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RESEARCH REPORT

ADDICTION SSA

Mega-analysis of the brain-age gap in substance use disorder: An ENIGMA Addiction working group study

Freda Scheffler[1,2] | Jonathan Ipser[1,2] | Devarshi Pancholi[3] | Alistair Murphy[3] | Zhipeng Cao[3] | Jonatan Ottino-González[4] | ENIGMA Addiction Working Group | Paul M. Thompson[5] | Steve Shoptaw[6,7] | Patricia Conrod[8] | Scott Mackey[3] | Hugh Garavan[3] | Dan J. Stein[1,2,9]

[1]Neuroscience Institute, University of Cape Town, Cape Town, South Africa

[2]Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa

[3]Department of Psychiatry, University of Vermont College of Medicine, Burlington, USA

[4]Department of Pediatrics, Division of Endocrinology, Diabetes, and Metabolism, Children's Hospital Los Angeles, Los Angeles, USA

[5]Imaging Genetics Center, Mark and Mary Stevens Institute for Neuroimaging and Informatics, Department of Neurology, Keck School of Medicine, University of Southern California, Marina del Rey, CA, USA

[6]Department of Family Medicine, UCLA, Los Angeles, CA, USA

[7]University of Cape Town, Cape Town, South Africa

[8]Department of Psychiatry, Université de Montreal, CHU Ste Justine Hospital, Montreal, Canada

[9]South African Medical Research Council (SAMRC) Unit on Risk and Resilience in Mental Disorders, University of Cape Town, Cape Town, South Africa

Correspondence
Freda Scheffler, Department of Psychiatry, University of Cape Town, Anzio Road, Observatory, 7925, Cape Town, South Africa.
Email: freda.scheffler@uct.ac.za

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Abstract

Background and Aims: The brain age gap (BAG), calculated as the difference between a machine learning model-based predicted brain age and chronological age, has been increasingly investigated in psychiatric disorders. Tobacco and alcohol use are associated with increased BAG; however, no studies have compared global and regional BAG across substances other than alcohol and tobacco. This study aimed to compare global and regional estimates of brain age in individuals with substance use disorders and healthy controls.

Design: This was a cross-sectional study.

Setting: This is an Enhancing Neuro Imaging through Meta-Analysis Consortium (ENIGMA) Addiction Working Group study including data from 38 global sites.

Participants: This study included 2606 participants, of whom 1725 were cases with a substance use disorder and 881 healthy controls.

Measurements: This study used the Kaufmann brain age prediction algorithms to generate global and regional brain age estimates using T1 weighted magnetic resonance imaging (MRI) scans. We used linear mixed effects models to compare global and regional (FreeSurfer lobestrict output) BAG (i.e. predicted minus chronological age) between individuals with one of five primary substance use disorders as well as healthy controls.

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Findings: Alcohol use disorder (β = −5.49, t = −5.51, p < 0.001) was associated with higher global BAG, whereas amphetamine-type stimulant use disorder (β = 3.44, t = 2.42, p = 0.02) was associated with lower global BAG in the separate substance-specific models.
Conclusions: People with alcohol use disorder appear to have a higher brain-age gap than people without alcohol use disorder, which is consistent with other evidence of the negative impact of alcohol on the brain.

KEYWORDS
addiction, brain age, ENIGMA, machine learning, neuroimaging, predicted brain age difference, substance use disorder

INTRODUCTION

Considerable research has recently been undertaken on brain-based markers of aging. Brain age estimation uses machine learning by training and testing a model on large training and test datasets, then using this model to predict an individual's brain age in an independent dataset [1]. The most frequently used outcome of interest is the difference between an individual's model-predicted brain age and their chronological age (i.e. the brain age gap [BAG]). Positive BAG values indicate greater brain age estimates (i.e. older appearing brains), whereas negative BAG values indicate smaller brain age estimates (i.e. younger appearing brains), relative to chronological age.

The BAG, otherwise known as brain predicted age difference (brain-PAD) or brain age gap estimation (brainAGE), has been investigated in a range of psychiatric disorders [1–4], and has been linked to cardiovascular risk factors [5] and lifestyle-related risk factors [6]. Among lifestyle-related risk factors, substance use is of particular interest because of its well-established link with increased morbidity and mortality [7].

In substance use disorder, tobacco and alcohol use are associated with a greater BAG [8–11]. For example, an average BAG of 4 years has been reported in those with alcohol use disorder versus those without alcohol use disorder, with evidence that the degree of accentuated brain aging is predicted by the amount of lifetime cumulative alcohol consumed [6]. Similarly, a BAG of 3.4 years has been reported in smokers versus non-smokers [12], with evidence of a dose-dependent relationship between smoking and brain age [13].

Several gaps in the literature on BAG in substance use disorder remain. For instance, we were unable to identify studies investigating BAG in substance use disorders other than alcohol and nicotine (e.g. cannabis, cocaine and amphetamine-type stimulants), or that investigate the associations between substance use disorder and region-specific BAG. Therefore, the present study aimed to use a previously validated machine learning model of brain age to compare relative global and predefined regional brain aging in individuals with a range of substance use disorders (i.e. alcohol, amphetamine-type stimulants, cannabis, cocaine, and nicotine) as well as healthy controls. More specifically, our objectives were to (1) establish the existence of group differences in global BAG between those with one of five substance use disorders and healthy controls; and (2) establish the existence of group differences in each regional BAG between those with one of five substance use disorders and healthy controls.

