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Neuroimaging evidence for structural correlates in adolescents resilient to polysubstance use: A five-year follow-up study

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Abstract
Early initiation of polysubstance use (PSU) is a strong predictor of subsequent addiction, however scarce individuals present resilience capacity. This neuroimaging study aimed to investigate structural correlates associated with cessation or reduction of PSU and determine the extent to which brain structural features accounted for this resilient outcome. Participants from a European community-based cohort self-reported their alcohol, tobacco and cannabis use frequency at ages 14, 16 and 19 and had neuroimaging sessions at ages 14 and 19. We included three groups in the study: the resilient-to-PSU participants showed PSU at 16 and/or 14 but no more at 19 ($n = 18$), the enduring polysubstance users at 19 displayed PSU continuation from 14 or 16 ($n = 193$) and the controls were abstinent or low drinking participants ($n = 460$). We conducted between-group comparisons of grey matter volumes on whole brain using voxel-based morphometry and regional fractional anisotropy using tract-based spatial statistics. Random-forests machine-learning approach generated individual-level PSU-behavior predictions based on personality and neuroimaging features. Adolescents resilient to PSU showed significant larger grey matter volumes in the bilateral cingulate gyrus compared with enduring polysubstance users and controls at ages 19 and 14 ($p<0.05$ corrected) but no difference in fractional anisotropy. The larger cingulate volumes and personality trait "openness to experience" were the best precursors of resilience to PSU. Early in adolescence, a larger cingulate gyrus differentiated adolescents resilient to PSU, and this feature was critical in predicting this outcome. This study encourages further research into the neurobiological bases of resilience to addictive behaviors.

Introduction

Polysubstance use (PSU), i.e. the use of two or more psychoactive substances (Redonnet et al., 2012), frequently emerges during adolescence (McKelvey et al., 2017; Tomczyk et al., 2016), leads to difficulties to quit (Camenga et al., 2014), and is a major predictor of subsequent addiction (Dani and Harris, 2005). While historically, research regarding determinants of adolescent substance use has focused on risk factors, resilience was recently tackled to explore putative protective factors associated with resistance to engagement in substance use (Burdzovic et al., 2016; Chan et al., 2017; Rudzinski et al., 2017). Furthermore, an acknowledged definition of resilience refers to a good outcome despite conditions that carry a major risk for the development of psychopathology (Rutter, 1999). Specifically, this study explored resilience as the capacity of a few adolescents to stop or markedly reduce a regular PSU that carries a high risk for the development of substance use disorder (SUD).

Neuroimaging findings have been reported in regions of the brain associated with SUD (Ashtari et al., 2011; De Bellis et al., 2000, 2005; Lopez-Larson et al., 2011; Nagel et al., 2005; Squeglia et al., 2015; Whelan et al., 2014) or resilience to psychopathology (Burt et al., 2016; Galinowski et al., 2015) but few studies have investigated whether such brain variations can be detected in adolescents specifically resilient to SUD or to a condition at-risk for SUD. On one hand, adolescents with SUD displayed a constellation of grey matter volume (GMV) reductions in the prefrontal cortex and hippocampus, overlapping between alcohol (De Bellis et al., 2000, 2005; Nagel et al., 2005; Squeglia et al., 2015; Whelan et al., 2014) and cannabis (Ashtari et al., 2011; Lopez-Larson et al., 2011). However, PSU has been under-explored in its naturalistic aspect (Jacobus et al., 2009; Jacobus et al., 2015a, 2015b) notwithstanding the risky dimension of PSU for the outcome of SUD at that critical period of brain maturation. Moreover, longitudinal studies suggested that brain features associated with alcohol use (Cheetham et al., 2014; Squeglia et al., 2017) and cannabis initiation (Cheetham et al., 2012) were detectable earlier in adolescence. On the other hand, resilience to psychopathology has been associated in adolescents by two cross-sectional neuroimaging studies with cerebral structural features such as higher fractional anisotropy (FA) in the corpus callosum (Galinowski et al., 2015) and larger GMV in the middle and superior frontal gyri (Burt et al., 2016) when defined as having a low risk of psychopathology despite exposure to negative life events. Deciphering whether cessation or reduction of PSU, a condition at-risk for SUD, is associated with brain structural features, and whether those are present earlier in adolescence, remains at stake.

Indeed, no report is available about neuroprotective correlates underlying the capacity to resist PSU in adolescents. Two major concerns might be attributable to this lack of knowledge in the neurobiological bases of addictive behaviors. Firstly, the search for dynamic "trajectories" of substance use are observable over time while longitudinal assessments are scarce. Secondly, the profile denoting the capacity to resist PSU is scarce across adolescence and only large cohorts allow differentiating specific subgroups of individuals in the general population.

Herein, we investigated brain structural correlates associated with resilience to PSU in adolescents from a large cohort (Schumann et al., 2010) using magnetic resonance imaging (MRI). We *a priori* hypothesized that adolescents resilient to PSU would display a directionality of brain structure features denoting larger GMV and higher FA, based on previous reports on adolescents resilient to psychopathology (Burt et al., 2016; Galinowski et al., 2015). The main objective was to explore GMV on whole brain, and FA in four major white-matter tracts, in participants resilient to PSU (RPSU) with respect to participants with an enduring PSU (ePSU) and to a control group (CG) composed of abstinent or low drinking participants. The secondary objectives were (i) to test the maturational course of grey matter between groups, (ii) to identify personality traits linked to the capacity to resist continuation of PSU and (iii) to assess the weight of neuroimaging and personality features measured at 14 in predicting resilience to PSU at 19.

Experimental procedures

Ethical considerations

The protocol of the study, approved by the respective ethics committees in the different countries, was in accordance with the Helsinki Declaration of 1975. All participants and their parents signed informed consent after receiving full information on the study at ages 14 and 16. All participants signed informed consent after receiving full information on the study at age 19.

Participants

The IMAGEN cohort is composed of 2261 adolescents included at age 14 in their respective site across Europe (London, Nottingham, Dublin, Berlin, Hamburg, Mannheim, Paris, and Dresden), having no prenatal exposure to alcohol, neither any major neurodevelopmental nor psychiatric disorder, nor any contraindications for MRI. A detailed description of recruitment and assessment methods has been previously published (Schumann et al., 2010). Over time, 1348 participants were assessed at 14, 16 and 19 *via* a computer-based platform (https://www.delosis.com/psytools/overview.html) comprising a battery of questionnaires investigating substance use behaviors, life events and personality.

