inaccuracies were manually corrected with FreeSurfer's editing tools in accordance with an internal, standardized quality control and editing protocol. Edited images were then reprocessed through the FreeSurfer pipeline to improve the accuracy of the automatic tracing method (21) and the output was visually inspected again. This process was repeated until all surface errors were corrected.

Subcortical Volume Analysis

Left and right hippocampus, amygdala, thalamus, nucleus accumbens, caudate, putamen and intra cranial volume (ICV) were calculated by the automated procedure for volumetric measures of the brain structures implemented in FreeSurfer for further statistical analysis.

Statistical Analysis

Cortical thickness and area maps were smoothed with a full width half maximum Gaussian kernel of 15 mm. FreeSurfer's Query, Design, Estimate, Contrast (QDEC) tool was used to test for cortical thickness and surface area differences between (i) whole group of SC users and controls, (ii) SC users without ADHD and controls, and (iii) SC users with ADHD and controls. A general linear model was used to identify between-group differences in thickness and area estimates with age as covariates of no interest. Multiple comparisons were corrected with a Monte Carlo Simulation using a p-value set at <0.05. Desikan-Killiany atlas was used to identify cortical structures.

The 12 subcortical structure volumes and ICV were imported into the SPSS 16.0 software for statistical analyses. A GLM was used to analyze subcortical volume differences between whole group of SC users and controls, with ICV as continuous predictors. To correct for multiple comparisons, the Bonferroni correction was applied ($p < 0.05/12 = 0.004$).

Demographic and clinical characteristics were assessed for normality of their distribution using Kolmogorov-Smirnov normality test. Parametric and non-parametric tests were used appropriately. Pearson's r and Spearman's ρ (when variables were not normally distributed) were used for examining the associations between the FreeSurfer results and clinical variables. For all analyses, the level of significance was $p < 0.05$. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, v16.0).

RESULTS

Demographic and Synthetic Cannabinoid Use Variables

Table 1 shows the demographics and measures of synthetic cannabinoid use.

Comparison of Thickness and Surface Area in All SC Users and Controls

In the left hemisphere, all SC user group showed significantly decreased cortical thickness in one cluster. The cluster was in the caudal middle frontal cortex and superior frontal cortex ($p=0.0005$) (Table 2, Fig. 1a). There were no significant differences in right cortical thickness between groups. There were no significant differences in surface area between the groups. There was no significant correlation between the duration of regular SC use (Spearman's $\rho=0.113$, $p=0.567$), amount of daily use (Spearman's $\rho=-0.089$, $p=0.654$) or age started SC use (Spearman's $\rho=-0.084$, $p=0.670$) and cortical thickness in the SC users group.

Comparison of Thickness and Surface Area in SC Users without ADHD and Controls

In the left hemisphere, SC users without ADHD group showed significantly decreased cortical thickness in one cluster. The cluster was in the caudal middle frontal cortex and superior frontal cortex ($p=0.0102$) (Table 2, Figure 1b). There were no significant differences in right cortical thickness between groups. There were no significant differences in surface area between the groups. There was no significant correlation between the duration of regular SC use (Spearman's $\rho=0.192$, $p=0.494$), amount of daily use (Spearman's $\rho=-0.295$, $p=0.286$) or age started SC use (Spearman's $\rho=-0.162$, $p=0.563$) and cortical thickness in the SC users without ADHD group.

Comparison of Thickness and Surface Area in SC Users with ADHD and Controls

In the left hemisphere, SC users with ADHD group showed significantly

decreased cortical thickness in one cluster. The cluster was in the caudal middle frontal cortex and superior frontal cortex ($p=0.0021$) (Table 2, Figure 1c). In the right hemisphere, SC users with ADHD group showed significantly decreased cortical thickness in one cluster. The cluster was in the precentral and postcentral gyrus ($p=0.0115$) (Table 2, Figure 1d). There were no significant differences in surface area between the groups.

Comparison of Subcortical Volumes in All SC Users and Controls

We found increased volumes in SC users in right nucleus accumbens, bilateral caudate and left amygdala at an uncorrected level, but only the result for the nucleus accumbens survived after Bonferroni correction (Table 3). Post-hoc t tests demonstrated significantly increased right nucleus accumbens volume in SC users without ADHD compared to controls ($t=3.126$, $p=0.004$) but not in SC users with ADHD ($t=1.983$, $p=0.059$).

DISCUSSION

In this study, we examined cortical thickness and surface area in SC users with and without comorbid ADHD and controls. We found that SC users both with and without ADHD groups have significantly reduced cortical thickness compared to controls in areas of the left caudal middle frontal and left superior frontal. In addition, SC users with ADHD also showed reduced cortical thickness in the right precentral and postcentral gyri. We also found increased right nucleus accumbens volume in SC users without ADHD, but not with ADHD, compared to controls.

