NeuroImage: Clinical 13 (2017) 188–200

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Distinct effects of childhood ADHD and cannabis use on brain functional architecture in young adults

Clare Kelly, PhD[a,b,c,d,*], F. Xavier Castellanos[d,e], Olivia Tomaselli[d,f], Krista Lisdahl[g], Leanne Tamm[h], Terry Jernigan[i,j,k,l], Erik Newman[i], Jeffery N. Epstein[m], Brooke S.G. Molina[n,o], Laurence L. Greenhill[p], Steven G. Potkin[q], Stephen Hinshaw[r], James M. Swanson[s], MTA Neuroimaging Group[1]:

[a] School of Psychology, Trinity College Dublin, Dublin, Ireland
[b] Department of Psychiatry, School of Medicine, Trinity College Dublin, Dublin, Ireland
[c] Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland
[d] Center for Neurodevelopmental Disorders, Child Study Center, New York University Langone Medical Center, New York, NY, USA
[e] Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY, USA
[f] National Adoption & Fostering Team, Michael Rutter Center, Maudsley Hospital, London, UK
[g] University of Wisconsin-Milwaukee, Psychology Department, 2441 E. Hartford Ave, Milwaukee, WI, USA
[h] Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, ML10006 Cincinnati, OH, USA
[i] Center for Human Development, University of California, San Diego, La Jolla, CA, USA
[j] Department of Cognitive Science, University of California, San Diego, La Jolla, CA, USA
[k] Department of Psychiatry, University of California, San Diego, La Jolla, CA, USA
[l] Department of Radiology, University of California, San Diego, La Jolla, CA, USA
[m] Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
[n] Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA
[o] Department of Psychology, University of Pittsburgh, Pittsburgh, PA, USA
[p] Department of Psychiatry, Columbia University, New York, NY, USA
[q] Department of Psychiatry and Human Behavior, School of Medicine, University of California Irvine, Irvine, CA, USA
[r] Department of Psychology, University of California-Berkeley, Berkeley, CA, USA
[s] Child Development Center, University of California, Irvine, Irvine, CA, USA

ARTICLE INFO

Article history:
Received 22 June 2016
Received in revised form 4 September 2016
Accepted 15 September 2016
Available online 15 September 2016

ABSTRACT

One of the most salient long-term implications of a childhood diagnosis of ADHD is an increased risk for substance use, abuse, or dependence in adolescence and adulthood. The extent to which cannabis use affects ADHD-related alterations in brain functional organization is unknown, however. To address this research gap, we recruited a sample of 75 individuals aged 21–25 years with and without a childhood diagnosis of ADHD Combined Type, who were either frequent users or non-users of cannabis. These participants have been followed longitudinally since age 7–9.9 years as part of a large multi-site longitudinal study of ADHD, the Multimodal

* Corresponding author at: Trinity College Institute of Neuroscience, School of Psychology, Department of Psychiatry, School of Medicine, Trinity College Dublin, Dublin 2, Ireland; Center for Neurodevelopmental Disorders, Child Study Center, NYU Langone Medical Center, New York, NY 10016, USA.
E-mail addresses: clare.kelly@tcd.ie, clare.kelly@nyumc.org (C. Kelly).

[1] The Multimodal Treatment Study of Children with ADHD (MTA) was a National Institute of Mental Health (NIMH) cooperative agreement randomized clinical trial, continued under an NIMH contract as a follow-up study and finally under a National Institute on Drug Abuse (NIDA) contract. Collaborators from NIMH: Benedetto Vitiello, M.D. (Child & Adolescent Treatment and Preventive Interventions Research Branch), Joanne B. Severe, M.S. (Clinical Trials Operations and Biostatistics Unit, Division of Services and Intervention Research), Peter S. Jensen, M.D. (currently at REACH Institute and Mayo Clinic), L. Eugene Arnold, M.D., M.Ed. (currently at Ohio State University), Kimberly Hoagwood, Ph.D. (currently at Columbia); previous contributors from NIMH to the early phases: John Richters, Ph.D. (currently at National Institute of Nursing Research); Donald Vereen, M.D. (currently at NIDA). Principal investigators and co-investigators from the sites are: University of California, Berkeley/San Francisco: Stephen P. Hinshaw, Ph.D. (Berkeley), Glen R. Elliott, Ph.D., M.D. (San Francisco); Duke University Medical Center: Karen C. Wells, Ph.D., Jeffery N. Epstein, Ph.D. (currently at Cincinnati Children's Hospital Medical Center), Desiree W. Murray, Ph.D.; previous Duke contributors to early phases: C. Keith Conners, Ph.D. (former PI); John March, M.D., M.P.H.; University of California, Irvine: James Swanson, Ph.D., Timothy Wigal, Ph.D.; previous contributor from UCLA to the early phases: Dennis P. Cantwell, M.D. (deceased); New York University: Howard B. Abikoff, Ph.D.; Montreal Children's Hospital/ McGill University: Lily Hechtman, M.D.; New York State Psychiatric Institute/Columbia University/Mount Sinai Medical Center: Laurence L. Greenhill, M.D. (Columbia), Jeffrey H. Newcorn, M.D. (Mount Sinai School of Medicine). University of Pittsburgh: Brooke Molina, Ph.D., Betsy Hoza, Ph.D. (currently at University of Vermont), William E. Pelham, Ph.D. (PI for early phases, currently at Florida International University). Follow-up phase statistical collaborators: Robert D. Gibbons, Ph.D. (University of Illinois, Chicago); Sue Marcus, Ph.D. (Mt. Sinai College of Medicine); Kwan Hur, Ph.D. (University of Illinois, Chicago). Original study statistical and design consultant: Helena C. Kraemer, Ph.D. (Stanford University). Collaborator from the Office of Special Education Programs/US Department of Education: Thomas Hanley, Ed.D. Collaborator from Office of Juvenile Justice and Delinquency Prevention/Department of Justice: Karen Stern, Ph.D. Additional investigators for Neuroimaging Substudy: Leanne Tamm, Ph.D., PI (Cincinnati Children's Hospital Medical Center), James Bjork, Ph.D. (Division of Clinical Neuroscience and Behavioral Research, NIDA; currently at Virginia Commonwealth University), Daniel Mathalon, M.D., Ph.D. (UC San Francisco), Allen Song, Ph.D. (Duke), Bradley Peterson, M.D. (Columbia), Steven Potkin, M.D. & Claudia Buss, Ph.D. (UC Irvine), Katerina Velanova, Ph.D. (Pittsburgh), Neuroimaging Consultants: Susan Tapert, Ph.D. & Joshua Kuperman, Ph.D. (UC San Diego), BJ Casey, Ph.D. & Leah Sommerville, Ph.D. (Sackler Institute, Cornell), Krista Lisdahl, Ph.D. (University of Wisconsin-Milwaukee). Neuroimaging Analysis and Interpretation: Terry Jernigan, Ph.D. & Anders Dale, Ph.D. (UC San Diego), F. Xavier Castellanos, M.D. & Clare Kelly, Ph.D. (New York University).