Trajectories of polysubstance use (PSU) and eligible participants

The Alcohol Use Disorders Identification Test (AUDIT) informs on alcohol use frequency, quantity and severity (Saunders et al., 1993). The European School Survey Project on Alcohol and other Drugs (ESPAD) (http://www.espad.org) informs on use of different licit and illicit substances during given time periods. The AUDIT and ESPAD questionnaires were used to identify subgroups of participants within the IMAGEN cohort, based on their alcohol, tobacco and cannabis use frequency. Further details on elaboration of PSU trajectories are provided in **AppS1**. Through the three time-points, the following groups were eligible for the study: (i) the resilient to PSU (RPSU) group ($n = 18$) fulfilled the criteria of PSU at 16 and/or 14 but no more at 19, (ii) the enduring PSU (ePSU) group ($n = 193$) regularly used at least two substances at 19 and 16, and for few of them also at 14, and (iii) the control group (CG) ($n = 460$) did neither use cannabis nor tobacco nor alcohol at 14, 16 and 19 (or only occasionally for alcohol). Flowchart of group selection is presented in **Fig. S1**. Using *t*-tests, we compared the AUDIT scores between RPSU and ePSU to verify that differences did not affect the outcomes in a significant way.

Structural brain imaging

Acquisitions of high-resolution magnetic resonance images has been conducted on 3T scanners from three manufacturers (Siemens, Philips and General Electrics). Participants were included in the analyses if they had structural MRI data at ages 19 and 14 (neuroimaging assessments were not conducted at age 16).

Anatomical T1-weighted MRI

The Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence based on the ADNI protocol was carried out with the following parameters: sagittal slice plane, Repetition Time (TR) = 2.3 s (s), Echo Time (TE) = 2.93 milliseconds (ms), 256 × 256 matrix, 160 slices, voxel size = 1.1 × 1.1 × 1.1 mm. Details regarding quality control and pre-processing steps are provided in **AppS2**. T1 dataset pre-processing steps and statistical analyses were run using the SPM12 software (www.fil.ion.ucl.ac.uk/spm/software/spm12). Overall the T1 dataset available for analyses was composed of $n = 312$ CG, $n = 130$ ePSU and $n = 14$ RPSU participants.

Diffusion-tensor imaging (DTI)

The diffusion-tensor images were acquired using an echo planar imaging sequence with 4 *b*-value=0 s/mm^2 and 32 diffusion encoding directions with *b*-value=1300 s/mm^2, 60 oblique-axial slices parallel to the anterior commissure/posterior commissure line, $_{TR=}$15 s, $_{TE}\approx$104 ms, 128 × 128 matrix, field of view 307 × 307 mm, voxel size = 2.4 × 2.4 × 2.4 mm. Diffusion dataset pre-processing steps, provided in **AppS3**, were run using FMRIB Diffusion Toolbox in the FSL5.0.9 software (www.fmrib.ox.ac.uk/fsl). DTI images were controlled for head movement, poor tensor computation or defective spatial normalization, thus $n = 48$ CG and $n = 17$ ePSU were removed. Overall, the DTI dataset available for analyses was composed of $n = 325$ CG, $n = 128$ ePSU and $n = 15$ RPSU participants.

Questionnaires

From the Life-Events Questionnaire (Newcomb et al., 1981), a score of negative life-events (NLE) was computed (Galinowski at al., 2015). Three questionnaires assessed personality dimensions: (i) the Neuroticism-Extraversion-Openness Five-Factor Inventory-NEO-FFI which indexes dimensions of extraversion, agreeableness, conscientiousness, neuroticism, and openness to experience (Costa and McCrae, 1995); (ii) the Substance Use Risk Profile Scale - SURPS with anxiety sensitivity, hopelessness, impulsivity, and sensation-seeking subscales (Woicik et al., 2009); (iii) the Temperament and Character Inventory - TCI-R which examines among other dimensions exploratory excitability, impulsiveness, extraversion, disorderliness and novelty-seeking subscales (Cloninger et al., 1993).

Statistical analyses

Voxel-based morphometry

At ages 19 and 14, cross-sectional comparisons of GMV on whole brain were performed between groups (RPSU, ePSU and CG) with voxel-wise two-sample *t*-tests in the framework of the general linear model with age, sex, T1 acquisition type (i.e. scanner manufacturers and/or software level to account for inter-scanner variance) and total intracranial volume as confounding variables. Significance was set for height threshold at $p<0.05$ family-wise error (FWE) corrected and cluster size > 575. We used the SPM extension Neuromorphometrics (http://www.neuromorphometrics.com/) to localize the differences and the Anatomist/Brainvisa software to create the figure (http://brainvisa.info/). A flexible factorial model explored the interaction of grey matter volumes on whole brain between groups across time with the same significance thresholds.

Tract-based spatial statistics

We used the Johns Hopkins University (JHU) atlas (Wakana et al., 2007) to create masks of white-matter tracts serving the regions where having identified GMV differences: the right cingulum and left cingulum (cingulate part), the bilateral corpus callosum and bilateral internal capsule (**Fig. S2**). At ages 19 and 14, four cross-sectional comparisons (one per mask) were performed between groups with voxel-wise two-sample *t*-tests on FA maps in the framework of the general linear model using a randomization-based method (5000 permutations) with age, sex and DTI acquisition type as confounding variables. Statistical thresholds were *a priori* set at $p<0.0125$ (0.05 Bonferroni corrected i.e. divided by the number of tracts, i.e. 4) FWE corrected and threshold-free cluster enhancement (TFCE) corrected (Smith and Nichols, 2009).

Questionnaires

The NLE and personality scores were compared between groups, at age 14, with one-way Anova tests using the JMP software (https://www.jmp.com). Statistical significance was *a priori* set at 0.0033 (0.05 Bonferroni corrected i.e. divided by the number of tests, i.e. 15). If significant, we conducted post-hoc two-sample *t*-tests.

Individual-level outcome predictions

Random forests is a non-linear model which generated individual-level outcome predictions at age 19, based on 14 variables (i.e. features) measured at age 14, among those which were differing between RPSU and ePSU participants. Equal number of variables of personality ($n = 4$ subscales), macrostructure ($n = 4$ grey matter values at the voxel maximum i.e. for each main region-of-difference), and microstructure ($n = 4$ mean FA values i.e. for each white matter tract-of-interest) were included in the models, added to sex and age ($n = 2$). The variables used were scores of extraversion, openness to experience, impulsivity, sensation seeking; GMV in bilateral anterior and middle cingulate; FA in the internal capsule and FA in the genu, body, splenium of the corpus callosum. Methodological details are described in **AppS4**. The predictive accuracy was assessed using the Area Under the Curve (AUC) of the receiver operating characteristic curve.