METHODS

Participants

Case and control data were contributed by 38 sites (n = 2606) participating in the Addiction Working Group of the Enhancing Neuro Imaging through Meta-Analysis Consortium (ENIGMA) consortium (https://www.enigmaaddictionconsortium.com), of whom 1725 were diagnosed with current Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) substance use disorder on at least one of the five substances of interest, namely alcohol, amphetamine-type stimulants, cannabis, cocaine and nicotine. Polysubstance use was permitted provided that individuals were not diagnosed with primary polysubstance use disorder. A lifetime history of neurological disease, a current DSM-IV axis I diagnosis other than depressive and anxiety disorders or any contraindication for magnetic resonance imaging (MRI) were considered exclusionary. Recreational use of addictive substances among control participants (mainly nicotine and alcohol) was not considered exclusionary, provided they were not diagnosed as dependent.

Measures

Each site collected individual-level age and sex data, as well as diagnoses, using a variety of instruments, for substance use disorder on alcohol, cannabis, cocaine, amphetamine-type stimulants or nicotine (see Table S1) [14].

Structural MRI data acquisition, processing and quality control

Structural T1-weighted MRI brain scans were acquired from all participants at each site. Site-specific scanner and acquisition details are provided in Table S1. Anonymized T1-weighted Neuroimaging Informatics Technology Initiative scans were prepared with FreeSurfer version 5.3 (http://surfer.nmr.mgh.harvard.edu/) [15]. Processed scans

were visually inspected for quality based on ENIGMA QC protocols (https://enigma.ini.usc.edu/protocols/imaging-protocols/protocol-for-quality-control-and-summary-statistics/). Furthermore, the Euler number, which is derived from the number of holes observed in a spherical cortical reconstruction of the brain, and has demonstrated utility as a measure of scan quality [16], was included as a covariate in all analyses. Analyses were performed on the Vermont Advanced Computing Center (VACC) system's Bluemoon cluster (https://www.uvm.edu/vacc/kb/knowledge-base/bluemoon/) at the University of Vermont.

For the brain age estimation, regional volume, thickness and surface area features derived by FreeSurfer 5.3 [17], as well as from 180 regions delineated using a multimodal cortical parcellation algorithm [18], were extracted for each participant and fed into the Kaufmann [4] male and female algorithms (available at https://github.com/tobias-kaufmann/brainage). These algorithms were trained and tested separately for males and females to account for sex differences in brain morphometry and age estimation. More specifically, the Kaufmann model was trained on 35 474 healthy individuals (n = 18 990 females) age 3 to 89 years. The sex-specific models are based on gradient tree boosting, which predicts the age of the brain based on a set of thickness, area and volume features. Kaufmann *et al.* [4] used fivefold cross-validations, which revealed a high correlation between chronological age and predicted brain age (males r = 0.94, females r = 0.93) for both sexes separately. The regional predicted brain age estimates were generated using the FreeSurfer Lobestrict segmentation from the occipital, frontal, temporal, parietal, cingulate, insula and subcortical (which includes the cerebellar) regions. These algorithms have been further validated in subsequent studies [19–21]. In favor of using harmonized predicted brain age estimates across datasets, we elected to test the Kaufmann algorithms in this dataset rather than generating yet another algorithm.

Global and regional brain age prediction accuracy among cases and controls

In the control group, the correlation between chronological age and predicted global brain age estimate (see Figure 1) was 0.69 (P < 0.001), with a mean absolute error (MAE) of 7.1 years. The corresponding correlation among cases was 0.64 (P < 0.001), with an MAE of 8.2 years. The correlation of chronological age with Kaufmann regional predicted brain age and associated MAE is presented in

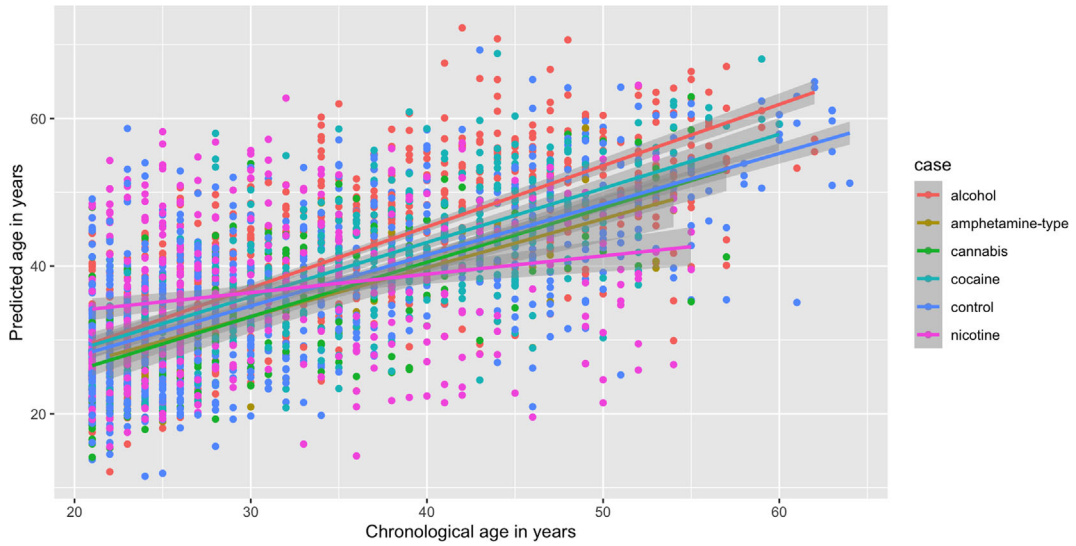

FIGURE 1 Scatter plot of chronological age and predicted age by substance use disorder group.