http://dx.doi.org/10.1016/j.nicl.2016.09.012

Keywords:
ADHD
Cannabis
Marijuana
fMRI
Functional connectivity
Neurocognitive

Treatment Study of Children with ADHD (MTA). We examined task-independent intrinsic functional connectivity (iFC) within 9 functional networks using a 2 × 2 design, which compared four groups of participants: (1) individuals with a childhood diagnosis of ADHD who currently use cannabis ($n = 23$); (2) individuals with ADHD who do not currently use cannabis ($n = 22$); (3) comparisons who currently use cannabis ($n = 15$); and (4) comparisons who do not currently use cannabis ($n = 15$). The main effects of childhood ADHD were primarily weakened iFC in networks supporting executive function and somatomotor control. Contrary to expectations, effects of cannabis use were distinct from those of diagnostic group and no interactions were observed. Exploratory brain-behavior analyses suggested that ADHD-related effects were primarily linked with poorer neurocognitive performance. Deficits in the integrity of functional networks supporting executive function and somatomotor control are consistent with the phenotypic and neurocognitive features of ADHD. Our data suggest that cannabis use does not exacerbate ADHD-related alterations, but this finding awaits replication in a larger sample. Longitudinal neuroimaging studies are urgently required to delineate the neurodevelopmental cascade that culminates in positive and negative outcomes for those diagnosed with ADHD in childhood.

1. Introduction

Attention/Deficit-Hyperactivity Disorder (ADHD) is increasingly conceptualized as reflecting delayed or disrupted brain development. Two decades of neuroimaging studies have revealed multiple loci of ADHD-related abnormalities throughout the brain (Cortese et al., 2012; Cubillo et al., 2012; Faraone et al., 2015; Friedman and Rapoport, 2015; Hart et al., 2013). Recently, techniques that assess functional interactions amongst brain regions, such as intrinsic functional connectivity (iFC), have heralded a shift in explanatory focus from discrete loci of dysfunction to dysconnectivity of large-scale functional circuits (Di Martino et al., 2014). Studies capitalizing on these techniques have revealed ADHD-related alterations in networks supporting higher-order cognitive functions including attention and executive control over behavior (e.g., the frontoparietal network), mind-wandering and social cognition (e.g., the default network), as well as in networks supporting primary sensory and motor functions (e.g., visual and somatomotor networks) (Castellanos and Aoki, 2016; Castellanos and Proal, 2012; Posner et al., 2014). A critical next step is to link these network alterations with specific aspects of the ADHD phenotype, so that we may begin to unravel the neurodevelopmental trajectories leading to both positive and negative long-term outcomes.

One of the most salient long-term implications of a childhood diagnosis of ADHD is an increased risk for substance use, abuse, or dependence in adolescence and adulthood (Charach et al., 2011; Klein et al., 2012; Lee et al., 2011). Indeed, many studies of adult ADHD include participants who report significant substance use, and many studies of substance-using populations report significant comorbidity for ADHD. Consistent with population-wide trends, cannabis is the most commonly used illicit substance amongst individuals with ADHD (Lee et al., 2011; Molina et al., 2013). A key question is how cannabis use, particularly during the sensitive developmental period of adolescence, affects or interacts with ADHD-related alterations in brain functional organization.