Results

Participants' characteristics

Among the ePSU participants ($n = 193$), 31.1% ($n = 60$) were alcohol *and* tobacco *and* cannabis users, 27.5% ($n = 53$) were alcohol *and* cannabis users, 22.8% ($n = 44$) were tobacco *and* cannabis users, 18.7% ($n = 36$) were alcohol *and* tobacco users. Among the RPSU participants ($n = 18$), 44.4% ($n = 8$) had used alcohol *and* cannabis, 22.2% ($n = 4$) had used alcohol *and* tobacco, 22.2% ($n = 4$) had used tobacco *and* cannabis, 11.1% ($n = 2$) had used alcohol *and* tobacco *and* cannabis. The rate of resilience to PSU among regular users represented 8.5% at age 19. The main characteristics of the participants included in the analyses (excluding those with images that did not pass the quality-control steps) are presented in **Table S1**. There was no difference in the AUDIT score between ePSU and RPSU at 14 years old ($t = 1.666$, df = 144.43, $p = 0.09789$) however, there were significant differences between these two groups at 16 years old ($t = 17.914$, df = 144.05, $p < 2.2e\text{-}16$, with mean of ePSU and mean of RPSU, 7.336 and 2.097, respectively) and at 19 years old ($t = 18.173$, df = 143.2, $p < 2.2e\text{-}16$, with mean of ePSU and mean of RPSU, 9.035 and 2.097, respectively).

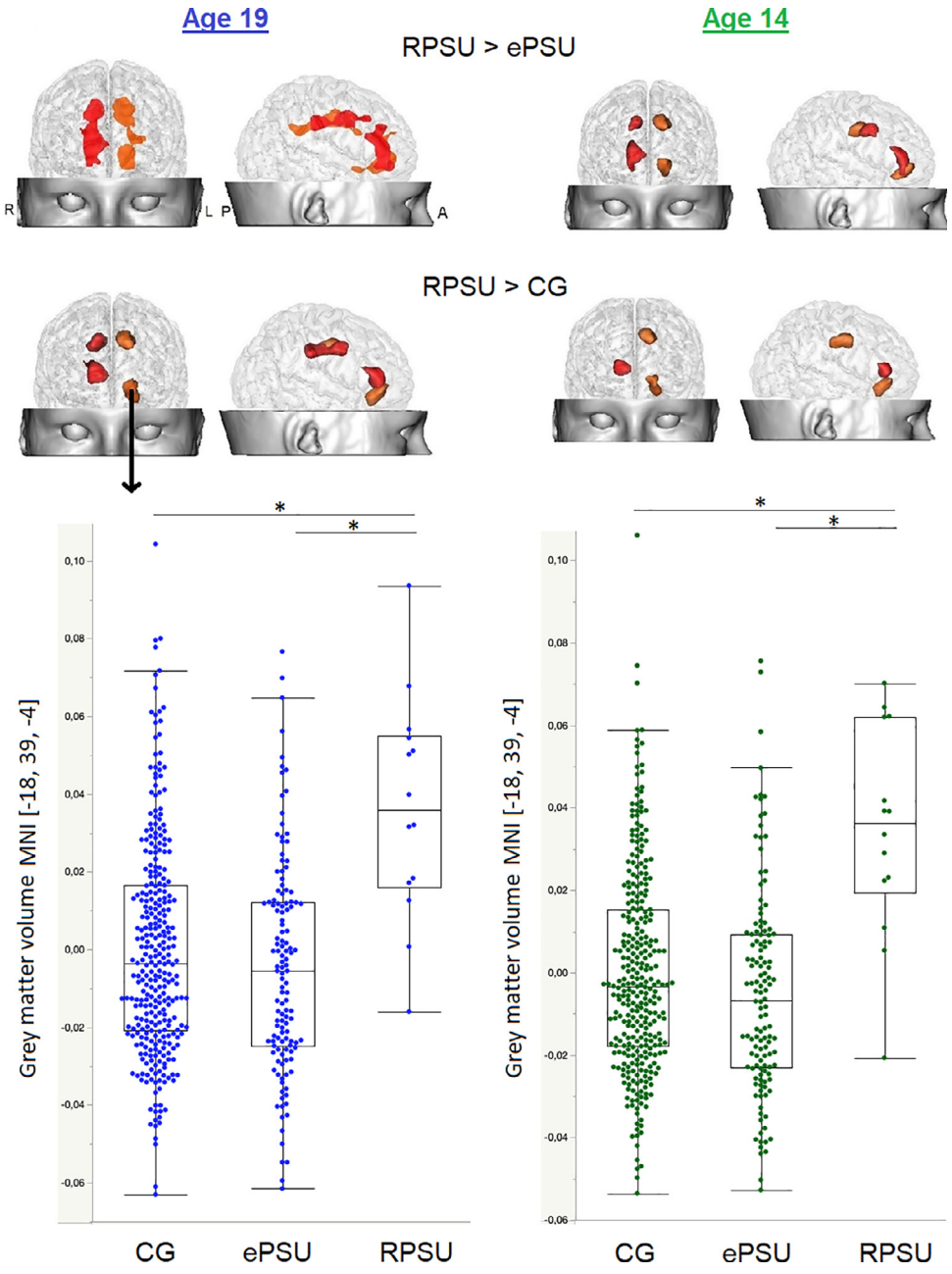

Fig. 1 Between-group comparisons of whole-brain grey matter volumes at ages 19 and 14. At 19 and 14, larger grey matter volumes were significantly detected in the resilient to polysubstance use (RPSU) group compared with both the enduring polysubstance use (ePSU) group and the control group (CG) in bilateral cingulate regions. Between-group comparisons used two-sample *t*-tests; significance was set for height threshold at $p<0.05$ Family-Wise Error corrected and cluster size>575. Results (red and orange colours) are displayed with height threshold at $p<0.001$ uncorrected and cluster size>575 voxels, for illustration purpose. R: Right; L: Left; A: Anterior; P: Posterior. The plot indicates the fitted values at the voxel MNI [−18, 39, −4] within the left anterior cingulate cortex at 19 (graph on the left) and 14 (graph on the right). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Voxel-based morphometry

Adolescents resilient to polysubstance use vs. *enduring polysubstance users*. At 19, the RPSU group presented larger GMV compared with the ePSU group in the right cingulate gyrus (anterior and middle parts), left cingulate gyrus (anterior, middle, posterior parts), bilateral superior frontal gyrus, right supplementary motor cortex, right medial orbital cortex, bilateral caudate nucleus and left putamen. The results are highly conserved when adding the impulsivity sore of the SURPS as covariate (**Fig. S3**). At 14, the RPSU participants already had larger GMV than the ePSU partici-

Table 1 Regions with larger grey matter volumes in participants resilient to polysubstance use compared with enduring polysubstance users, at 19 and 14.