TABLE 1 Regional BAG and MAE.

	Cingulate	Frontal	Insula	Occipital	Parietal	Subcortical	Temporal
Cases							
R	0.46	0.56	0.48	0.38	0.52	0.52	0.44
MAE	15.3	12.3	12.7	12.9	13.2	8.6	11.9
Controls							
R	0.52	0.63	0.50	0.37	0.57	0.60	0.46
MAE	12.2	9.4	11.4	12.2	10.6	8.0	11.1

Abbreviations: BAG, brain age gap; MAE, mean absolute error; R, Pearson's correlation.

Table 1. Among the controls, the correlation between chronological age and cingulate (0.52; 12.2), frontal (0.63; 9.4), insula (0.5; 11.4), occipital (0.37; 12.2), parietal (0.57;10.6), subcortical/cerebellar (0.6; 8.0) and temporal (0.46; 11.1) brain age estimates was moderate with a high mean absolute error. The correlation between chronological age and cingulate (0.46; 15.3), frontal (0.56; 12.3), insula (0.48; 12.7), occipital (0.38; 12.9), parietal (0.52; 13.2), subcortical/cerebellar (0.52; 8.6) and temporal (0.44; 11.9) brain age estimates among the cases was similarly moderate and with a high mean absolute error.

Statistical analysis

The authors would like to note that this analysis was not pre-registered and that the results should be considered exploratory. Groups were compared using analysis of variance (ANOVA) and χ^2 tests. A mega-analysis was conducted using the predicted brain age estimates from the Kaufmann *et al*. [4] global and regional brain age models, as applied to T1-weighted MRI scans for individual participants. Global and regional BAG were then calculated for each individual as the predicted brain age estimate minus chronological age. For objective 1, similar to the original Kaufmann analysis, we fitted a linear mixed-effects model including all 2606 subjects to predict global BAG with age, age squared, sex and group (controls and 5 substance use disorder groups) as fixed effects covariates and site included as a random effect. For objective 2, linear mixed effects models were constructed for each regional BAG estimate. For objectives 1 and 2, the least square means for the factors of the group variable, consisting of six groups, were false discoveryrate (FDR)-corrected.

We ran separate linear mixed-effects models for each substance as secondary or sensitivity analyses. For these analyses, we included only sites with cases and controls matched for age and sex to identify differences in global BAG as a function of the specific substance of use. For example, the alcohol model included only sites with individuals with an alcohol use disorder and age- and sex-matched healthy controls. This was to account for the systematic age differences detected between individuals with different substance use disorders. All linear mixed-effects models were estimated using the restricted maximum likelihood approach and the *nloptwrap* optimizer.

RESULTS

Sample characteristics

Comparison of cases (n = 1725) with controls (n = 881) on demographic characteristics found that those with nicotine and cannabis use disorder were 2 to 6 years younger on average than those with alcohol, cocaine and amphetamine-type stimulant use disorder (see Table 2). A substance-specific difference was also revealed in the sex distribution of the sample (p < 0.001), with relatively few female participants among cocaine-dependent participants, and a relatively large proportion of female participants among nicotine-dependent subjects.

TABLE 2 Substance-specific sample characteristics.

	Control (n = 881)	Alcohol (n = 736)	Amphetamine-type stimulant (n = 54)	Cannabis (n = 219)	Cocaine (n = 324)	Nicotine (n = 392)	Statistic	P
Age, mean (SD), range	32.7 (10.8), 21–64	34.1 (10.6), 21–62	36.1 (10.5), 22–54	30.7 (9.1), 21–57	37.9 (8.8), 21–60	31.5 (9.4), 21–55	F = 20.8	<0.001
Sex, female n (%)	294 (33.4)	227 (30.8)	20 (37)	76 (34.7)	67 (20.7)	179 (45.7)	X = 52.9	<0.001
Global BAG, mean (SD)	3.76 (8.42)	6.32 (8.0)	1.09 (7.69)	2.97 (7.48)	3.76 (7.82)	5.26 (12.08)	F = 11.46	<0.001
Cingulate BAG, mean (SD)	9.62 (11.61)	16.2 (9.74)	10.93 (9.33)	11.56 (11.78)	11.33 (9.02)	14.17 (12.51)	F = 32.2	<0.001
Frontal BAG, mean (SD)	6.71 (9.65)	12.16 (9.42)	7.87 (7.6)	5.45 (10.28)	9.45 (8.15)	11.16 (12.56)	F = 33.7	<0.001
Insula BAG, mean (SD)	7.37 (12.16)	12.63 (9.86)	9.92 (9.86)	7.0 (12.31)	7.85 (9.05)	10.59 (13.01)	F = 21.76	<0.001
Occipital BAG, mean (SD)	8.40 (12.34)	11.57 (10.78)	5.09 (11.61)	10.45 (13.01)	8.06 (9.98)	10.17 (12.88)	F = 9.03	<0.001
Parietal BAG, mean (SD)	7.77 (10.38)	12.97 (9.48)	10.20 (10.19)	6.95 (11.10)	10.31 (8.32)	11.37 (13.13)	F = 25.11	<0.001
Subcortical/cerebellar BAG, mean (SD)	2.62 (9.98)	2.73 (9.86)	−2.51 (12.09)	0.76 (9.28)	−0.44 (11.52)	2.37 (12.72)	F = 7.38	<0.001
Temporal BAG, mean (SD)	7.47 (11.62)	9.58 (10.44)	6.53 (11.07)	7.85 (12.26)	8.3 (8.88)	9.05 (14.18)	F = 3.36	=0.005

Abbreviation: BAG, brain age gap.

