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Structural brain characteristics of anabolic–androgenic steroid dependence in men

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ABSTRACT

Aim To identify differences in brain morphology between dependent and non-dependent male anabolic–androgenic steroid (AAS) users. **Design** This study used cross-sectional data from a longitudinal study on male weightlifters. **Participants** Oslo University Hospital, Norway. **Setting** Eighty-one AAS users were divided into two groups; AAS-dependent ($n = 43$) and AAS-non-dependent ($n = 38$). **Measurements** Neuroanatomical volumes and cerebral cortical thickness were estimated based on magnetic resonance imaging (MRI) using FreeSurfer. Background and health information were obtained using a semi-structured interview. AAS-dependence was evaluated in a standardized clinical interview using a version of the Structured Clinical Interview for DSM-IV, adapted to apply to AAS-dependence. **Findings** Compared with non-dependent users, dependent users had significantly thinner cortex in three clusters of the right hemisphere and in five clusters of the left hemisphere, including frontal, temporal, parietal and occipital regions. Profound differences were seen in frontal regions (left pars orbitalis, cluster-wise $P < 0.001$, right superior frontal, cluster-wise $P < 0.001$), as has been observed in other dependencies. Group differences were also seen when excluding participants with previous or current non-AAS drug abuse (left pre-central, cluster-wise $P < 0.001$, left pars orbitalis, cluster-wise $P = 0.010$). **Conclusion** Male dependent anabolic–androgenic steroid users appear to have thinner cortex in widespread regions, specifically in pre-frontal areas involved in inhibitory control and emotional regulation, compared with non-dependent anabolic–androgenic steroid users.

Keywords Anabolic–androgenic steroids, dependence, addiction, cerebral cortex, cortical thinning, nucleus accumbens, pre-frontal cortex, neuroimaging.

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INTRODUCTION

Anabolic–androgenic steroids (AAS) are synthetic derivatives of the male sex hormone testosterone, first isolated and synthesized in the late 1930s. Today AAS use is considered a major recent form of substance abuse, and is a growing public health concern throughout the Western world [1]. The estimated prevalence of AAS use varies between 1 and 5%, depending on the age group studied [2,3]. AAS have both androgenic (masculinizing) and anabolic (protein-synthesizing) effects, and is taken in doses 10–100 times greater than the natural male production of testosterone [4,5]. AAS easily pass the blood–brain barrier and affect the central nervous system (CNS) [6,7]. Androgen receptors (AR) are widely expressed in the CNS, not least in regions such as the amygdala, hippocampus, hypothalamus, brain stem and cerebral cortex [8,9]. AAS is commonly administered in cycles of 6–18 weeks [10], with drug-free periods in between intended to prevent tolerance towards AAS and allow recovery of natural hormonal functioning [11,12]. Many AAS users report that they experience positive mood, more energy and better self-confidence while on cure [2,13], whereas withdrawal symptoms such as depression, irritability, anxiety, fatigue and insomnia are commonly experienced in drug-free periods [14]. There seems to be a growing trend to administer AAS continuously in a pattern referred to as 'cruise and blast' [15,16], where users alternate between periods

with high and low doses, mainly to avoid withdrawal symptoms. Long-term use is associated with a wide range of adverse side effects, both physical [17–20], psychiatric [1,21] and cognitive [22,23]. The risk of adverse side effects may increase with the duration of use [10]. Thirty per cent of AAS users develop a dependence syndrome [24], characterized by withdrawal symptoms and continued use despite the experience of adverse effects [5,25]. Dependent AAS users report more intra- and interpersonal problems compared to non-dependent users, and AAS dependence is associated with higher levels of aggressive and antisocial behaviours [26–28].