Region	Cluster level		Peak level		MNI coordinates		
	Cluster size (voxel number)	*p*-value	*t* value	*p*-value	*x*	*y*	*z*
19 year olds							
L anterior cingulate gyrus	1432	**0.0065***	5.67	**1.3262e-08***	−18	39	−4
L putamen/accumbens			3.64	1.4963e-04	−20	16	−12
L superior frontal gyrus			3.17	8.0853e-04	−15	51	24
R anterior cingulate gyrus	1909	**0.0022***	5.61	**1.8329e-08***	18	36	8
R superior frontal gyrus, medial segment			3.85	6.6853e-05	15	36	30
R medial orbital gyrus			3.56	2.0344e-04	18	42	−9
R caudate			3.29	5.3220e-04	26	20	20
L anterior cingulate gyrus			3.11	9.8520e-04	−2	39	6
R middle cingulate gyrus	1758	**0.0031***	5.13	**2.1765e-07***	12	−27	32
R supplementary motor cortex			3.82	7.4901e-05	15	21	39
L middle cingulate gyrus	2027	**0.0017***	4.74	**1.4465e-06***	−14	−8	44
L posterior cingulate gyrus			3.92	5.0574e-05	−15	−40	26
L caudate			3.71	1.1746e-04	−21	15	26
14 year olds							
L anterior cingulate gyrus	669	0.0423	5.30	**9.1482e-08***	−18	40	−4
R anterior cingulate gyrus	942	0.0188	4.99	**4.3498e-07***	18	36	8
R middle cingulate gyrus	677	0.0412	4.36	8.1414e-06	14	3	42
L middle cingulate gyrus	1040	0.0143	4.36	8.1906e-06	−16	−10	36

*p values in bold are significant at $p<0.05$ Family-Wise Error corrected, other regions are reported for height threshold at $p<0.001$ uncorrected and cluster size>575 voxels. R: Right; L: Left; MNI: Montreal Neurological Institute (coordinates *x, y, z* in mm). Sample size: $n = 14$ resilient to polysubstance use and $n = 130$ enduring polysubstance use.

pants in the bilateral anterior cingulate gyrus. There was no region of larger GMV in the ePSU group compared with the RPSU group (Fig. 1 and Table 1).

Adolescents resilient to polysubstance use vs. control group. At 19, the RPSU group presented larger GMV compared with the CG in the right caudate nucleus, right cingulate gyrus (anterior and middle parts), left cingulate gyrus (anterior and middle parts). At age 14, the RPSU group already had larger GMV than the CG in the right anterior and left middle cingulate gyri. There was no region of larger GMV in the CG compared with the RPSU participants (Fig. 1 and Table 2).

Enduring polysubstance users vs. control group. No difference in GMV was detected between the ePSU and CG participants.

Interaction. There was no interaction between the RPSU and the other groups across time. However, there was a significant interaction between the ePSU and CG participants across time, indicating lower adolescent-maturational grey-matter decline in the ePSU adolescents compared with the CG in numerous brain regions (**Fig. S4**).

Tract-based spatial statistics

The RPSU participants did not differ in FA values from the two other groups neither at 19 nor at 14. At 14, the ePSU participants had higher FA value than the CG in the corpus callosum but no more at age 19. At 19 but not at 14, the CG had higher FA than the ePSU participants in the internal capsule (**Table S2**).

Questionnaires

Table 3 shows that the CG had faced fewer NLE than the RPSU and ePSU groups. The ePSU participants had higher scores of extraversion (NEO-FFI), sensation seeking and impulsivity (SURPS), exploratory excitability, impulsiveness, extravagance, disorderliness and novelty seeking (all scores of TCI-R) than the CG. Compared with the ePSU, the CG had higher scores of agreeableness and conscientiousness (NEO-FFI). The RPSU participants had lower scores of conscientiousness (NEO-FFI) and higher scores of impulsiveness and extravagance (TCI-R) than the CG, but lower impulsivity scores than the ePSU participants (SURPS).

Individual-level outcome predictions

The random forests model RPSU/ePSU resulted in an AUC of 0.75 (Fig. 2B). The strongest precursors of the outcome were the GMV in the bilateral anterior and middle cingulate gyrus, and the personality score of openness to experience. Sex, age, other personality and neuroimaging features (i.e. FA values) had minor weights in the prediction (Fig. 2A). The

Table 2 Regions with larger grey matter volumes in participants resilient to polysubstance use compared with control participants, at 19 and 14.

Region	Cluster level		Peak level		MNI coordinates		
	Cluster size (voxel number) (voxel number)	*p*-value	*t value*	*p*-value	*x*	*y*	*z*
19 year olds							
R anterior cingulate gyrus	1096	0.0147	5.61	**1.8223e-08***	16	36	8
R caudate			3.29	5.3625e-04	26	20	20
R middle cingulate gyrus	1416	0.0067	5.16	**1.8476e-07***	12	−27	33
L anterior cingulate gyrus	764	0.0363	5.07	**2.9779e-07***	−18	38	−4
L middle cingulate gyrus	1472	**0.0059***	5.05	**3.1631e-07***	−14	−6	42
14 year olds							
R anterior cingulate gyrus	671	0.0420	4.80	**1.1085e-06***	16	36	8
L middle cingulate gyrus	1206	0.0092	4.73	**1.5163e-06***	−12	−4	42
L anterior cingulate gyrus	601	0.0526	4.64	2.3308e-06	−18	38	−6

*p values in bold are significant at $p<0.05$ Family-Wise Error corrected, other regions are reported for height threshold at $p<0.001$ uncorrected and cluster size>575 voxels. R: Right; L: Left; MNI: Montreal Neurological Institute (coordinates *x, y, z* in mm). Sample size: $n = 14$ resilient to polysubstance use and $n = 312$ control.

Table 3 Comparisons of personality between the control group (CG), enduring PSU (ePSU) group and resilient to PSU (RPSU) group, at age 14.

Characteristics, mean (SD) Participant number $N = 456$	CG (1) 312	ePSU (2) 130	RPSU (3) 14	*p*-value	Post-hoc
Negative life events	2.45	3.52	3.86	**<0.0001***	1<2 1<3
NEO-FFI					
Neuroticism	22.73 (7.45)	23.20 (8.26)	24.64 (6.50)	0.5843	
Extraversion	28.59 (5.83)	31.06 (5.68)	29.14 (5.01)	**0.0003***	2>1
Openness to experience	26.83 (5.50)	27.71 (5.95)	24.29 (7.96)	0.0686	
Agreeableness	30.70 (4.92)	28.41 (5.16)	28.07 (4.57)	**<0.0001***	1>2
Conscientiousness	29.28 (7.11)	26.03 (6.67)	25.14 (6.46)	**<0.0001***	1>2 1>3
SURPS					
Anxiety sensitivity	11.38 (2.30)	11.05 (2.12)	10.93 (1.90)	0.3091	
Hopelessness	12.99 (3.15)	13.52 (2.70)	13.57 (3.25)	0.2258	
Impulsivity	11.32 (1.97)	12.59 (1.97)	11.50 (1.16)	**<0.0001***	2>3 2>1
Sensation-seeking	13.28 (2.59)	14.46 (2.33)	13.21 (2.46)	**<0.0001***	2>1
TCI-R					
Exploratory excitability	33.76 (4.08)	35.43 (3.79)	34.14 (3.98)	**0.0004***	2>1
Impulsiveness	25.03 (3.89)	27.23 (3.91)	27.50 (3.70)	**<0.0001***	3>1 2>1
Extravagance	27.01 (3.79)	29.75 (4.54)	29.71(3.95)	**<0.0001***	2>1 3>1
Disorderliness	21.35 (3.56)	23.67 (3.52)	22.79 (3.31)	**<0.0001***	2>1
Novelty-seeking	55.12 (6.14)	59.10 (5.61)	56.93 (5.03)	**<0.0001***	2>1