Substance use disorder case/control differences in global BAG

The mean global and regional BAG per substance group is presented in Table 2 and Figure 2. In model 1, an increase in age squared (β = −0.006, *t* = −3.92, *p* < 0.001) was associated with lower BAG. Neither age (β = 0.11, *t* = 0.92, *p* = 0.4), sex (β = −0.35, *t* = −0.97, *p* = 0.3) nor Euler number (β = −0.001, *t* = −0.61, *P* = 0.5) were associated with differences in global BAG. The FDR corrected least square means with control as the reference category revealed a significant difference between controls and alcohol (β = 4.51, *t* = 5.95, *P* < 0.001), trend differences for amphetamine-type (β = −2.78, *t* = −1.91, *P* = 0.09) and cocaine (β = 1.49, *t* = 2.10, *P* = 0.09) and no differences for cannabis (β = −0.60, *t* = −0.79, *P* = 0.5) and nicotine (β = 0.17, *t* = 0.19, *P* = 0.9) in global BAG.

Substance use disorder case/control differences in regional BAG

The FDR-corrected least square means (LSM) for the substance use factors for all the regional models are presented in Table 3 and Figure 3. Alcohol was associated with significantly greater BAG than controls in all of the regional models, the cingulate (β = 3.4, *t* = 3.5, *P* = 002), frontal (β = 3.54, *t* = 3.85, *P* < 0.001), occipital (β = 3.39, *t* = 3.39, *p* = 0.004), parietal (β = 3.39, *t* = 3.61, *P* = 0.002), subcortical/cerebellar (β = 3.23, *t* = 3.46, *P* = 0.003) and temporal (β = 5.25, *t* = 5.17, *P* < 0.001), except for the insula (β = 2.43, *t* = 2.38, *P* = 0.07) model. The regional BAG for amphetamine-type stimulants was not significantly different from the controls in all of the models, cingulate (β = 1.35, *t* = 0.78, *P* = 0.5), frontal (β = 1.34, *t* = 0.80, *P* = 0.5), insula (β = 0.89, *t* = 0.49, *P* = 0.8), occipital (β = 0.30, *t* = 0.17, *P* = 0.9), parietal (β = 0.95, *t* = 0.56, *P* = 0.6) and temporal (β = −0.89, *t* = −0.49, *p* = 0.8), apart from the subcortical/cerebellar (β = −5.04, *t* = −2.84, *P* = 0.01) model where amphetamine-type stimulants was associated with smaller BAG compared with controls. Similarly, cannabis was also not associated with significantly different regional BAG when compared with controls, with cingulate (β = 0.81, *t* = 0.90, *P* = 0.5), frontal (β = −0.42, *t* = −0.48, *P* = 0.6), insula (β = −0.74, *t* = −0.77, *P* = 0.7), occipital (β = 1.24, *t* = 1.32, *P* = 0.2), parietal (β = 0.50, *t* = 0.57, *P* = 0.6), subcortical/cerebellar (β = −1.48, *t* = −1.60, *P* = 0.2) and temporal (β = 0.43, *t* = 0.46, *P* = 0.8) models all *P* > 0.5. Cocaine was associated with a greater BAG compared with controls in the cingulate (β = 2.65, *t* = 3.07, *P* = 0.005 model) and occipital (β = 2.67, *t* = 3.00, *P* = 0.007) models. The insula (β = 1.99, *t* = 2.18, *P* = 0.07) was associated with a trend level difference only, and none of the other models reached significance with frontal (β = 1.67, *t* = 2.02, *P* = 0.1), parietal (β = 1.65, *t* = 1.97, *P* = 0.1), subcortical/cerebellar (β = 0.49, *t* = 0.57, *P* = 0.6), and temporal (β = 1.35, *t* = 1.50, *P* = 0.3). Nicotine was not associated with differences in regional BAG in any of the models, either, cingulate (β = 0.68, *t* = 0.56, *P* = 0.6), the frontal (β = 1.21, *t* = 1.07, *P* = 0.5), insula (β = 0.07, *t* = 0.06, *P* = 0.9), occipital (β = −1.87, *t* = −1.52, *P* = 0.2), parietal (β = 0.56, *t* = 0.48, *P* = 0.6), subcortical/cerebellar (β = −0.5, *t* = −0.48, *P* = 0.6), and temporal (β = 0.12, *t* = 0.10, *P* = 0.9).