Although the mechanisms underlying AAS dependence are not fully understood, it seems that AAS have elements in common with other drugs of abuse [29]. The aetiology of AAS dependence is probably multi-factorial [5,30,31], implicating body-image, neuroendocrine factors and hedonic mechanisms. First, obsession with body image and muscular size may be both a reason for initiating and continuing AAS use [30,32]. However, recent findings suggest an association between body-image disorder and initiation of AAS, but not with development of dependence [33]. Secondly, hypothalamic pituitary testicular (HPT) suppression can lead to fatigue, loss of libido and depression, and AAS use may be continued in order to alleviate unpleasant symptoms [30]. Thirdly, the rewarding and reinforcing effects of AAS may contribute to continuation of abuse. Although AAS do not produce immediate reward in the form of acute intoxication [34] there are many psychological reinforcing effects, such as better self-confidence and body-image and social unity with peers [35,36]. In addition, evidence from animal studies supports a more direct neurobiological reinforcing effect of AAS [30]. It has been demonstrated that rats and hamsters self-administer testosterone and AAS [37–39], some even to the point of death [29]. The rewarding effects of AAS have also been demonstrated through the conditioned place preference (CPP) paradigm [40–42].

Long-term exposure to various types of addictive substances may induce structural changes in the brain [43–48], and such morphological changes seem to be important mediators for addictive behaviour [49]. Furthermore, supraphysiological doses of testosterone may have neurotoxic effects on different cell types, including neurones [50–52]. Our group and others have recently shown that long-term AAS use is associated with structural and functional brain differences, although the direction of causality could not be determined [53–56]. The aim of the present study was to explore potential brain correlates of AAS dependence, including measures of regional brain volume and cortical thickness. In a sample of weightlifters included in our previous studies, we tested for differences in brain morphology between dependent and non-dependent AAS users. To the best of our knowledge, comparisons of brain structure within the AAS group have not been conducted before. Based on previous research and models of reward processing and dependency, regions of particular interest included the nucleus accumbens (NA), implicated in reward processing [57], and pre-frontal cortex, involved in cognitive functions such as inhibitory control and emotional regulation [58].

METHODS

Participants

The study participants included previous or current male AAS users reporting ≥ 1 year of cumulative AAS exposure (summarizing on-cycle periods). Our sample comprised 81 AAS users, divided into two groups: AAS-dependent (n = 43) and AAS-non-dependent (n = 38). The sample partly overlaps with the one described in detail by Bjørnebekk *et al.* [53] and Westlye *et al.* [54]. Prior to participation, all participants received a brochure with a description of the study and provided written informed consent.

Ethical approval

The study was approved by the Regional Committees for Medical and Health Research Ethics South East Norway (REC) (2013/601), and all research was carried out in accordance with the Declaration of Helsinki.

Materials and methods

A semi-structured interview was administered in order to obtain relevant background and health information. The interview covered motives behind their AAS use, age of onset, administration pattern, years of use, length and number of cycles, side effects, average weekly dosage, where in the cycle they were at the time of assessment and whether and when they had ceased using AAS. We calculated total 'life-time AAS exposure' as the product of life-time average weekly dose calculated as mg of testosterone equivalent and life-time weeks of AAS exposure, in line with previous studies [26,59,60]. The presence of AAS dependence was evaluated in a standardized clinical interview by trained study personnel using a version of the Structured Clinical Interview for DSM-IV (SCID II) [61], adapted to apply to AAS dependence [25]. Compared to the standard version, this version only makes small interpretive changes that take into account that AAS is not ingested to achieve an immediate 'high' of acute intoxication, and adds explanatory information on how the other criteria relate to AAS abuse. Preliminary analyses suggest adequate psychometric properties [62]. The presence of previous or current drug abuse was determined by the drug and the alcohol dependence scales from the Millon Clinical Multiaxial Inventory–III (MCMI-III), and self-reports on previously

used substances outside medical use. Participants who obtained a base rate (BR) score of 75 or above on one of the MCMI-III drug scales (indicating the presence of a clinical syndrome) fulfilled the criteria of having a 'previous or current non-AAS drug abuse'. If participants obtained BR scores close to 75 (> 70), then the evaluation was guided by a self-report questionnaire from the Mini-International Neuropsychiatric Interview (MINI)-plus psychiatric diagnostic interview instrument (version 5.0), (evaluating substance dependence), and information from drug scales from the Achenbach System of Empirically Based Assessment (ASEBA), Adult Self-Report (ASR) questionnaire [63] (past 6 months drug and alcohol use). Measures of behavioural, emotional and social problems was obtained from selected syndrome scales from the ASEBA, ASR questionnaire [63]. The intelligence quotient (IQ) was estimated using the vocabulary and the matrix reasoning subtests from the Wechsler Abbreviated Scale of Intelligence (WASI) [64].