NEO-FFI, Neuroticism-Extraversion-Openness Five-Factor Inventory; SURPS, Substance Use Risk Profile Scale; TCI-R, Temperament and Character Inventory Revised. A one sample Anova model was used to compare the scores between groups. Post-hoc two-sample *t*-tests were performed if significant; *p values in bold are significant at $p<0.0033$ (i.e. 0.05 Bonferroni corrected i.e. divided by the number of tests, i.e. 15).

random forests model RPSU/CG resulted in an AUC of 0.70 (**Fig. S5**).

Discussion

The present study sought to identify structural differences in participants resilient to polysubstance use (RPSU) who showed cessation or reduction of their polysubstance use with respect to participants with an enduring polysubstance use (ePSU) and with a control group (CG) composed of abstinent or low drinking participants. This is the first neuroimaging report on brain correlates associated with trajectories of polysubstance use in adolescents followed from 14 to 19. At age 19, RPSU adolescents displayed larger GMV than

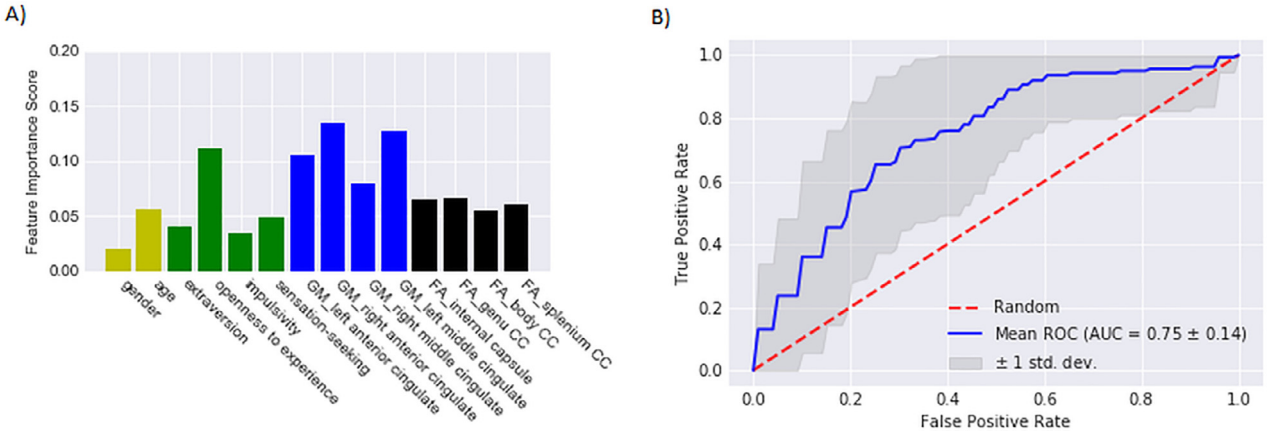

Fig. 2 Random forests classification generated individual outcome predictions of resilience or continuation of polysubstance use at age 19 based on neuroimaging and personality features measured at age 14. A) Variables (i.e. features) included in the individual-level prediction model and their relative weight in the model. The variables were, in order: sex, age, extraversion, openness to experience, impulsivity, sensation-seeking, GM (grey matter) volumes in the bilateral anterior and middle cingulate, FA (fractional anisotropy) in the internal capsule, FA in the genu, body and splenium of the corpus callosum (CC). B) Model performance was quantified using the area under the curve (AUC) of the receiver operating characteristic curve, which quantifies the model's ability to correctly assign a participant to resilient to or enduring polysubstance use.

both the ePSU and CG participants in the bilateral cingulate regions and right caudate nucleus, but no difference in fractional anisotropy in the bilateral cingulum, corpus callosum and internal capsule. The RPSU participants already displayed larger GMV in the bilateral cingulate gyrus at age 14, which were among the best precursors of the outcome of resilience to PSU at 19 with the personality trait "openness to experience". The present study thus suggests that cerebral determinants are critically involved in the emergence of resilience to PSU in adolescents, i.e. brain structural correlates are among the best precursors of the outcome.

We reported on a small sample of adolescents achieving cessation or reduction of PSU. The difference in the AUDIT score between ePSU and RPSU at 16 years old might impact the outcome measure or not. Indeed, it is possible that ePSU participants have a more severe alcohol drinking pattern at 16 so they are less likely to stop or refrain their use at 19, but in the meantime, this more severe pattern might arise from preexisting brain structural correlates, that were among the best precursors of the outcome in the study. The difference in the AUDIT score between ePSU and RPSU at 19 years old is, by definition, logical, since ePSU continued PSU while rPSU refrained or stopped their use. According to a survey in the 90s (Chen and Kandel, 1995), the end of the second decade is commonly associated with peaks of initiation of tobacco, alcohol and cannabis, and the natural course of substance use shows recovery occurring later and spontaneously, with recovery rates reaching 6% for alcohol, 42% for tobacco and 69% for cannabis at ages 28–29. Indeed, consistent studies showed that the prevalence of alcohol abuse rose at 18 and 21, then dropped to 10% at 25 (Wells et al., 2006) while the prevalence of cannabis use declined earlier (von Sydow et al., 2001). Since a natural reduction in substance use from adolescence to emerging adulthood has been consistently observed, the social plasticity hypothesis (Cousijn et al., 2018) implies that adolescent resilience to substance use disorders results from social devaluation of substance use and improved behavioural control, as individuals get responsible roles, including serious employment, marriage, and childbearing. Nevertheless, there is a lack of information on recovery from substance abuse. The generalizability of our results in the general population is unknown inasmuch as no epidemiological survey is available on recovery from polysubstance abuse in adolescents.

