Archival Report

Biological Psychiatry

Structural Brain Imaging of Long-Term Anabolic-Androgenic Steroid Users and Nonusing Weightlifters

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ABSTRACT

BACKGROUND: Prolonged high-dose anabolic-androgenic steroid (AAS) use has been associated with psychiatric symptoms and cognitive deficits, yet we have almost no knowledge of the long-term consequences of AAS use on the brain. The purpose of this study is to investigate the association between long-term AAS exposure and brain morphometry, including subcortical neuroanatomical volumes and regional cortical thickness.

METHODS: Male AAS users and weightlifters with no experience with AASs or any other equivalent doping substances underwent structural magnetic resonance imaging scans of the brain. The current paper is based upon high-resolution structural T1-weighted images from 82 current or past AAS users exceeding 1 year of cumulative AAS use and 68 non–AAS-using weightlifters. Images were processed with the FreeSurfer software to compare neuroanatomical volumes and cerebral cortical thickness between the groups.

RESULTS: Compared to non–AAS-using weightlifters, the AAS group had thinner cortex in widespread regions and significantly smaller neuroanatomical volumes, including total gray matter, cerebral cortex, and putamen. Both volumetric and thickness effects remained relatively stable across different AAS subsamples comprising various degrees of exposure to AASs and also when excluding participants with previous and current non-AAS drug abuse. The effects could not be explained by differences in verbal IQ, intracranial volume, anxiety/depression, or attention or behavioral problems.

CONCLUSIONS: This large-scale systematic investigation of AAS use on brain structure shows negative correlations between AAS use and brain volume and cortical thickness. Although the findings are correlational, they may serve to raise concern about the long-term consequences of AAS use on structural features of the brain.

Keywords: Anabolic-androgenic steroids, Cerebral cortex, Cortical thinning, Gray matter, Neuroimaging, Putamen

http://dx.doi.org/10.1016/j.biopsych.2016.06.017

Anabolic-androgenic steroids (AASs) comprise a large class of synthetic derivatives of the male sex hormone testosterone that are primarily used in an illicit manner for cosmetic or ergogenic purposes (1–3). Prolonged high-dose AAS use is associated with a range of adverse health consequences, including cardiovascular effects (4,5), psychiatric disorders (6–9), and cognitive deficits (10,11). Few studies have examined potential brain structural alterations (12), which is critical because AASs readily pass the blood-brain barrier and can affect the central nervous system. Testosterone's main activity in the brain occurs via binding to cytoplasmic androgen receptors (ARs) (13). ARs are widely distributed in the brain and abundantly expressed in the brain stem, hypothalamus, amygdala, hippocampus, and cerebral cortex (14–16), and these regions are implicated in a wide range of functions, including the regulation of emotion and cognition.

Supraphysiological doses of AASs may cause apoptotic effects on a variety of cell types, including neurons (17–21), may lead to impaired cognition in animal models (22,23), and are associated with lower cognitive function in humans (10). These findings, coupled with reports of AAS-induced alterations in mood and behavior (7,11), suggest that supraphysiologic AAS doses may induce neurochemical or structural alterations in the brain. This is supported by a recent neuroimaging study of 10 AAS users that suggested that chronic AAS use was associated with structural, neurochemical, and functional alterations in the brain (12). In addition, other AAS-induced medical effects may further threaten brain health. In particular, cardiovascular conditions—considered to be among the most serious risks associated with AAS use—are known to be associated with larger effects of age on brain structure (24), vascular brain disease (25), cognitive decline (26), and dementia (26,27). These cardiovascular effects associated with AAS use (5) with the potential to compromise brain and cognition include hypertension (24,28), atherosclerosis (29), and dyslipidemia (30). Therefore, many indices suggest that prolonged AAS use with supraphysiological doses may be associated with structural alterations of the brain.

ISSN: 0006-3223

We examine the association between long-term exogenous AAS exposure and brain morphometry. Male participants engaged in heavy resistance strength training with or without experience with AASs underwent structural magnetic resonance imaging (MRI) scans of the brain. Based on the findings of neurotoxic effects of supraphysiological AAS doses, negative relationships between AAS use and regional brain volumes and cortical thickness are expected.