Cannabinoids exert both neuroprotective and neurotoxic effects in brain (Fowler et al., 2010; Sarne et al., 2011). One contributing factor is the developmental period during which exposure occurs (Downer and Campbell, 2010); when cannabis use is initiated during developmentally critical periods such as adolescence, it may disturb the maturational refinement of functional circuits (Bossong and Niesink, 2010; Lubman et al., 2015), a neurotoxic effect. Accordingly, regions rich in cannabinoid receptors, including prefrontal cortex, striatum, medial temporal lobe, and cerebellum, as well as white matter structures such as the corpus callosum, exhibit both structural and functional abnormalities amongst cannabis users (e.g., Arnone et al., 2008; Battistella et al., 2014; Filbey et al., 2014; Medina et al., 2010; Zalesky et al., 2012) (for reviews see Baker et al., 2013; Batalla et al., 2013; Jacobus and Tapert, 2014; Lorenzetti et al., 2014). Initial iFC studies suggest that functional interactions within large-scale networks are also altered, though both weakened (Orr et al., 2013) and strengthened iFC (Behan et al., 2013), or a mixed pattern (Houck et al., 2013) have been observed. Most recently, Filbey et al. (2014) found strengthened iFC within orbitofrontal cortex in chronic cannabis users relative to controls, with earlier-onset users exhibiting the strongest iFC. The authors concluded that, in line with observations from task-based fMRI studies of chronic cannabis users (Batalla et al., 2013), strengthened iFC may reflect a compensatory adaptation, suggesting that chronic cannabis use is associated with complex neuroadaptive processes that remain to be fully understood.

It is important to understand how cannabis use interacts with neurocognitive vulnerabilities related to ADHD. The effects of cannabis use on brain functional organization in ADHD have not previously been examined; the current study addresses this research gap. We recruited a subsample of participants from a large multi-site longitudinal study of ADHD, the Multimodal Treatment Study of Children with ADHD (MTA), and used iFC analyses to examine the integrity of large-scale functional networks in young adults with and without a childhood diagnosis of ADHD who were either frequent users or non-users of cannabis. This 2 × 2 design permitted the assessment of main effects of ADHD diagnosis and cannabis use, as well as their interaction. Consistent with the pattern of neurocognitive deficits typically observed in ADHD, we expected to see relatively weakened iFC within circuits supporting executive function and somatomotor control. Although evidence concerning the effects of cannabis use on iFC is mixed, we expected that ADHD-related alterations would be exacerbated by cannabis use in this young sample.

2. Methods and materials

The MTA sample includes 579 individuals diagnosed in childhood with ADHD Combined Type, followed longitudinally at 2–3 year intervals since ascertainment and 14-month randomized-controlled trial treatment at age 7–9.9 years. It also includes 289 individuals matched for age and neighborhood who were recruited to a local normative comparison group (LNCG). Data for the present study were obtained when a subsample participated as 21–25 year olds in a multi-site neuroimaging protocol (6 sites: New York University, University of Pittsburgh, Universities of California, Irvine & Berkeley, Duke University, and Columbia University) aimed at examining the impact of cannabis use on brain structure and function in individuals with a childhood diagnosis of ADHD. The study was approved by each site's Institutional Review Board. Informed consent was obtained from all participants. All work was carried out in accordance with *The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.*

2.1. Participants

MTA participant demographics and procedures for initial diagnosis and treatment have been described (The MTA Cooperative Group,

1999). Participants were recruited to the neuroimaging study during the follow-up assessments at 14- and 16-years after MTA baseline. A total of 129 individuals participated, constituting 4 groups in a 2 × 2 design crossing childhood ADHD with current cannabis use: (1) individuals with a childhood diagnosis of ADHD who currently use cannabis (ADHD-CAN; $n = 44$); (2) individuals with a childhood diagnosis of ADHD who do not currently use cannabis (ADHD-NU; $n = 44$); (3) individuals from the LNCG who currently use cannabis (LNCG-CAN; $n = 20$); and (4) individuals from the LNCG who do not currently use cannabis (LNCG-NU; $n = 21$).

Of these 129 participants, 52 were excluded for the following reasons:

- Excessive motion during the resting state fMRI scan, defined as mean root mean square framewise displacement (rmsFD, Jenkinson et al., 2002) >0.15 mm or >30% of volumes exceeding 0.15 mm rmsFD (8 ADHD-CAN, 8 ADHD-NU, 2 LNCG-CAN, and 3 LNCG-NU).
- Incomplete resting state scan (1 ADHD-NU).
- Retrospective failure to meet study inclusion/exclusion criteria or inconsistencies between self- and other-reports of substance use (3 ADHD-CAN, 2 ADHD-NU).
- Incidental findings (1 ADHD-CAN, 1 ADHD-NU).
- Excessive susceptibility artifact (1 LNCG-NU).
- For CAN, less than weekly cannabis use (9 ADHD-CAN, 3 LNCG-CAN).
- For NU, at least 1 prior assessment point where weekly cannabis use was reported (8 ADHD-NU, 2 LNCG-NU).

Additionally, 2 female participants were selected at random to be excluded from the ADHD- NU group to reduce imbalanced sex ratios across groups.

Sample sizes and demographic details for each group following these exclusions, along with other relevant variables, are shown in Table 1.