Here, the superior frontal gyrus was larger in the participants RPSU compared with the participants ePSU at age 19, as previously identified in adolescents resilient to psychopathology (Burt et al., 2016). The larger bilateral cingulate gyrus in the RPSU at both ages 19 and 14 is a new finding. Neuroimaging studies consistently describe cingulate regions as epicenters that play a role in the genesis of voluntary choices, guidance on evaluating their outcome, notably when the environment is changing (Walton et al., 2007). Anatomically, the whole cingulate gyrus receives information from prefrontal and limbic regions, and directly connects to the motor system in particular the anterior subdivision of the cingulate cortex which is involved in emotional regulation (Bush et al., 2000; Vogt, 2016) in the context of conscious conflicts (Dehaene et al., 2003). A meta-analysis of regional cerebral blood flow predictors of relapse and recovery from substance use showed that right putamen activation has been associated with relapse vulnerability and resilience, while increased baseline activation of the rostral anterior cingulate cortex is consistently associated with improved treatment outcomes (Forster et al., 2018). Also involved in reward-based cognitive processes (Shidara and Richmond, 2002) during preoccupation and anticipation phases of the addictive process (Volkow et al., 2016), the anterior cingulate cortex is thought to intervene after sessions with the therapist

in conscious decision-making process to refrain addiction in the context of psychosocial therapy with motivational interviewing (Feldstein Ewing et al., 2011).

Regarding white-matter integrity, the absence of difference in FA in the corpus callosum is discrepant with previous findings in resilient adolescents having a low risk of psychopathology despite exposure to negative life events (Galinowski et al., 2015). While higher FA values in the corpus callosum was observed at age 14 in the ePSU participants compared with the CG, at age 19, FA value was higher in participants from CG compared with the participants ePSU in the internal capsule. Substance use during adolescence may interfere with healthy synaptic pruning and myelination that continue into early adulthood. As previously suggested for alcohol (Chanraud et al., 2009), changes relative to substance use might occur first in the white matter therefore FA changes in the corpus callosum and in the internal capsule might relate to the premises of sustainable substance-induced changes.

The present findings substantiate the view that GMV differences pre-exist in early adolescence depending on the outcome of substance-use behaviors at age 19. Indeed, no interaction of GMV was detected in the RPSU compared with the other groups across time, strengthening the pre-existing nature of such characteristics in that group. Prior research showed that brain structural particularities predicted alcohol-related problems (Cheetham et al., 2014) and cannabis initiation (Cheetham et al., 2012) in adolescents. Prospectively, we used after Squeglia et al. (2017), a random forests model that is superior to other machine learning techniques to generate individual-level outcome predictions. Here, macrostructure features (GMV in the cingulate gyrus) prevailed over both microstructure (FA in the corpus callosum and internal capsule) and most of personality features (extraversion, sensation seeking and impulsivity), except openness to experience, in predicting accurately subsequent enduring PSU or resilience to PSU. The personality trait resiliency, which is the ability to flexibly adapt impulse control relative to contextual demand, has been shown to be a protective factor against alcohol problems and drug use in early adolescence. Cortical-striatal connectivity, in particular the subthalamic nucleus which a key basal ganglia structure, might link impulse control and cognitive processing to modulate substance use outcome (Weiland et al., 2012).

These results should be interpreted in the context of four limitations. Firstly, the smallness of the present sample of RPSU adolescents is accounted for by the scarcity of this characteristic in our cohort, the stringency of the eligibility criteria and quality-control processes, as well as the availability of neuroimaging data for each participant at both ages 19 and 14. Supporting the validity of our results, (i) the cingulate gyrus identified in morphometry analyses on the whole brain was bilaterally well-delimited at both time-points, although images were acquired distinctly at five years of interval, (ii) no other regional difference in macrostructure was detected with SPM12 at a less stringent statistical height threshold ($p<0.001$ uncorrected and cluster size>575 voxels), (iii) the ePSU and CG subgroup sizes remained large ($n = 130$ and $n = 312$ in the morphometry analyses), ensuring a sufficient statistical sensitivity (e.g. power of the t-test in the voxel maximum = 0.99) and statistical tests were conducted assuming inequality of variances between the subgroups, (iv) the random forests model confirmed the validity of the RPSU subgroup since individual classification upon several features reached significant accuracy. This should foster further studies encompassing analyses contrasting small samples of well-characterized individuals and larger cohorts. Secondly, we collected declarative data from participants (i.e. self-report questionnaires) to assess substance use that may be subject to unreliability due to intentional underreporting or effects of the context of assessment. Therefore, to compensate this relative uncertainty, we made categorical groups (i.e. abstinent, occasional and regular) to re-center the information. Regarding the AUDIT questionnaire, which provides a clinical score of problematic alcohol use, its optimal thresholds vary with age (Reinert and Allen, 2007) such as in adolescents (Vulser et al., 2018). Here, we used the stringent adult AUDIT threshold to constitute well-differentiated groups of participants and limit the risk of false positive finding. Thirdly, we focused on the three most commonly used substances in adolescents, thus other substances were not studied.

To conclude, a most striking fact emerging from the literature is probably the paucity of neuroimaging work conducted on resilience underlain by neuro-biological traits, even less investigated in the field of addiction science. Herein, the identification of discrete and localized brain structural variations in the cingulate gyrus of adolescents resilient to polysubstance use might fuel therapeutic models such as cognitive interventions targeting cingulate functions in adolescents at-risk of substance use disorders. Moreover, such insights into neuroprotective regions that interface key regions of the reward system may warrant further exploration within clinical samples to broaden the body of knowledge of brain networks involved in addictive behaviors.

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Contributors

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Authors Irina Filippi and André Galinowski and Jean-Luc Martinot wrote the first draft of the manuscript.

All authors contributed to and have approved the final manuscript.

Conflict of interest

Dr Banascheski has served as an advisor or consultant to Bristol-Myers Squibb, Desitin Arzneimittel, Eli Lilly, Medice, Novartis, Pfizer, Shire, UCB, and Vifor Pharma; he has received conference attendance support, conference support, or speaking fees from Eli Lilly, Janssen McNeil, Medice, Novartis, Shire, and UCB. Dr Gowland has received a research grant from Lyndra and an honorarium paid to her employer from GlaxoSmithKline. Dr Poustka has received conference attendance support or speaking fees from Medice, Novartis, and Shire. Dr Walter has received a speaking honorarium from Servier. The present work is unrelated to these relationships. The other authors have no potential conflict of interest or biomedical financial disclosure to make.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2021.03.001.

References

Ashtari, M., Avants, B., Cyckowski, L., Cervellione, K.L., Roofeh, D., Cook, P., Gee, J., Sevy, S., Kumra, S., 2011. Medial temporal structures and memory functions in adolescents with heavy cannabis use. J. Psychiatr. Res. 45 (8), 1055–1066.

Burdzovic Andreas, J., Pape, H., Bretteville-Jensen, A.L., 2016. Who are the adolescents saying "No" to cannabis offers. Drug Alcohol Depend. 163, 64–70.

Burt, K.B., Whelan, R., Conrod, P.J., Banaschewski, T., Barker, G.J., Bokde, A.L.W., Bromberg, U., Büchel, C., Fauth-Bühler, M., Flor, H., Galinowski, A., Gallinat, J., Gowland, P., Heinz, A., Ittermann, B., Mann, K., Nees, F., Papadopoulos-Orfanos, D., Paus, T., Pausova, Z., Poustka, L., Rietschel, M., Robbins, T.W., Smolka, M.N., Ströhle, A., Schumann, G., Garavan, H., 2016. Structural brain correlates of adolescent resilience. J. Child Psychol. Psychiatry 57 (11), 1287–1296.