Image acquisition and analysis

Magnetic resonance imaging (MRI) data were obtained on a Siemens Skyra 3 T scanner equipped with a 24-channel head coil. Structural MRI data was acquired with a T1-weighted 3D magnetization-prepared rapid gradient-echo (MPRAGE) sequence with the following parameters: repetition time = 2300 ms; echo time = 2.98 ms; inversion time = 850 ms; flip angle = 8°; bandwith = 240 HZ/pixel; field of view = 256 mm; voxel size = 1.0 × 1.0 × 1.0 mm; 176 slices sagittally orientated; acquisition time = 9:50. Scan quality was consecutively inspected during the scanning session and re-run in cases of movement to ensure good quality. All data sets were automatically processed and analysed using FreeSurfer (version 5,3; http://surfer.nmr.mgh.harvard.edu), which is described in detail elsewhere [65,66]. The cortical surface was reconstructed for each subject to measure both surface area and thickness at each surface location or vertex. The individual thickness maps were smoothed using a Gaussian kernel of 15 mm. Subcortical volumes were obtained from the automatic volume segmentation procedure [67,68] and, based on previous findings and current brain-based models of drug dependence, we selected a limited number of regions of interest. The selection was performed before the statistical tests were conducted, and included the accumbens area, caudate, putamen, amygdala and hippocampus. Total grey matter was used as a global measure in addition to estimated intracranial volume (ICV), which was computed and included in the volumetric analyses. All reconstructed data sets were visually inspected. The quality of the spatial registration and tissue segmentations was considered to be of sufficiently good quality to avoid manual editing, thus ensuring that we will have no impact on the data.

Statistical analyses

Comparisons of demographic data between the dependent and non-dependent users were performed using the two-tailed independent sample *t*-test for continuous data and χ^2 tests for categorical data. Differences between the groups were considered significant at $P < 0.05$. We used multivariate analysis of covariance (MANCOVA) to test for differences in neuroanatomical volumes, with regional brain volumes as dependent variable, group as the independent variable and age and intracranial volume (ICV) included as continuous covariates. Preliminary assumption testing was conducted, with no serious violations noted. We corrected for multiple comparisons using Bonferroni correction for correlated measures [63], where the correlation between the dependent variables is taken into account, $\alpha_{original}0.5/6$ dependent variables with a Pearson's $r = 0.41$ yielded $P_{adjusted} = 0.017$. For cortical thickness, we fitted a general linear model (GLM) at each vertex using thickness as the dependent variable, group as the independent variable and age as covariate. In an attempt to adjust for other substance abuse, we conducted exploratory analyses where we omitted participants classified as having 'previous or current non-AAS drug abuse'. Furthermore, in an attempt to distinguish pre-morbid vulnerability from exposure effects of AAS and other drugs of abuse, we re-ran the main analysis, including measures of weekly reported alcohol consumption, use of illegal drugs (besides AAS) and life-time AAS exposure as additional covariates in the model. To reduce the probability of type I errors, we performed cluster-size correction for multiple comparisons using Z Monte Carlo simulations with 5000 iterations, as implemented in FreeSurfer [69,70]. A cluster-forming threshold of $P < 0.05$ (two-sided) was applied.

RESULTS

Demographics and user characteristics

Demographic and other clinical data can be found in Table 1. There were no significant differences between the groups in age, education, IQ, height, weight or body mass index (BMI). The groups had approximately the same alcohol consumption, on average, < 2 units per week. Both groups initiated the AAS use in their early 20s. There was a trend to higher weekly intake of AAS (mg/week) by the dependent group, albeit not reaching statistical significant level. The dependent group had used AAS for more years [mean = 10.3, standard deviation (SD) = 5.6] than the non-dependent (mean = 7.7, SD = 5.1) group ($t_{(79)} = -2.19$, $P = 0.031$, $d = 0.60$).