Potential participants were identified based on self-reported cannabis use per the Substance Use Questionnaire (SUQ) and Substance Use Recency Questionnaire (SURQ) (Molina et al., 2013; Molina and Pelham, 2003). The SUQ assesses use of alcohol, tobacco products, cannabis, and other drugs over the past year; the SURQ assesses use of alcohol, tobacco products, cannabis, and other drugs over the past 30 days. The SUQ also measures age of onset of regular (weekly) use of cannabis and alcohol. For this study, participants reporting use of cannabis *at least weekly* during the past year or past 30 days were classified as CAN, and as NU if they reported using cannabis fewer than 4 times during the past year. Fig. 1 illustrates the reported frequency of cannabis use over the past year and past 30 days across the 4 groups, as well as the reported age of onset of regular cannabis use. From Fig. 1, we can see that in the ADHD-SU group, 4 participants reported abstaining from cannabis use in the past month. However, looking at their reported use over the past year, 2 of these 4 participants reported using cannabis several times a day, 1 reported using cannabis 1–3 times per week, and 1 reported using 4–6 times per week. No participants in the LNCG-SU group reported zero days of cannabis use in the past month. One participant in the LNCG-SU group reported using cannabis monthly over the past year, but reported 18 days of cannabis use over the past 30 days.

Supplementary Figs. S1 and S2 illustrate the reported frequency of alcohol consumption and cigarette smoking over the past year and past 30 days across the 4 groups, as well as the reported first age of alcohol intoxication and first age of regular smoking.

The majority of the participants with childhood ADHD still exhibited significant ADHD-related impairment (24 of 45 participants). Participants were classified as having "persistent" ADHD if they had either a self-report and/or a parent-report endorsing the "often" or "very frequent" experience of at least 4 symptoms in at least one ADHD domain (i.e., inattentive or hyperactive/impulsive). Participants were classified as "desistant" if both a self-report and a parent-report lacked an endorsement of symptom persistence. Only 3 participants (1 ADHD-CAN, 2 ADHD-NU) reported currently taking ADHD medication. The primary comorbidities were substance-related: Cannabis Dependence ($n = 5$), Cannabis Abuse ($n = 12$), Alcohol Dependence ($n = 1$), Alcohol Abuse ($n = 15$; results were unchanged when these participants were omitted, see Supplemental Information), Other Substance Abuse ($n = 3$). Additionally, 1 participant met criteria for Major Depressive Disorder, 1 for Hypomania, and 2 for Conduct Disorder.

Exclusionary criteria included MRI contraindications, neurologic injury or a history of traumatic brain injury, or current use of psychotropic medications other than for ADHD. Participants were excluded if they reported monthly or more frequent recreational use of illicit substances beside cannabis.

2.2. MRI data

Neuropsychological and neuroimaging data were collected during a single session. Participants abstained from cannabis and alcohol for 36 h, from over-the-counter and prescription medications (including ADHD medication) for 24 h, and from nicotine and caffeine for 1-h prior to data collection.

Neuropsychological measures (Tamm et al., 2013) were collected first, followed by a one-hour MRI session that included acquisition of structural (T1, T2, diffusion-weighted) and functional (task-independent, task-based) imaging data. These sessions took place at one of six sites, each equipped with a 3T MRI scanner.

2.2.1. Anatomical data

High-resolution anatomical T1-weighted volumes were acquired using a sagittal 3D inversion recovery spoiled gradient echo (IR-SPGR) sequence that was developed for the Pediatric Imaging, Neurocognition, and Genetics study (Brown et al., 2012 see Table 2).

2.2.2. Resting state fMRI (R-fMRI)

Resting state scan parameters are shown in Table 2. Participants were verbally instructed to "continue to stay still, keep your eyes open, and stay awake, even though you don't have to do anything during this part," and were shown a white fixation-cross in the center of a black screen.

2.3. R-fMRI data preprocessing

Data processing was performed using AFNI (http://afni.nimh.nih.gov/afni/), FSL (http://fsl.fmrib.ox.ac.uk), and ANTs (http://stnava.github.io/ANTs) and comprised (1) volume-based motion-correction, (2) grand-mean scaling, (3) linear and quadratic detrending (4) nuisance signal regression on 24 motion parameters (3 translational and

Table 1
Summary of demographic information for each of the 4 groups: ADHD-CAN (individuals with a childhood diagnosis of ADHD who currently use cannabis), ADHD-NU (ADHD participants who do not currently use cannabis), LNCG-CAN (local normative comparison group participants who currently use cannabis), and LNCG-NU (LNCG who do not currently use cannabis).

Group	N	Age (SD)	% female	% right-handed	IQ (SD)	% current ADHD	% smokers	# of alcohol binges in past 30 days (SD)	# of days if cannabis use in past 30 days (SD)	In-scanner motion: rmsFD (SD)
ADHD-CAN	23	24.7 (1.2)	4%	83%	103 (1.1)	61% (2 unknown)	56%	2.0 (0.3)	13.9 (0.9)	0.083 (0.002)
ADHD-NU	22	25.3 (1.3)	27%	50%	105.4 (1.5)	45% (3 unknown)	18%	2.3 (0.3)	0.1 (0.02)	0.085 (0.002)
LNCG-CAN	15	24.5 (1.3)	13%	87%	110.9 (2.0)	N/A	33%	2.8 (0.3)	19.5 (0.6)	0.08 (0.003)
LNCG-NU	15	24.4 (1.1)	33%	80%	111.5 (1.9)	N/A	7%	0.7 (0.1)	0.1 (0.02)	0.08 (0.002)