For the regional BAG models, age was not associated with differences in the cingulate (β = 0.11, *t* = 0.75, *P* = 0.5), frontal (β = 0.39, *t* = 2.85, *P* = 0.004), insula (β = −0.03, *t* = −0.17, *P* = 0.9), occipital (β = −0.34, *t* = −2.31, *P* = 0.02), parietal (β = 0.03, *t* = 0.20, *P* = 0.8), subcortical/cerebellar (β = −0.25, *t* = −1.65, *P* = 0.1), nor temporal (β = 0.03, *t* = 0.19, *P* = 0.9). Greater age squared was associated with smaller BAG in the cingulate (β = −0.009, *t* = −5.02, *P* < 0.001), frontal (β = −01, *t* = −5.96, *P* < 0.001), insula (β = −0.007, *t* = −3.44, *P* < 0.001), occipital (β = −0.004, *t* = −2.24, *P* = 0.03), parietal (β =

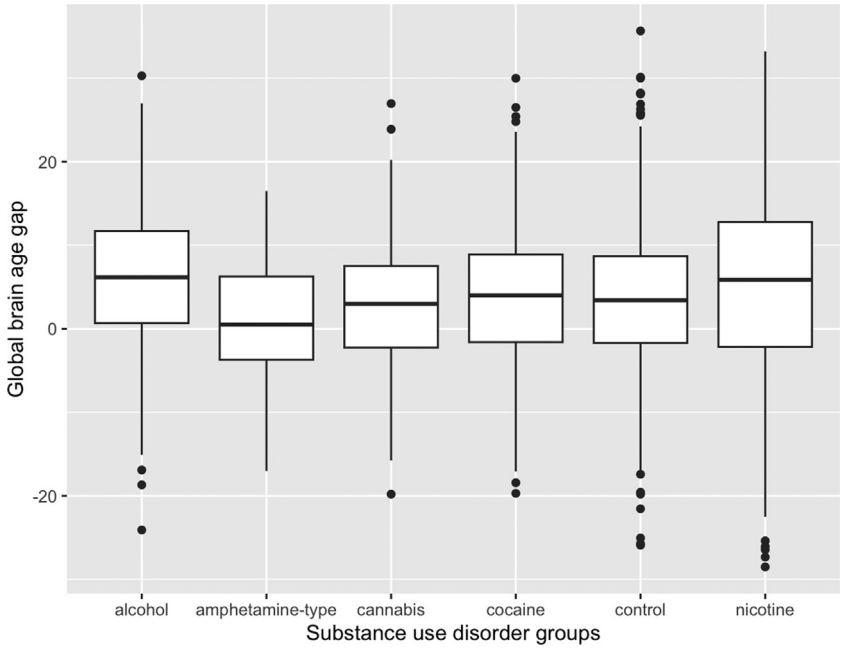

FIGURE 2 Boxplot of global brain age gap (BAG).

TABLE 3 LSM of regional BAG.

Regional BAG	Control	Alcohol	Amphetamine-type stimulants	Cannabis	Cocaine	Nicotine
Cingulate, LSM[a] (CI)	10.9 (8.86–12.9)	14.3 (11.76–16.8)	12.2 (8.25–16.2)	11.7 (9.12–14.2)	13.5 (11.06–16.0)	11.5 (8.71–14.4)
Frontal, LSM[a] (CI)	7.43 (5.86–9.0)	10.97 (8.86–13.08)	8.77 (5.14–12.39)	7.01 (4.83–9.19)	9.09 (7.04–11.15)	8.63 (6.22–11.05)
Insula, LSM (CI)	8.71 (6.86–10.6)	11.14 (8.70–13.6)	9.60 (5.55–13.7)	7.97 (5.47–10.5)	10.70 (8.33–13.1)	8.78 (6.01–11.5)
Occipital, LSM[a] (CI)	8.98 (7.21–10.74)	12.36 (10.02–14.71)	9.28 (5.34–13.23)	10.22 (7.81–12.62)	11.65 (9.37–13.93)	7.11 (4.44–9.78)
Parietal, LSM[a] (CI)	8.91 (7.14–10.7)	12.31 (10.0–14.6)	9.86 (6.11–13.6)	9.41 (7.07–11.8)	10.56 (8.32–12.8)	9.47 (6.87–12.1)
Subcortical/cerebellar, LSM[a] (CI)	1.99 (0.64–3.33)	5.22 (3.29–7.15)	−3.05 (−6.75–0.65)	0.51 (−1.57–2.59)	2.48 (0.57–4.39)	1.44 (−0.80–3.69)
Temporal, LSM[a] (CI)	7.81 (5.87–9.75)	13.06 (10.55–15.57)	6.92 (2.87–10.97)	8.24 (5.69–10.79)	9.16 (6.73–11.60)	7.93 (5.10–10.76)

Abbreviations: BAG, brain age gap; FDR, false-discovery-rate; LSM, least square means.
[a]LSM FDR-corrected.

−0.008, t = −4.17, P < 0.001) and temporal (β = −0.008, t = −4.04, P < 0.001) models, but not with the subcortical/cerebellar (β = −0.002, t = −1.01, P = 0.3) model. Male sex was associated with greater regional BAG in the cingulate (β = 0.88, t = 2.17, P = 0.03), frontal (β = 0.94, t = 2.39, P = 0.02), occipital (β = 1.21, t = 2.86, P = 0.004), parietal (β = 0.97, t = 2.46, P = 0.01) and temporal (β = 0.84, t = 1.99, P = 0.05) models, but not in the insula (β = 0.47, t = 1.09, P = 0.3) model, and trend-level difference in the subcortical/cerebellar (β = −0.72, t = −1.67, P = 0.09) model. Euler number was inversely associated with regional BAG in the insula (β = −0.007, t = −3.03, P = 0.003) and parietal (β = −0.009, t = −4.37, P < 0.001) models, but not the occipital (β = −0.001, t = −0.63, P = 0.5), subcortical/cerebellar (β = 0.003, t = 1.58, P = 0.1) and temporal (β = −0.0002, t = −0.09, P = 0.9) models, and trend-level only in the cingulate (β = −0.004, t = −1.74, P = 0.08) and frontal (β = −0.003, t = −1.73, P = 0.08) models.