Table 1 Demographics and other clinical characteristics.

	Dependent (n = 43)	*Non-dependent (n = 38)*			
Attribute	*Mean (SD)*	*Mean (SD)*	*t*	*P-value*	*d*
Age (years)	32.77 (8.02)	33.22 (8.56)	0.35	0.724	0.13
Education (years)	13.83 (2.24)	14.59 (2.77)	1.35	0.180	0.50
WASI vocabulary T	50.00 (8.79)	52.21 (8.67)	1.16	0.251	0.25
WASI matrix reasoning T	52.74 (9.03)	56.00 (6.81)	1.81	0.074	0.52
Alcohol units per week	1.77 (3.86)	1.61 (2.34)	–0.25	0.823	0
Height (cm)	181.21 (7.56)	180.15 (6.08)	–0.69	0.493	0.15
Weight (kg)	99.52 (14.66)	94.22 (12.61)	–1.73	0.084	0.38
BMI	30.14 (4.50)	29.04 (3.67)	–1.19	0.236	0.28
Estimated weekly AAS dose	1376.9 (872.7)	1009.9 (807.4)	–1.93	0.058	0.43
Total years of AAS use	10.32 (5.57)	7.70 (5.13)	–2.19	**0.031***	0.60
AAS debut age	20.89 (6.63)	22.89 (5.75)	1.46	0.147	0.36
Anxious/depressed T	58.62 (9.93)	54.25 (7.01)	–2.13	**0.037***	0.49
Attention problems T	58.42 (6.61)	55.34 (5.01)	–2.14	**0.036***	0.54
Drug use T	60.34 (15.34)	54.63 (8.36)	–1.92	0.061	0.49
Alcohol consumption T	57.89 (6.94)	58.09 (7.74)	0.11	0.909	0.15
Aggressive behaviour T	58.62 (7.85)	53.58 (5.28)	–3.04	**0.003***	0.82
Total problems raw score	45.12 (27.33)	29.52 (18.35)	–2.68	**0.010***	0.69
	n (%)	*n* (%)	χ^2		OR
Physical side effects of AAS	40 (93)	29 (76.3)	4.46	**0.035***	40.14
Psychological side effects of AAS	39 (90.7)	22 (57.9)	11.67	**0.001***	70.09
Cognitive side effects of AAS	28 (65.1)	9 (23.7)	14.83	**0.001***	60.48
Previous or current non-AAS drug abuse	21 (48.8)	11 (28.9)	3.34	0.068	20.34
Cigarette smoker	9 (20.9)	6 (16.2)	0.290	0.590	00.73
Psychopharmaca (previous or current)					
Antidepressants	7 (16.6)	4 (10.6)			
Anxiolytics	5 (11.9)	3 (7.9)			
Opioids	4 (9.3)	0 (0)			
> 1 type	3 (7)	0 (0)			
None reported	27 (62.8)	30 (78.9)			

AAS = anabolic–androgenic steroid; T = T score; BMI = body mass index; WASI = Wechsler Abbreviated Scale of Intelligence; SD = standard deviation; OR = odds ratio. *Significant difference between the groups.

Self-reported side effects and psychological screening

The dependent AAS users reported significantly more side effects compared to the non-dependent users; see Tables 1 and 2. The majority of the dependent AAS users reported some physical (93%, $n = 40$), psychological (90.7%, $n = 39$) and cognitive (65.1%, $n = 28$) side effects of AAS. The dependent group also scored significantly higher on anxiety/depression syndrome ($t_{(67)} = -2.13$, $P = 0.037$, $d = 0.49$), attention problems ($t_{(66)} = -2.14$, $P = 0.036$, $d = 0.54$), aggressive behaviour ($t_{(66)} = -3.04$, $P = 0.003$, $d = 0.82$) and total problems ($t_{(63)} = -2.68$, $P = 0.010$, $d = 0.69$). Of the dependent AAS users 48.9%, n = 21 had a previous or current drug abuse compared to 28.9%, $n = 11$ of the non-dependent users, but the difference was not statistically significant $\chi^2_{(1)} = 3.34$, $P = 0.068$, odds ratio (OR) = 2.34. More cases of psychopharmaca use were seen in the dependent group, where antidepressants were the most frequently prescribed drug. However, the majority of both the dependent (62.8%, $n = 27$) and non-dependent (78.9%, $n = 30$) group had never been prescribed psychotrophic medications of any kind.