Bush, G., Luu, P., Posner, M.I., 2000. Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn. Sci. (Regul. Ed.) 4 (6), 215–222.

Camenga, D.R., Kong, G., Bagot, K., Hoff, R.A., Potenza, M.N., Krishnan-Sarin, S., 2014. Marijuana, alcohol use and attempted smoking cessation in adolescent boys and girls. Subst. Abus. 35 (4), 381–386.

Chan, G.C.K., Kelly, A.B., Carroll, A., Williams, J.W., 2017. Peer drug use and adolescent polysubstance use: do parenting and school factors moderate this association? Addict. Behav. 64, 78–81.

Chanraud, S., Leroy, C., Martelli, C., Kostogianni, N., Delain, F., Aubin, H.J., Reynaud, M., Martinot, J.L., 2009. Episodic memory

in detoxified alcoholics: contribution of grey matter microstructure alteration. PLoS One 4 (8).
Cheetham, A., Allen, N.B., Whittle, S., Simmons, J.G., Yücel, M., Lubman, D.I., 2012. Orbitofrontal volumes in early adolescence predict initiation of cannabis use: a 4-year longitudinal and prospective study. Biol. Psychiatry 71 (8), 684–692.
Cheetham, A., Allen, N.B., Whittle, S., Simmons, J., Yücel, M., Lubman, D.I., 2014. Volumetric differences in the anterior cingulate cortex prospectively predict alcohol-related problems in adolescence. Psychopharmacology 231 (8), 1731–1742.
Chen, K., Kandel, D.B., 1995. The natural history of drug use from adolescence to the mid-thirties in a general population sample. Am. J. Publ. Health 85 (1), 41–47.
Cloninger, C.R., Svrakic, D.M., Przybeck, T.R., 1993. A psychobiological model of temperament and character. Arch. Gen. Psychiatry 50 (12), 975–990.
Costa, P.T., McCrae, R.R., 1995. Domains and facets: hierarchical personality assessment using the revised NEO personality inventory. J. Pers. Assess. 64 (1), 21–50.
Cousijn, J., Luijten, M., Ewing, S.W.F., 2018. Adolescent resilience to addiction: a social plasticity hypothesis. Lancet Child Adolesc. Health 2 (1), 69–78.
Dani, J.A., Harris, R.A., 2005. Nicotine addiction and comorbidity with alcohol abuse and mental illness. Nat. Neurosci.. [cited 2019 Mar 23]. Available from https://www-nature-com.gate2.inist.fr/articles/nn1580 .
De Bellis, M.D., Clark, D.B., Beers, S.R., Soloff, P.H., Boring, A.M., Hall, J., Kersh, A., Keshavan, M.S., 2000. Hippocampal volume in adolescent-onset alcohol use disorders. AJP 157 (5), 737–744.
De Bellis, M.D., Narasimhan, A., Thatcher, D.L., Keshavan, M.S., Soloff, P., Clark, D.B., 2005. Prefrontal cortex, thalamus, and cerebellar volumes in adolescents and young adults with adolescent-onset alcohol use disorders and comorbid mental disorders. Alcohol. Clin. Exp. Res. 29 (9), 1590–1600.
Dehaene, S., Artiges, E., Naccache, L., Martelli, C., Viard, A., Schürhoff, F., Recasens, C., Martinot, M.L., Leboyer, M., Martinot, J.L., 2003. Conscious and subliminal conflicts in normal subjects and patients with schizophrenia: the role of the anterior cingulate. Proc. Natl. Acad. Sci. U.S.A. 100 (23) 13722–7.
Feldstein Ewing, S.W., Filbey, F.M., Hendershot, C.S., McEachern, A.D., Hutchison, K.E., 2011. Proposed model of the neurobiological mechanisms underlying psychosocial alcohol interventions: the example of motivational interviewing. J. Stud. Alcohol. Drugs. 72 (6), 903–916.
Forster, S.E., Dickey, M.W., Forman, S.D., 2018. Regional cerebral blood flow predictors of relapse and resilience in substance use recovery: a coordinate-based meta-analysis of human neuroimaging studies. Drug Alcohol. Depend. 185, 93–105.
Galinowski, A., Miranda, R., Lemaitre, H., Paillère Martinot, M.L., Artiges, E., Vulser, H., Goodman, R., Penttilä, J., Struve, M., Barbot, A., Fadai, T., Poustka, L., Conrod, P., Banaschewski, T., Barker, G.J., Bokde, A., Bromberg, U., Büchel, C., Flor, H., Gallinat, J., Garavan, H., Heinz, A., Ittermann, B., Kappel, V., Lawrence, C., Loth, E., Mann, K., Nees, F., Paus, T., Pausova, Z., Poline, J.B., Rietschel, M., Robbins, T.W., Smolka, M., Schumann, G., Martinot, J.L., 2015. Resilience and corpus callosum microstructure in adolescence. Psychol. Med. 45 (11), 2285–2294.
Jacobus, J., McQueeny, T., Bava, S., Schweinsburg, B.C., Frank, L.R., Yang, T.T., Tapert, S.F., 2009. White matter integrity in adolescents with histories of marijuana use and binge drinking. Neurotoxicol. Teratol. 31 (6), 349–355.
Jacobus, J., Squeglia, L.M., Infante, M.A., Castro, N., Brumback, T., Meruelo, A.D., Tapert, S.F., 2015a. Neuropsychological performance in adolescent marijuana users with co-occurring alcohol use: a three-year longitudinal study. Neuropsychology 29 (6), 829–843.
Jacobus, J., Squeglia, L.M., Meruelo, A.D., Castro, N., Brumback, T., Giedd, J.N., Tapert, S.F., 2015b. Cortical thickness in adolescent marijuana and alcohol users: a three-year prospective study from adolescence to young adulthood. Dev. Cogn. Neurosci. 16, 101–109.
Lopez-Larson, M.P., Bogorodzki, P., Rogowska, J., McGlade, E., King, J.B., Terry, J., Yurgelun-Todd, D., 2011. Altered prefrontal and insular cortical thickness in adolescent marijuana users. Behav. Brain Res. 220 (1), 164–172.
McKelvey, K.L., Ramo, D.E., Delucchi, K., Rubinstein, M.L., 2017. Polydrug use among urban adolescent cigarette smokers. Addict. Behav. 66, 145–150.
Nagel, B.J., Schweinsburg, A.D., Phan, V., Tapert, S.F., 2005. Reduced hippocampal volume among adolescents with alcohol use disorders without psychiatric comorbidity. Psychiatry Res. 139 (3), 181–190.
Newcomb, M.D., Huba, G.J., Bentler, P.M., 1981. A multidimensional assessment of stressful life events among adolescents: derivation and correlates. J. Health Soc. Behav. 22 (4), 400–415.
Redonnet, B., Chollet, A., Fombonne, E., Bowes, L., Melchior, M., 2012. Tobacco, alcohol, cannabis and other illegal drug use among young adults: the socioeconomic context. Drug Alcohol. Depend. 121 (3), 231–239.
Reinert, D.F., Allen, J.P., 2007. The alcohol use disorders identification test: an update of research findings. Alcohol. Clin. Exp. Res. 31 (2), 185–199.
Rudzinski, K., McDonough, P., Gartner, R., Strike, C., 2017. Is there room for resilience? A scoping review and critique of substance use literature and its utilization of the concept of resilience. Subst. Abuse Treat. Prev. Policy. [cited 2017 Nov 20], 12. Available from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5603070/ .
Rutter, M., 1999. Resilience concepts and findings: implications for family therapy. J. Fam. Ther. 21 (2), 119–144.
Saunders, J.B., Aasland, O.G., Babor, T.F., de la Fuente, J.R., Grant, M., 1993. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption – II. Addiction 88 (6), 791–804.
Schumann, G., Loth, E., Banaschewski, T., Barbot, A., Barker, G., Büchel, C., Conrod, P.J., Dalley, J.W., Flor, H., Gallinat, J., Garavan, H., Heinz, A., Itterman, B., Lathrop, M., Mallik, C., Mann, K., Martinot, J.L., Paus, T., Poline, J.B., Robbins, T.W., Rietschel, M., Reed, L., Smolka, M., Spanagel, R., Speiser, C., Stephens, D.N., Ströhle, A., Struve, M., 2010. The IMAGEN study: reinforcement-related behaviour in normal brain function and psychopathology. Mol. Psychiatry 15 (12), 1128–1139.
Shidara, M., Richmond, B.J., 2002. Anterior cingulate: single neuronal signals related to degree of reward expectancy. Science 296 (5573), 1709–1711.
Smith, S.M., Nichols, T.E., 2009. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage 44 (1), 83–98.
Squeglia, L.M., Tapert, S.F., Sullivan, E.V., Jacobus, J., Meloy, M.J., Rohlfing, T., Pfefferbaum, A., 2015. Brain development in heavy drinking adolescents. Am. J. Psychiatry 172 (6), 531–542.
Squeglia, L.M., Ball, T.M., Jacobus, J., Brumback, T., McKenna, B.S., Nguyen-Louie, T.T., Sorg, S.F., Paulus, M.P., Tapert, S.F., 2017. Neural predictors of initiating alcohol use during adolescence. Am. J. Psychiatry 174 (2), 172–185.
Tomczyk, S., Isensee, B., Hanewinkel, R., 2016. Latent classes of polysubstance use among adolescents—a systematic review. Drug Alcohol Depend. 160, 12–29.
Vogt, B.A., 2016. Midcingulate cortex: structure, connections, homologies, functions and diseases. J. Chem. Neuroanat. 74, 28–46.