Substance use disorder case/control differences according to the primary substance of use in global BAG

Alcohol use disorder (β = −5.49, t = −5.51, P < 0.001) was associated with higher global BAG (see Table 4), whereas amphetamine-type stimulant use disorder (β = 3.44, t = 2.42, P = 0.02) was associated with lower global BAG. Neither cannabis (β = 0.47, t = 0.67, P = 0.5), cocaine (β = −1.24, t = −1.65, P = 0.1), nor nicotine (β = −0.44, t = −0.38, P = 0.7) use disorders were associated with differences compared to healthy controls in global BAG in the separate substance specific models.

DISCUSSION

To date, this is the first study to investigate the BAG in substance use disorders beyond alcohol and nicotine. Consistent with the extant body of knowledge, alcohol was associated with a greater, positive BAG compared to healthy controls across all global and regional BAG models, indicating an older appearing brain for those with alcohol use disorder. Amphetamine-type stimulant use disorder was associated with a smaller, but still positive BAG in the amphetamine-type stimulant-only global BAG model, meaning that the model predicted an older age for those with an amphetamine-type stimulant use disorder, but less than that predicted for the controls. However, amphetamine-type stimulant use disorder was associated with a negative BAG in the subcortical and cerebellar regional model, suggesting that the algorithm predicted a younger appearing brain than chronological age for those with amphetamine-type stimulant use disorder compared to healthy controls. No significant differences were observed for cannabis, cocaine and nicotine when compared with controls. These observations persisted when we ran our sensitivity analyses for cannabis, cocaine and nicotine and their matched controls separately.

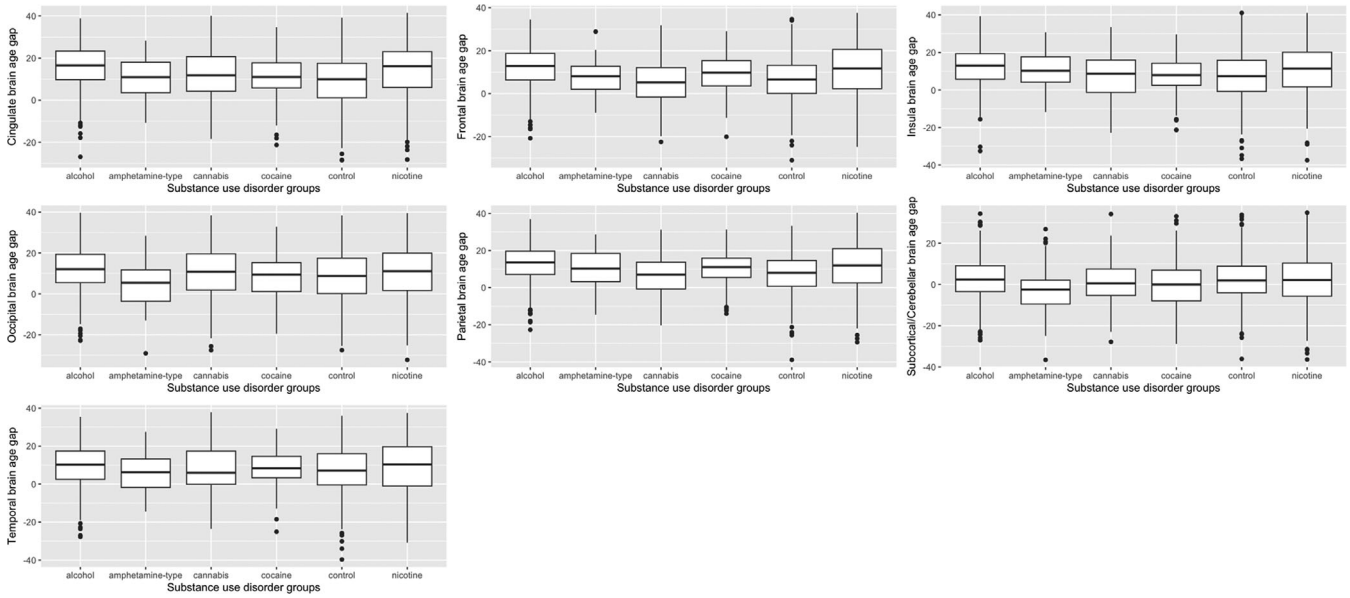

FIGURE 3 Boxplot series of regional brain age gap (BAG).

Our findings of higher global BAG in alcohol use disorder are consistent with prior literature on the BAG in alcohol use disorder [8, 11], and with literature demonstrating the neurotoxic effects of alcohol. Even moderate alcohol use is associated with decreased brain volume in early middle age in both males and females [22]. Although the exact molecular mechanism is not yet known [6], chronic oxidative stress may play a role [23]. Conversely, the association between amphetamine-type stimulant use disorder diagnosis and lower BAG was somewhat unexpected. Methamphetamine use is similarly associated with neurotoxicity [24]. Indeed, chronic methamphetamine use is associated with reduced gray matter volume in various brain regions, including the anterior cingulate cortex, dorsolateral prefrontal cortex, orbitofrontal cortex, superior temporal cortex and hippocampus [25]. However, this differential impact on predicted brain age may be a function of the duration of abstinence at the time of the scan, and the associated differences in the timing and extent of sequelae following cessation of a particular substance.