Neuroanatomical volumes and cortical thickness

Neuroanatomical volumes in each group are presented in Table 3. There were no statistically significant differences between the groups in total grey matter volume, putamen, caudate, hippocampus or amygdala. The only difference reaching nominal statistical significance was NA volume ($F_{(1, 77)} = 5.23$, $P = 0.025$, $\eta^2_p = 0.06$), but the effect did not survive the Bonferroni correction (adjusted alpha level of 0.017), thus we did not conduct further between-group analyses.

Table 4 and Fig. 1 show results from the corrected GLM analyses comparing cortical thickness between the dependent and non-dependent groups. The main analysis

Table 2 Self-reported side effects in relation to AAS use.

	Dependent (n = 43)		*Non-dependent (n = 38)*				
Psychological	*n*	*%*	*n*	*%*	χ^2	*P-value*	*OR*
Depression	27	62.9	14	36.8	5.43	**0.020***	2.89
Fatigue	29	67.4	13	34.2	80.92	**0.003***	30.98
Anxiety	9	20.1	0	0.0	80.95	**0.003***	–
Aggression	28	65.1	10	26.3	120.19	**< 0.001***	50.23
Short fuse	24	55.8	12	31.6	40.78	**0.028***	20.74
Mood swings	21	48.8	11	28.9	30.34	0.068	20.34
Sleep problems	26	60.5	12	31.6	60.76	**0.009***	30.31
Reduced appetite	21	48.8	4	10.5	130.88	**< 0.001**	80.11
Medical							
Kidney-related issues	11	25.6	6	15.8	10.17	0.280	10.8
Liver-related issues	20	46.5	7	18.4	70.16	**0.007***	30.85
Cholesterol	11	26.6	9	23.7	0.039	0.843	10.11
Blood pressure	23	53.5	11	28.9	40.99	**0.026***	20.82
Acne	23	53.5	22	57.9	0.159	0.690	00.84
Cardiomyopathy or arterial fibrillation	11	25.6	10	26.3	0.006	0.940	00.96
Neuroendocrine							
Reduced sex drive	35	81.4	23	60.5	40.32	**0.038***	20.85
Sexual dysfunction	25	58.1	13	34.2	40.64	**0.031***	20.67
Gynaecomastia	17	39.5	12	31.6	0.556	0.456	10.42
Cognitive							
Memory problems	22	51.2	6	15.8	110.16	**0.001***	50.59

*Significant difference between the groups. AAS =

Table 3 Group differences in brain volumes between dependent and non-dependent AAS users.

	Non-dependent (n = 38)		*Dependent (n = 43)*					
	Mean	*SD*	*Mean*	*SD*	*d.f.*	*F*	*P-value*	η_p^2
Total grey matter	681 088.81	59 727.67	678 140.33	53970.07	3	0.88	0.352	0.011
Caudate	7849.43	911.20	8155.68	1 012.01	3	2.09	0.152	0.026
Putamen	12 861.14	1517.79	12 768.52	1 468.95	3	0.40	0.530	0.005
Hippocampus	9287.49	893.31	9298.32	904.85	3	0.02	0.888	0.000
Amygdala	4023.38	548.79	4019.15	450.60	3	0.03	0.857	0.000
Accumbens	1478.93	269.53	1597.93	193.69	3	5.23	**0.025***	0.064

Values are mm^3. *Significant difference between the groups at a nominal level ($P < 0.05$). Multivariate analysis of variance with regional volumes as dependent values, group as the independent variable and age and intracranial volume (ICV) as continuous covariates. AAS = anabolic–androgenic steroid.

showed that dependent AAS users had significantly thinner cortex in five clusters of the left hemisphere and tree clusters of the right hemisphere, covering frontal, temporal, parietal and occipital regions. Table 4 and Fig. 2 show the results after adjusting for drug, alcohol and AAS exposure, where significantly thinner cortex was observed in the AAS-dependent group in a pre-central cluster of the left hemisphere and in lateral occipital regions of the right hemisphere. When omitting participants classified as having 'previous or current non-AAS drug abuse' from the analyses, significant effects remained in pre-central and pre-frontal regions in the left hemisphere.