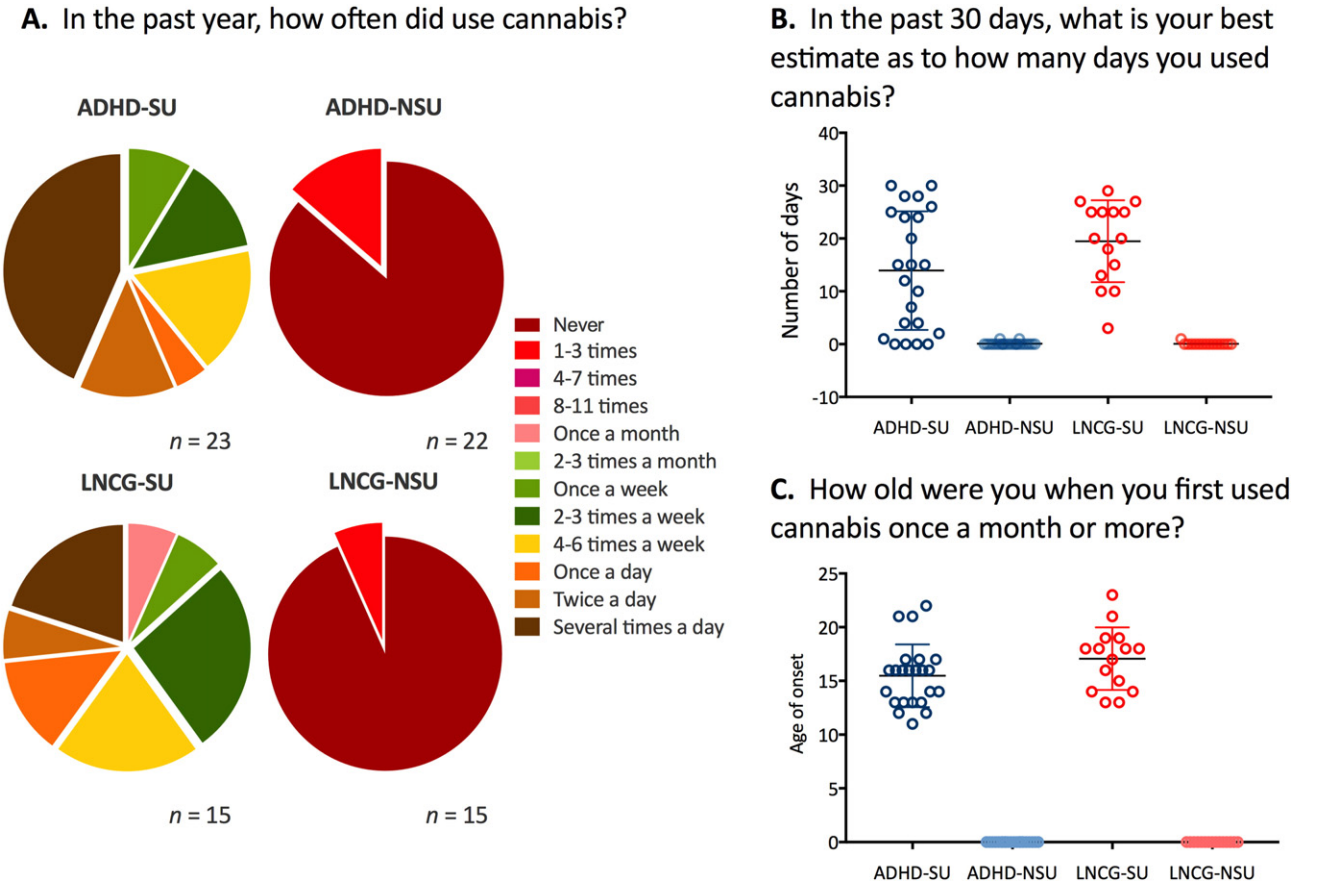

Fig. 1. Self-reported reported frequency of cannabis use over the past year (A) and past 30 days (B) across the 4 groups. (C) shows the self-reported age of onset of regular cannabis use in the SU groups.

3 rotational parameters describing participant motion at each TR, 6 parameters describing participant motion at TR-1, and the squares of these terms) and the global signal, (5) spatial smoothing (6 mm FWHM), and (6) band-pass temporal filtering (0.009–0.1 Hz).

Functional-to-anatomical co-registration was performed using FSL's implementation of bbr (boundary-based registration, Greve and Fischl, 2009). Diffeometric normalization of each participant's anatomical to MNI152 template space (2 mm resolution) was performed using ANTs. This nonlinear transformation to template space was also applied to the functional data.

2.4. Intrinsic functional connectivity analyses

We adopted a data-driven approach for detecting functional networks (intrinsic connectivity networks; ICNs). First, we performed an independent components analysis (ICA) of all participants' preprocessed data using FSL's Melodic (temporal concatenation mode). Dimensionality was free to vary. We then used FSL's Dual Regression to derive participant-level estimates of iFC within each of the 10 identified ICNs, simultaneously.