METHODS AND MATERIALS

Participants

The sample was drawn from the research project "Long-term androgenic anabolic steroid use on brain structure, cognitive functioning and emotional processing" coordinated from the Department of Physical Medicine and Rehabilitation, at the section of neuropsychology, Oslo University Hospital, Oslo, Norway. The participants in the study are men engaged in heavy resistance strength training belonging to one of the following groups: 1) current or previous AAS users reporting ≥1 year of cumulative AAS exposure (summarizing on-cycle periods) and 2) men who have never tried AASs or equivalent doping substances. Participants were recruited through a Facebook project page; posts on Internet forums for bodybuilding, strongman, fitness, and weightlifting; and forums (open and closed) that directly target steroid users. In addition, posters and flyers were distributed in select gyms in Oslo. All participants received an informational brochure with a complete description of the study before participation, and written informed consent was collected. The participants were compensated for their participation with 1000 Norwegian kroner (approximately $125).

In total, 159 men participated in the study, divided into 89 current or past AAS users and 70 nonusing controls. All participants in the control group underwent MRI scanning, but two participants were later excluded—one based upon the radiological evaluation, and one because he did not match the AAS group on strength and training regimens (with reported maximum bench presses, squats, and deadlifts that were 2.6, 2.8, and 3.3 SDs below the sample mean, respectively). In the AAS group, seven participants were excluded for various reasons: three did not fulfill the criteria of having ≥1 year of cumulative AAS exposure, one did not show up for the MRI session, and another did not show up for the neuropsychological evaluation. In addition, MRI scan results could not be obtained from two users, one because of a pacemaker implant and one that experienced panic when approaching the scanner (participant exclusion details can be found in Figure 1). Our final sample was 150 participants, with 82 current or previous AAS users and 68 nonusing controls.

Information about the material used and the findings in relation to mapping the characteristics of AAS use, medical history, and use of traditional use of drugs of abuse are presented in the Supplement.

Doping Analysis

Urine samples were collected during the neuropsychological evaluation and analyzed for AASs and narcotics using gas chromatography and mass spectrometry at the World Anti-Doping Agency–accredited Norwegian Doping Laboratory at the Oslo University Hospital, as described elsewhere (31). Stimulants were analyzed with liquid chromatography and mass spectrometry.

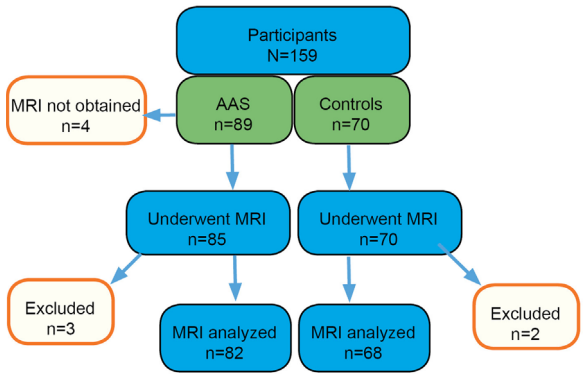

Figure 1. Flow chart. AAS, anabolic-androgenic steroid users; MRI, magnetic resonance imaging.

Briefly, the criteria used to determine the use of AASs or testosterone were as follows: 1) urine samples positive for AAS compounds and 2) a testosterone to epitestosterone (T/E) ratio > 15. A T/E ratio > 4 has been commonly applied by the World Anti-Doping Agency as a population-based criteria for samples requiring additional analysis with isotope ratio mass spectrometry or follow-up to indicate testosterone abuse (32). However, when applying this criterion in research and routine analyses, cases of naturally occurring T/E ratios > 4 do appear (33). Isotope ratio mass spectrometry analyses were not performed in this study, and the stricter T/E ratio > 15 was applied, which is equivalent according to Hullstein *et al.* (31).

Image Acquisition

MRI data were collected using a 3.0T Siemens Skyra scanner (MAGNETOM Skyra; Siemens AG, Erlangen, Germany) equipped with a 24-channel Siemens head coil. Anatomical 3-dimensional T1-weighted magnetization-prepared rapid acquisition gradient-echo sequences were used for volumetry and cortical surface analyses with the following parameters: repetition time = 2300 ms; echo time = 2.98 ms; inversion time = 850 ms; flip angle = 8°; bandwidth = 240 Hz/pixel; field of view = 256 mm; voxel size = 1.0 × 1.0 × 1.0 mm; 176 slices sagittally oriented; acquisition time = 9:50.

The magnetization-prepared rapid acquisition gradient-echo sequences were our first-priority sequence. The qualities of these scans were immediately inspected at the scanning session and rerun in case of movement in order to ensure that the scans were of good quality. For one participant who was anxious during the scanning, we could not run the sequence again. However, this participant did not show up for the neuropsychological evaluation, so he was omitted from the dataset for another reason.

Imaging Analysis

All datasets were automatically processed and analyzed using FreeSurfer software (version 5.3; http://surfer.nmr.mgh.harvard.edu), which is described in detail elsewhere (34–39) (see