Previous investigations of brain age prediction cross-dataset validation reported MAE ranges of 5.23 to 8.98 years [26], our MAE of 7.1 and 8.2 for cases and controls remain within the acceptable range. Moreover, narrower age ranges in test data were found to have better performance estimates than test datasets with broader age ranges [26], although this might be because of predictions being closer to the mean of the group instead of model performance *per se*. Furthermore, the algorithm used in this study used region-based features, and it is possible that an algorithm using voxel-based features may perform better [27]. Alternatively, multimodal brain age algorithms may yield better brain age predictions than single-modality algorithms [28]. However, the Kaufmann model used in this study still demonstrates reasonable accuracy across different datasets [29, 30]. Last, the known regression bias [4, 31] in brain age estimates whereby brain age in younger individuals tends to be over-estimated, and under-estimated in older individuals, is present in this analysis. Although bias corrections can be done in both training and test datasets, these methods come with additional constraints [26]. Although age was significantly different among cases and controls in the total group, this is likely a function of the large sample size rather than being clinically significant. Given our sub-group sample size and systematic age differences between substance use disorder groups, we elected not to use bias correction beyond including age and age squared in all of the models and excluding participants younger than 20 and older than 65. We also included a sensitivity analysis by running separate global BAG models for each substance use disorder group and their age- and sex-matched healthy controls, and these bore out the findings from the global BAG model, which included the total sample stratified by substance use disorder and healthy controls.

Several limitations deserve emphasis. First, the performance of the Kaufmann algorithm in this dataset was moderate, due perhaps largely to scanner and sequence differences between the training and the present test dataset. Although it is also possible that a voxelwise gray matter volume feature-based algorithm may perform better, the additional constraints present in this dataset may override any gains from using an alternative algorithm. Second, the larger MAE for the regional models tempers the interpretation of these findings, but is likely a function of the smaller number of available features (i.e. information) for these models compared to the global model. The regional findings should, therefore, be considered particularly preliminary. Third, the amphetamine-type stimulants group in particular was smaller than the other groups, therefore, we cannot exclude a type II error. However, these findings persisted when we ran the global BAG model for amphetamine-type stimulant disorder and matched healthy controls only. Fourth, the different datasets included in this study used a variety of diagnostic and screening measures to classify individuals as having a substance use disorder, therefore, it is likely that

TABLE 4 Global BAG by substance use disorder.

Substance use disorder	BAG, control, mean (SD)	BAG, case, mean (SD)	Partial η^2	Group	Age	Age^2	Sex	Euler number
Alcohol	2.09 (9.95)	5.79 (9.29)	0.08	β = −5.49, t = −5.51, P < 0.001	β = 0.70, t = 1.98, P = 0.05	β = −0.01, t = −3.06, P = 0.002	β = 0.54, t = 0.47, P = 0.6	β = −0.003, t = −1.24, P = 0.2
Amphetamine-type stimulants	4.09 (8.27)	1.09 (7.69)	0.06	β = 3.44, t = 2.42, P = 0.02	β = −0.34, t = −0.53, P = 0.6	β = −0.000009, t = −0.01, P = 0.9	β = −2.02, t = −1.25, P = 0.2	β = 0.01, t = 1.32, P = 0.2
Cannabis	3.09 (7.07)	2.68 (7.41)	8.04E−04	β = 0.47, t = 0.67, P = 0.5	β = −0.02, t = −0.07, P = 0.9	β = −0.003, t = −0.84, P = 0.4	β = −1.1, t = −1.47, P = 0.1	β = −0.01, t = −2.60, P = 0.01
Cocaine	2.76 (7.97)	4.06 (8.17)	6.38E−03	β = −1.24, t = −1.65, P = 0.1	β = 0.43, t = 1.11, P = 0.3	β = −0.009, t = −1.77, P = 0.08	β = −2.48, t = −2.39, P = 0.02	β = 0.004, t = 0.89, P = 0.4
Nicotine	8.76 (7.96)	7.81 (7.82)	7.90E−04	β = 0.44, t = 0.38, P = 0.7	β = −2.73, t = −1.87, P = 0.06	β = 0.04, t = 1.66, P = 0.1	β = 0.51, t = 0.35, P = 0.7	β = −0.001, t = −0.24, P = 0.8

Abbreviation: BAG, brain age gap.

this variation affected our results. Nevertheless, the demonstrated group differences observed despite this variation support the argument of an underlying neurobiological effect of substance use disorders independent of the type of substance used. Fifth, the incomplete accounting for polysubstance use should also be acknowledged as a limitation. Last, the incomplete phenotype and substance use behavior data relating to substance use behavior limited our investigation. Future studies should recruit more participants from the upper and lower ends of the age range, more detailed substance use behavioral data and a wider range of substances to ensure better representation.

Our study is the first to investigate the relationship between BAG and different substance use disorders. Greater global BAG in individuals with alcohol use disorder is consistent with other evidence of the negative impact of alcohol. However, the small effect sizes and lack of significant differences observable for cannabis, cocaine and nicotine, and the unexpected smaller BAG observed in amphetamine-type stimulant use disorder suggests that brain age may be less useful as a biomarker of health in the context of substance use disorders compared to its efficacy in other lifestyle-related risk factors. Nonetheless, studies should continue to cross-validate brain age prediction algorithms to further their clinical utility in identifying a standardized brain-based biomarker of health. Further work is needed to fully delineate the mechanisms that underpin global and regional BAG patterns in substance use disorder.