Next, using FSL's FEAT, a series of group-level 2 × 2 ANOVAs were performed to identify main and interacting effects of diagnostic group (ADHD/LNCG) and user status (CAN/NU) on iFC within each of 9 ICNs (one white matter ICN was excluded). Covariates were: data acquisition site, sex, age, handedness, IQ, motion (mean rmsFD), smoking status, and number of alcohol binges in the past month. Regions exhibiting a main effect of diagnosis or cannabis use or their interaction were identified using F-tests, spatially constrained to occur within the boundaries of the ICN identified during the initial ICA. Gaussian Random Field-based correction for multiple comparisons was performed, with an omnibus correction for the number of ICNs examined (9 ICNs; voxel-wise $Z > 2.77$, cluster-level $p < 0.0056$, corrected). Where a significant main effect or interaction was identified, post-hoc t-tests compared means between groups.

Table 2
Anatomical T1 and resting state fMRI data collection parameters across the 6 sites. Note that although UC Berkeley was one of the 6 MTA sites that took part in the current neuroimaging protocol, scanning for that site was performed at UCSF.

				Anatomical T1 parameters							R-fMRI parameters					
MTA site	Tesla	Make	Model	TR	TE	Flip angle	TI	Slice thickness	# slices	In-plane resolution	TR	TE	Flip angle	# TRs	Slice thickness	# slices
Duke University	3 T	GE	Discovery 750	8.04	3.156	8	600	1.2 mm	166	1x1mm	2000 ms	30 ms	77	180	5 mm	32
Columbia University	3 T	GE	Signa	7.756	2.976	8	600	1.2 mm	166	1x1mm	2000 ms	30 ms	77	180	5 mm	32
UC Irvine	3 T	Siemens	Trio	2170	4.33	7	1100	1.2 mm	160	1x1mm	2000 ms	30 ms	77	180	5 mm	32
UCSF	3 T	Siemens	Trio	2170	4.33	7	1100	1.2 mm	160	1x1mm	2000 ms	30 ms	77	180	5 mm	32
University of Pittsburgh	3 T	Siemens	Trio	2170	4.33	7	1100	1.2 mm	160	1x1mm	3000 ms	30 ms	90	128	3.5 mm	46
NYU	3 T	Siemens	Trio	2170	4.33	7	1100	1.2 mm	160	1x1mm	3000 ms	30 ms	90	128	3.5 mm	46

2.5. Post-hoc exploratory brain-behavior analyses

To explore the behavioral significance of our findings, we examined the relationship between iFC in regions exhibiting a main effect of diagnosis or cannabis use and targeted variables of interest. In addition to ADHD persistence (t-tests compared "persistent" and "desisted" participants), we examined measures selected from amongst the neuropsychological indices of executive function (EF) collected as part of the larger study (Tamm et al., 2013). Specifically, we explored brain-behavior relationships for (1) motor response inhibition [Go/NoGo percent commission errors], (2) cognitive interference [time to complete the Inhibition condition of the Delis-Kaplan Executive Function System Color Word Interference Task (D-KEFS-CWI); longer time indicates greater cognitive interference], (3) processing speed [time to complete the Trail Making Task Part B (TMT-B); longer time indicates slower processing speed], (4) risky decision-making [Iowa Gambling Task (IGT) net score, calculated as advantageous card choices minus disadvantageous card choices; higher net score indicates less risky choice behavior], and (5) delayed recall [measured using the Hopkins Verbal Learning Task (HVLT); higher scores indicate better recall]. The effects of diagnosis and cannabis use on the EF measures themselves have been described in Tamm et al. (2013). Before computing exploratory brain-behavior correlations, iFC and the behavioral scores were regressed on group analysis covariates (acquisition site (iFC data only), sex, age, handedness, IQ, mean rmsFD (iFC data only), smoking status, and number of alcohol binges in the past month).

3. Results

Independent components analysis of all participants' data with dimensionality free to vary identified 10 large-scale intrinsic connectivity networks (ICNs; Fig. 2), identified as: (Network (N)1) default, (N2) somatomotor, (N3) dorsal attention, (N4) cingulo-opercular (also known as the salience network), (N5) medial visual, (N6) white matter and cerebrospinal fluid, (N7) lateral visual, (N8) right hemisphere frontoparietal, (N9) left hemisphere frontoparietal, and (N10) a predominantly subcortical network involving amygdala, putamen, and thalamus but also posterior components of the default network, including hippocampus and lateral temporal cortex.

3.1. Main effects of ADHD

Significant main effects of diagnosis were detected in 4 ICNs.

Within the somatomotor network (N2; Fig. 3A), two large regions comprising left and right lateral and medial motor cortex (cluster (c)1 and c2 in Fig. 3B, respectively) exhibited weaker iFC in ADHD relative to LNCG (Fig. 3C).