DISCUSSION

Using neuroimaging, we have demonstrated structural brain differences between dependent and non-dependent AAS users. The dependent AAS users had thinner

Table 4 Group differences in cortical thickness between dependent and non-dependent AAS users.

Cortex area	*Cluster size (mm^2)*	*Talairach coordinates*			
		X	*Y*	Z	
All included (n = 71)					CWP
Left pars orbitalis	2628.07	−39.9	38.9	−12.3	0.00030
Left middle temporal	2063.62	−55.4	−11.8	−25.6	0.00400
Left lingual	2551.14	−17.9	−55.4	−7.1	0.00060
Left caudal middle frontal	1467.06	−39.4	5.7	47.2	0.03650
Left supramarginal	2136.22	−55.1	−42.4	44.1	0.00300
Right cuneus	2494.42	8.6	−76.5	24.8	0.00050
Right superior frontal	2928.09	12.2	48.2	0.6	0.00020
Right lingual	1807.09	10.8	−61.4	−1.4	0.01050
Excluding non-AAS drug abuse (n = 49)					
Left pre-central	2952.09	−37.5	−14.7	38.5	0.00030
Left pars orbitalis	1849.65	−38.4	37.6	−11.1	0.00980
Alcohol, drugs and life-time AAS exposure (n = 66)					
Left pre-central	1698.81	−32.9	−9.5	48.2	0.01510
Right lateral occipital	1795.22	12.8	−100.7	9.8	0.01110

The cortical area, the size of the significant cluster, Talairach coordinates corresponding to the most significant vertex within each cluster, and clusterwise *P*-values (CWPs) are shown. All findings are in the direction of thinner cortices in the AAS (anabolic–androgenic steroid)-dependent group.

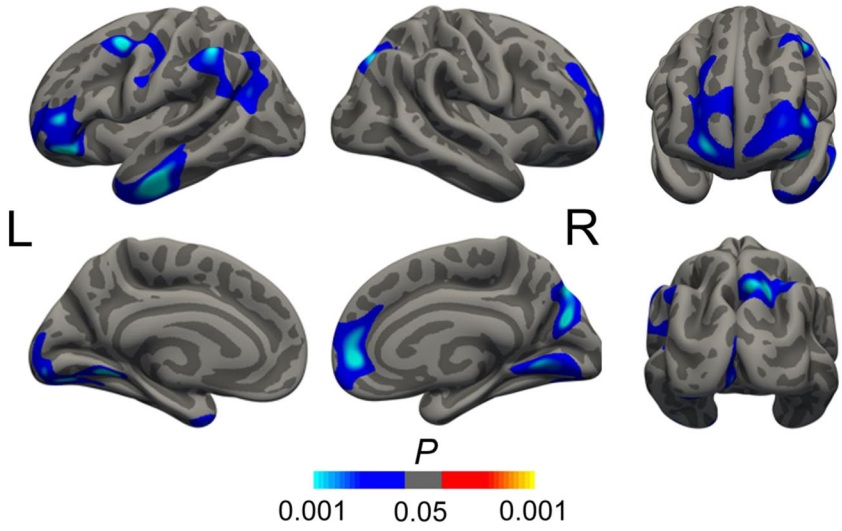

Figure 1 Vertex-wise comparisons of cortical thickness between the dependent and non-dependent anabolic–androgenic steroid (AAS) group. Shades of blue indicate clusters with thinner cortices in the dependent AAS group. No effects were seen in the opposite direction (i.e. thicker cortices). [Colour figure can be viewed at wileyonlinelibrary.com]

cortex in widespread regions, specifically in pre-frontal regions. Additionally, they reported more side effects and intra- and interpersonal issues. Potential implications of the results are discussed below.