ENIGMA ADDICTION WORKING GROUP

Albert Batalla, Kathleen Brady, Janna Cousijn, Alain Dagher, Francesca M. Filbey, John J. Foxe, Eduardo A. Garza-Villarreal, Anna E. Goudriaan, Robert Hester, Kent E. Hutchison, Anne Marije Kaag, Emese Kroon, Chiang-Shan R. Li, Edythe D. London, Valentina Lorenzetti, Maartje Luijten, Rocio Martín-Santos, Aimee L. McRae, Reza Momenan, Martin P. Paulus, Godfrey D. Pearlson, Liesbeth Reneman, Ramiro Salas, Lianne Schmaal, Marieke L. J. Schouw, Rajita Sinha, Nadia Solowij, Elliot A. Stein, Ruth J. Van Holst, Dick J. Veltman, Antonio Verdejo-García, Reinout W. Wiers, Murat Yucel.

AUTHOR CONTRIBUTIONS

Freda Scheffler: Conceptualization (lead); formal analysis (lead); methodology (lead); writing—original draft (lead). **Jonathan Ipser:** Conceptualization (supporting); formal analysis (supporting); methodology (supporting); writing—original draft (equal). **Devarshi Pancholi:** Data curation (lead). **Alistair Murphy:** Methodology (equal); writing—original draft (supporting). **Zhipeng Cao:** Methodology (equal); writing—original draft (supporting). **Jonatan Ottino-González:** Methodology (equal); writing—original draft (supporting); writing—review and editing (supporting). **Albert Batalla:** Methodology (equal); writing—original draft (supporting). **Kathleen Brady:** Methodology (equal); writing—original draft (supporting). **Janna Cousijn:** Funding acquisition (equal); methodology (equal); writing—original draft (supporting); writing—review and editing (supporting). **Alain Dagher:** Methodology (equal); writing—original draft (supporting). **Francesca Filbey:** Methodology (equal);

writing—original draft (supporting). **John Foxe:** Methodology (equal); writing—original draft (supporting). **Eduardo Adrian Garza Villarreal:** Methodology (equal); writing—original draft (supporting). **Anna E. Goudriaan:** Methodology (equal); writing—original draft (supporting). **Rob Hester:** Methodology (equal); writing—original draft (supporting). **Kent Edward Hutchison:** Methodology (equal); writing—original draft (supporting). **Anne Marije Kaag:** Methodology (equal); writing—original draft (supporting). **Emese Kroon:** Methodology (equal); writing—original draft (supporting). **Chiang-Shan Li:** Methodology (equal); writing—original draft (supporting). **Edythe D. London:** Funding acquisition (equal); methodology (equal); writing—original draft (supporting). **Valentina Lorenzetti:** Funding acquisition (equal); methodology (equal); writing—original draft (supporting). **Maartje Luijten:** Methodology (equal); writing—original draft (supporting). **Rocio Martin-Santos:** Methodology (equal); writing—original draft (supporting). **Aimee McRae:** Methodology (equal); writing—original draft (supporting). **Reza Momenan:** Methodology (equal); writing—original draft (supporting). **Martin P. Paulus:** Methodology (equal); writing—original draft (supporting). **Godfrey Pearlson:** Methodology (equal); writing—original draft (supporting). **Liesbeth Reneman:** Methodology (equal); writing—original draft (supporting). **Ramiro Salas:** Methodology (equal); writing—original draft (supporting). **Lianne Schmaal:** Methodology (equal); writing—original draft (supporting). **Marieke L. J. Schouw:** Methodology (equal); writing—original draft (supporting). **Rajita Sinha:** Methodology (equal); writing—original draft (supporting). **Nadia Solowij:** Funding acquisition (equal); methodology (equal); writing—original draft (supporting). **Elliot Stein:** Methodology (equal); writing—original draft (supporting). **Ruth Janke van Holst:** Methodology (equal); writing—original draft (supporting). **Dick J. Veltman:** Methodology (equal); writing—original draft (supporting). **Antonio Verdejo-García:** Methodology (equal); writing—original draft (supporting). **Reinout Wiers:** Methodology (equal); writing—original draft (supporting). **Murat Yücel:** Funding acquisition (equal); methodology (equal); writing—original draft (supporting). **Paul M. Thompson:** Data curation (equal); investigation (equal); methodology (equal); resources (equal); writing—original draft (supporting). **Steve Shoptaw:** Conceptualization (supporting); supervision (supporting); writing—original draft (supporting). **Patricia Conrod:** Project administration (equal); resources (equal); writing—original draft (supporting). **Scott Mackey:** Conceptualization (supporting); data curation (lead); methodology (equal); resources (supporting); writing—original draft (supporting). **Hugh Garavan:** Conceptualization (supporting); formal analysis (supporting); investigation (supporting); methodology (supporting); resources (equal); writing—original draft (supporting). **Dan J. Stein:** Conceptualization (equal); funding acquisition (equal); supervision (equal); writing—original draft (equal).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. D.J.S. has received consultancy honoraria from Discovery Vitality, Johnson & Johnson, Kanna, L'Oreal, Lundbeck, Orion, Sanofi, Servier, Takeda and Vistagen.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the ENIGMA consortium Addiction Working Group. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of the ENIGMA consortium Addiction Working Group.

ORCID

Freda Scheffler https://orcid.org/0000-0002-8898-8599
Devarshi Pancholi https://orcid.org/0009-0004-9698-6069
Zhipeng Cao https://orcid.org/0000-0003-2624-2182
Jonatan Ottino-González https://orcid.org/0000-0003-2910-9926
Steve Shoptaw https://orcid.org/0000-0002-3583-0026

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SUPPORTING INFORMATION

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