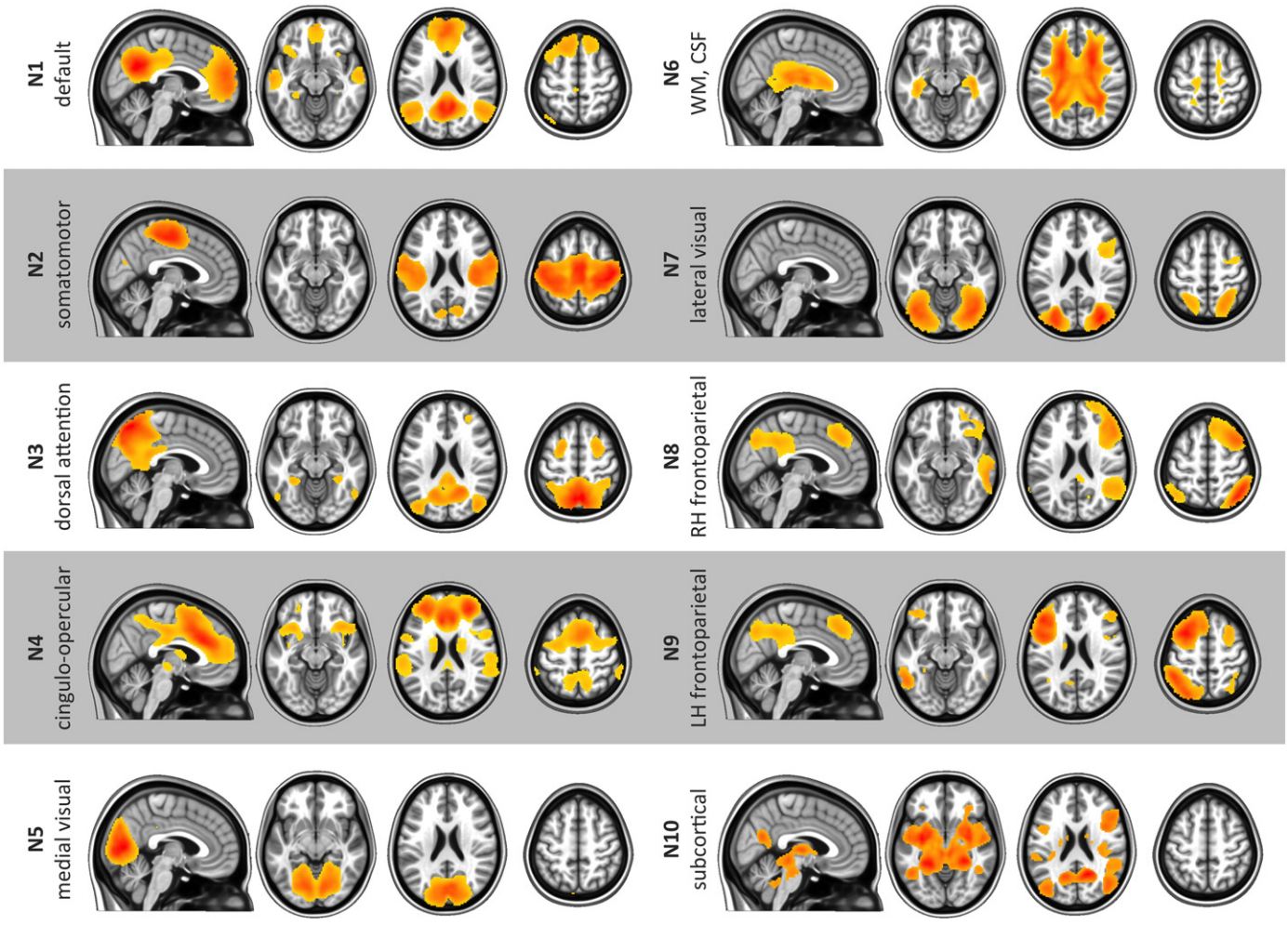

Fig. 2. Ten intrinsic connectivity networks (ICNs) revealed by ICA of all participants' data. The networks are identified as follows: (N1) default, (N2) somatomotor, (N3) dorsal attention, (N4) cingulo-opercular (also known as the salience network), (N5) medial visual, (N6) white matter and cerebrospinal fluid, (N7) lateral visual, (N8) right hemisphere frontoparietal, (N9) left hemisphere frontoparietal, and (N10) a predominantly subcortical network involving amygdala, putamen, and thalamus but also posterior components of the default network, including hippocampus, retrosplenial and lateral temporal cortex. Each map shows the group-level iFC within each ICN, with Gaussian Random Field-based correction for multiple comparisons (voxel-wise $Z > 2.3$, cluster-level $p < 0.05$, corrected). Images are displayed according to neurological convention (right is right).