Similar to our findings, a previous study found decreased cortical thickness in bilateral superior frontal cortex and right caudal middle frontal in adolescent cannabis users compared to controls (7). But, they also found increased cortical thickness in the bilateral lingual, right superior temporal, right inferior parietal and left paracentral regions in the cannabis users. Our results are partly in line with another previous study, which found decreased cortical thickness in the bilateral superior frontal sulcus, right cingulate gyrus and left precentral gyrus (8). However,

Table 1. Demographic and clinical characteristics

	SC users without ADHD (n=15)	SC users with ADHD (n=13)	Controls (n=13)	Statistic	P value
Age	15.9±0.9 (14–17)	16.0±1.2 (14–18)	16.5±1.3 (14–18)	$F_{(2,40)}=1.167$	0.322
Education (years)	8.9±0.6 (8–10)	9.0±0.8 (8–10)	9.2±0.8 (8–10)	$\chi^2=2.098$	0.350
Age at first use (years)	13.0±1.9 (8–15)	13.7±1.5 (11–17)		$t=-1.077$	0.291
Duration of regular use (months)	13.9±4.7 (7–23)	14.4±5.3 (9–27)		$t=-0.238$	0.814
Daily use (gr/day)	4.8±1.2 (3–7)	5.0±1.0 (3–7)		$t=-0.488$	0.630
Duration of abstinence (days)	8.1±5.5 (2–21)	8.5±5.5 (2–22)		$t=-0.343$	0.751

Data are presented as mean ± standard deviation (minimum-maximum). SC, synthetic cannabinoid; ADHD, attention deficit/hyperactivity disorder.

Table 2. Significant clusters detected decreased cortical thickness in SCU groups compared to controls after Monte-Carlo correction

Group	Hem	Size (mm ²)	Cluster No	Region	Talairach (x, y, z)			p value
All SC <Controls	L	2459	1	Superior Frontal	-24.2	14.2	40.6	0.0005
SC without ADHD <Controls	L	1698	1	Caudal Middle Frontal	-24.5	13.7	42.4	0.0102
SC with ADHD <Controls	L	2073	1	Caudal Middle Frontal	-30.7	5.4	48.3	0.0021
	R	1686	2	Precentral Gyrus	54.4	-1.5	31.9	0.0115

SC, synthetic cannabinoid users; ADHD, attention deficit/hyperactivity disorder; Hem, hemisphere; Th, thickness; L, left; R, right.

Figure 1. a–d. Cortical thickness differences between groups. Color bar represents $\log_{10}$ p-values, with blue representing a reduction in thickness: Thinner cortical regions in all SCU users in comparison to controls (**a**). Thinner cortical regions in SCU users without ADHD in comparison to controls (**b**). Thinner cortical regions in SCU users with ADHD in comparison to controls (**c, d**).

our results are in contrast to a previous study of young adults with cannabis use, which identified decreased cortical thickness only in the right fusiform gyrus (9). Lopez-Larson et al.'s (7) study has a more similar sample to the current study, with respect to age and duration of substance use. However, in the Lopez-Larson et al.'s study groups were differed in gender, which may provide different results. In addition, other previous

studies (8, 9) samples were older in age and had a longer duration of cannabis use. Therefore, different patterns of cortical thickness could be due to different sample characteristics of the studies.

Including our study, three of the four studies in cannabis/SC users found decreased cortical thickness in the superior frontal cortex. Furthermore,

Table 3. Subcortical volume comparisons between groups

	SC users (n=28)	Controls (n=13)	Statistic	P value
Left Hippocampus	4582±483	4583±338	F=0.177	0.676
Right Hippocampus	4860±459	4740±340	F=2.332	0.135
Left Amygdala	1778±194	1789±128	F=0.124	0.727
Right Amygdala	1820±178	1774±88	F=4.473	0.041
Left Accumbens	672±89	622±100	F=2.307	0.137
Right Accumbens	731±77	650±85	F=9.481	0.004*
Left Caudate	4008±499	3751±394	F=6.658	0.014
Right Caudate	4008±537	3763±446	F=5.337	0.026
Left Putamen	6064±851	6028±502	F=0.416	0.523
Right Putamen	5912±712	5707±497	F=1.909	0.175
Left Thalamus	8423±665	8430±769	F=0.309	0.581
Right Thalamus	7746±565	7828±562	F=0.065	0.800

Data are presented as mean ± standard deviation.

SC, synthetic cannabinoid.