Structural brain differences between dependent and non-dependent AAS users

AAS users who fulfilled the criteria for AAS-dependence had significantly thinner cortex in frontal, temporal, parietal, occipital and pre-frontal regions compared to non-dependent users. There was a non-significant trend of higher consumption of illegal drugs in the dependent group, and it could be argued that the observed differences in brain morphology could be related to non-AAS drug exposure effects, or potentially the combined effects of AAS and other substances of abuse. When excluding participants with 'previous or current non-AAS drug abuse' fewer cortical group differences were seen, due possibly to reduced sample size and reduction in power. The findings

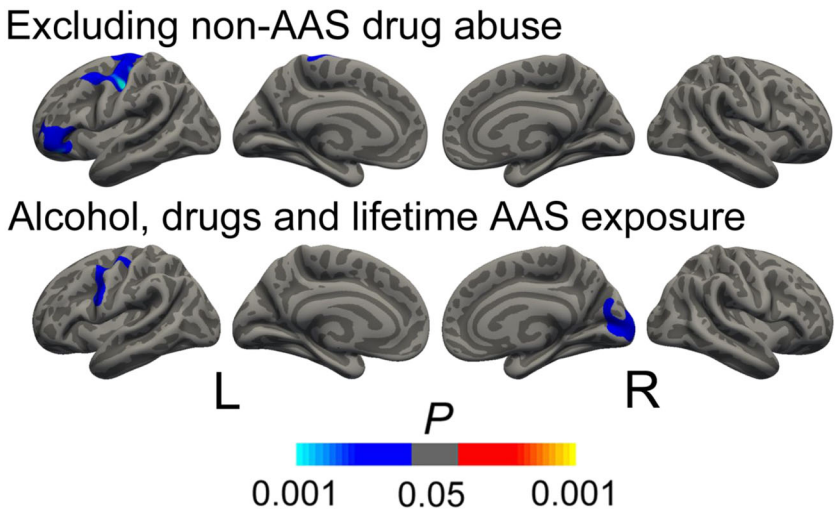

Figure 2 Vertex-wise comparisons of cortical thickness between the dependent and non-dependent anabolic–androgenic steroid (AAS) group controlled for potential confounding variables. Shades of blue indicate clusters with thinner cortices in the dependent AAS group. No effects were seen in the opposite direction (i.e. thicker cortices). [Colour figure can be viewed at wileyonlinelibrary.com]

of thinner cortex in clusters covering pre-central and pre-frontal regions of the left hemisphere remained significant, and could potentially comprise brain correlates of AAS dependence. AAS dependents had larger NA volume compared to the non-dependents, but the effect did not survive Bonferroni correction. Enlargement of NA and thinner cortex in regions involved in inhibitory control has been reported in other dependencies [43,48,71]. The underlying mechanisms are not fully understood, although individual differences in both impulsivity [72–74] and vulnerability to the reinforcing effects of drugs [75,76] seem to influence drug-seeking behaviour and the development of dependence.

Pre-frontal regions and dependence

Pre-frontal cortex is associated with numerous cognitive functions, such as self-regulation, mental flexibility, attention and inhibition [58]. Studies show that different types of substance dependency are associated with lower grey matter volume, particularly in frontal and pre-frontal regions [43,47,48]. In accordance with this, our results demonstrated that dependent AAS users had significantly thinner cortex in pre-frontal regions. The largest cluster covered orbitofrontal cortex (OFC), a region considered to play an important role in addiction [77], especially related to inhibitory control and regulation [78–80]. OFC dysfunction has been associated with aggression and violent behaviour [81], drug addiction [80,82] and obsessive–compulsive disorder [83–85], where compulsive behaviour and the lack of inhibitory control is a common denominator [79]. Impaired inhibitory control and cognitive flexibility could serve as an explanation for the maladaptive behaviour of continued drug use, despite adverse side effects that characterize dependencies [79]. In accordance with, this we found that the vast majority of the dependent AAS users reported physical, psychological and cognitive side effects of the AAS, and continued use despite adverse effects. Additionally, AAS dependents scored higher on aggressive behaviour, which is in line with previous reports [26,33,86], and could be related to OFC dysfunction. It has been demonstrated that testosterone can impair abilities dependent on OFC such as behavioural flexibility [87], and it has been hypothesized that testosterone increases the propensity towards aggression through reduction in OFC activity [88].