Volkow, N.D., Koob, G.F., McLellan, A.T., 2016. Neurobiologic advances from the brain disease model of addiction. N. Engl. J. Med. 374 (4), 363–371.

von Sydow, K., Lieb, R., Pfister, H., Höfler, M., Sonntag, H., Wittchen, H.U., 2001. The natural course of cannabis use, abuse and dependence over four years: a longitudinal community study of adolescents and young adults. Drug Alcohol. Depend. 64 (3), 347–361.

Vulser, H., Martinot, M.L.P, Artiges, E., Miranda, R., Penttilä, J., Grimmer, Y., van Noort, B.M., Stringaris, A., Struve, M., Fadai, T., Kappel, V., Goodman, R., Tzavara, E., Massaad, C., Banaschewski, T., Barker, G.J., Bokde, A.L.W., Bromberg, U., Brühl, R., Büchel, C., Cattrell, A., Conrod, P., Desrivières, S., Flor, H., Frouin, V., Gallinat, J., Garavan, H., Gowland, P., Heinz, A., Nees, F., Papadopoulos-Orfanos, D., Paus, T., Poustka, L., Rodehacke, S., Smolka, M.N., Walter, H., Whelan, R., Schumann, G., Martinot, J.L., Lemaitre, H., 2018. Early variations in white matter microstructure and depression outcome in adolescents with subthreshold depression. Am. J. Psychiatry 175 (12), 1255–1264.

Wakana, S., Caprihan, A., Panzenboeck, M.M., Fallon, J.H., Perry, M., Gollub, R.L., Hua, K., Zhang, J., Jiang, H., Dubey, P., Blitz, A., van Zijl, P., Mori, S., 2007. Reproducibility of quantitative tractography methods applied to cerebral white matter. Neuroimage 36 (3), 630–644.

Walton, M.E., Croxson, P.L., Behrens, T.E.J., Kennerley, S.W., Rushworth, M.F.S., 2007. Adaptive decision making and value in the anterior cingulate cortex. Neuroimage 36 (Suppl 2), 142–154 T.

Weiland, B.J., Nigg, J.T., Welsh, R.C., Yau, W.Y.W., Zubieta, J.K., Zucker, R.A., Heitzeg, M.M., 2012. Resiliency in adolescents at high risk for substance abuse: flexible adaptation via subthalamic nucleus and linkage to drinking and drug use in early adulthood. Alcohol. Clin. Exp. Res. 36 (8), 1355–1364.

Wells, J.E., Horwood, L.J., Fergusson, D.M., 2006. Stability and instability in alcohol diagnosis from ages 18 to 21 and ages 21 to 25 years. Drug Alcohol Depend. 81 (2), 157–165.

Whelan, R., Watts, R., Orr, C.A., Althoff, R.R., Artiges, E., Banaschewski, T., Barker, G.J., Bokde, A.L., Büchel, C., Carvalho, F.M., Conrod, P.J., Flor, H., Fauth-Bühler, M., Frouin, V., Gallinat, J., Gan, G., Gowland, P., Heinz, A., Ittermann, B., Lawrence, C., Mann, K., Martinot, J.L., Nees, F., Ortiz, N., Paillère-Martinot, M.L., Paus, T., Pausova, Z., Rietschel, M., Robbins, T.W., Smolka, M.N., Ströhle, A., Schumann, G., Garavan, H., 2014. Neuropsychosocial profiles of current and future adolescent alcohol misusers. Nature 512 (7513), 185–189.

Woicik, P.A., Stewart, S.H., Pihl, R.O., Conrod, P.J., 2009. The substance use risk profile scale: a scale measuring traits linked to reinforcement-specific substance use profiles. Addict. Behav. 34 (12), 1042–1055.