*Significant p-value after Bonferroni correction.

we also found thinner caudal middle frontal cortex in the SC users, which is the part of dorsolateral prefrontal cortex (DLPFC) together with the superior frontal cortex. In addition, the reduced cortical thickness in DLPFC was also found in the studies of ADHD (22). DLPFC has been implicated in top-down cognitive control, which has shown to be impaired in both substance users and individuals with ADHD (23). Two previous studies found an inverse correlation between impulsivity scores and cortical thickness of the left superior frontal cortex (24) and middle frontal cortex (25) in healthy populations. Given that impulsivity plays a pivotal role in the etiology of both substance dependence and ADHD (26), our results might be associated with neuronal mechanisms underlying impulsivity. Taken together, our findings might reflect a predisposition rather than a consequence of SC use. However, due to the cross-sectional nature of our study, we are unable to establish a clear temporal relationship between SC use and decreased cortical thickness. Furthermore, lack of ADHD group free from substance limits the interpretation of findings. Given the prefrontal cortex is rich in endocannabinoid receptors (27), another possible explanation for the decreased cortical thickness might be toxic effects of SC use. In line with this, a recent study showed significantly altered dendritic arborization of pyramidal neurons in layer II/III in the prefrontal cortex in the adult rats that were chronically treated with SC during adolescent (28).

In the current study, SC users with ADHD showed decreased cortical thickness in the right precentral and postcentral gyri compared to controls. In the context of no significant differences in these regions between SC users without ADHD and controls, decreased cortical thickness might be ADHD-specific. In line with our findings, previous studies also found decreased cortical thickness in the several brain regions, including the precentral gyrus (16, 22). Similar to our findings, a previous study investigated the effects of both ADHD and cannabis use on cortical thickness found thinner precentral and postcentral cortical thickness in young adults who had persistent ADHD after controlling for cannabis use (8). Taken together, our findings of decreased cortical thickness in the precentral and postcentral gyri might be related to ADHD rather than SC use.

Our finding of increased nucleus accumbens volume in SC users without ADHD is not in line with a previous study (11) that found reduced thalamic volumes in young adult SC users. In contrast to our study, groups were not matched for ADHD and cigarette smoking in a previous study and cigarette smoking has been associated with gray matter abnormalities (29). Furthermore, while the previous study conducted a whole brain analysis using SPM, the current study utilized a region of interest (ROI) analysis using FreeSurfer. Thus, these different patterns of abnormalities might be explained by different sample characteristics and analyses software in the two studies. Gilman et al. (13) found increased nucleus accumbens volume in cannabis users at trend-level. However, a recent study found no differences in subcortical volumes, including nucleus accumbens in cannabis users compared to controls (14). Different cannabidiol levels in cannabis seem to affect differences in brain morphology (2). In the context of SC products do not contain cannabidiol, alterations in nucleus accumbens volume might be more pronounced in our study.

The current study has several potential limitations. The most obvious is the cross-sectional nature of the study, and thus, potential changes in cortical thickness measurements over the course of illness in SC users remains speculative. Second, our sample was relatively small, due to our strict exclusion and inclusion criteria, which may have reduced power to detect group differences. Third, we were unable to determine the chemical contents of the synthetic cannabinoid products to which individuals were exposed. A recent study in Turkey found that JWH-018 was the most frequent (99.4%) type of synthetic cannabinoids within 1179 samples and JWH-081 was found in 777 samples (65.9%) together with

JWH-018 (30). Therefore, it could be argued that our findings were mainly due to the use of the JWH group. Another limitation is that the measures of alcohol, past substance and SC use were self-reported, and under-reporting is a reasonable concern. Furthermore, although both SC users and controls were active smokers, we did not account for measures such as amount and frequency of smoking in the analyses. Another limitation of the study is that we used a liberal initial vertex-wise threshold that may lead to false-positive results. In addition, we cannot extend our findings to females with SC use as our sample included only males. Finally, we did not have patients with ADHD, which limits our ability to test the effect of ADHD on cortical thickness and surface area in a sample free from substance use. Given the limitations of this study, our results should be considered preliminary.

In this study, we found the first evidence of decreased cortical thickness in adolescent SC users in DLPFC. In addition to DLPFC, SC users with ADHD also showed decreased cortical thickness in motor areas. These results suggest that similar to cannabis use, SC use has also negative effects on brain morphology and comorbidity of ADHD and substance dependence may show different cortical thickness and subcortical volume alterations than substance use alone.

Ethics Committee Approval: The study was approved by Ege University Ethics Committee.

Informed Consent: All subjects/parents gave written informed consent to participate in the study.

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