High-dose AAS use is associated with various adverse medical side effects, including hypogonadism and cardiovascular effects, with possible secondary effects on brain function [89–91]. Furthermore, it has been demonstrated that supraphysiological doses of testosterone can have neurotoxic effects on different cell types, including neurones [50–52]. Although the mechanisms of the proposed AAS-induced neurotoxity are unclear, it is possible that prolonged AAS exposure is associated with a risk of progressive deterioration of brain tissue [53]. The dependent group had used AAS for more years and it is possible that parts of the observed difference could be due to AAS-related cerebral thinning, similar to what has been suggested with other substance dependencies, specifically alcohol dependence [47,48]. The orbitofrontal effects are of interest, as they could potentially reflect differences in the brain associated with prolonged AAS exposure, and comprise a potential correlate of the transition from first use to addiction. Group differences were still seen in pre-central and lateral occipital regions after controlling for life-time AAS exposure, drug and alcohol use, and may hypothetically

reflect pre-existing characteristics. Although we adjusted for confounding variables it is important to note that confounding may still exist, e.g. through clinical features not assessed as part of this project or through interactions between clinical variables.

Symptom load and brain correlates

The dependent group reported significantly more side effects from AAS use. This was especially evident for psychological and cognitive domains, such as depression and memory problems. There is substantial evidence that substance use disorders and psychiatric disorders frequently co-occur [92,93], probably involving common pre-morbid neurobiological vulnerability [94,95]. Although not possible to test with cross-sectional data, it could be that the higher prevalence of adverse effects in the AAS-dependent individuals is related to the observed differences in cortical thickness. For instance, more dependent AAS users report depression as a side effect, and they also scored significantly higher on the depression syndrome scale. Some of the clusters with thinner cortex seen in dependent users, e.g. orbitofrontal, rostral anterior cingulate, pre-central, inferior and medial temporal and lingual regions, have also been also associated with depression [96–98] and combined anxiety and depression [99]. Moreover, dependent AAS users reported more memory problems as a side effect. Cortical thickness and memory performance are linked in healthy and pathological ageing [100–102], and observed thinner cortex in these regions may be associated with more self-reported memory problems in AAS-dependent participants.

Limitations

Some limitations should be considered when interpreting the results of the present study. First, the cross-sectional retrospective design does not allow claims regarding causality. We cannot know to what degree the observed differences in brain structure and psychological symptoms were present prior to AAS initiation, or caused by high-dose long-term AAS use. However, the two alternatives are not mutually exclusive. Hypothetically, an underlying vulnerability poses a risk for initiation of use, followed by brain structural alterations after prolonged use which, in turn, could increase sensitivity and potentially trigger further use. Secondly, AAS use is associated with a number of health risks, including cardiovascular changes [17,20] that can themselves affect the brain, and we did not have the possibility to control for this. However, such risks may not be confined to AAS dependency, but may be associated to a greater extent with life-time AAS exposure, which was controlled for. Thirdly, this was a structural MRI study, where we make theoretical speculations on how structural alterations affect the function of the neural circuits; however, further research is needed to explore the functional correlates.

CONCLUSION

Our analysis revealed structural brain differences between dependent and non-dependent AAS users. Specifically, the dependent group showed thinner cortex in pre-frontal regions involved in inhibitory control and emotional regulation. This is in accordance with the proposed addictive properties of AAS and poses a potential explanation to why some users progress from innocent initial use to hazardous use and dependence. Increased awareness of neurobiological correlates of AAS dependence could have important implications for preventive work and personalized interdisciplinary treatment.

Declaration of interests

None.

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