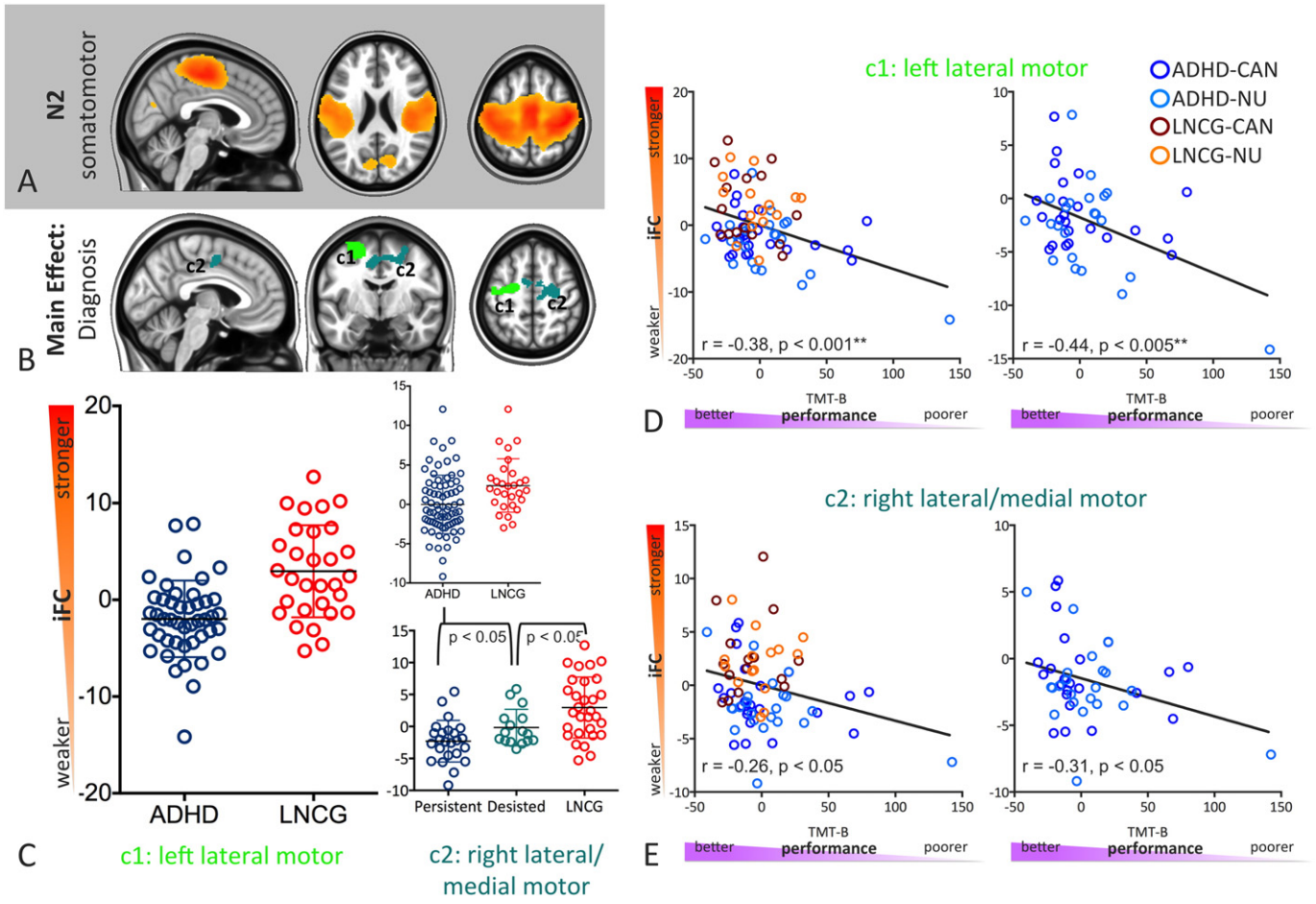

Fig. 3. Significant main effects of ADHD diagnosis and brain-behavior relationships for N2, the somatomotor network. Panel (A) displays the network within which we tested for main and interacting effects of diagnostic group (ADHD/LNCG) and user status (CAN/NU) on iFC. (B) shows the two clusters within N2 that exhibited a main effect of ADHD diagnosis: both c1 in left lateral primary motor cortex and c2 in right lateral and medial primary motor and supplementary motor cortex exhibited weaker iFC in ADHD relative to LNCG (C). The right hemisphere lateral/medial motor region (c2) exhibited an effect of ADHD persistence, such that individuals who were classified as having persistent ADHD exhibited the weakest iFC, while individuals who were classified as desisted exhibited iFC that was intermediate between those with persistent ADHD and the LNCG participants. Functional connectivity within both c1 and c2 exhibited a significant negative correlation with processing speed (time to complete TMT-B), both across all participants and within the ADHD group alone (relationships for c1 are shown in D, relationships for c2 are shown in E). **Indicates a brain-behavior relationship significant at $p < 0.0083$ (i.e., corrected for the number of associations explored for each cluster). *Please note that on the plots, iFC below 0* ***does not indicate*** *negative iFC, but weaker within-network iFC; iFC values are zero-centered because they have been regressed on nuisance covariates (data acquisition site, sex, age, handedness, IQ, participant motion, smoking status, recent alcohol binges). Scores on behavioral measures are similarly zero-centered because they have also been regressed on nuisance covariates (sex, age, handedness, IQ, smoking status, recent alcohol binges).* Regions exhibiting a main effect of diagnosis or cannabis use or their interaction were identified using F-tests, spatially constrained to occur within the boundaries of the ICN identified during the initial ICA. Gaussian Random Field-based correction for multiple comparisons was performed, with an omnibus correction for the number of ICNs examined (9 ICNs; voxel-wise $Z > 2.77$, cluster-level $p < 0.0056$, corrected). Images are displayed according to neurological convention (right is right).

Within the dorsal attention network (N3; Fig. 4A), a region in right posterior parietal cortex, in the posterior intraparietal sulcus (Fig. 4B), exhibited stronger iFC in ADHD relative to LNCG (Fig. 4C).

Within the cingulo-opercular network (N4; Fig. 5A), one region in left inferior premotor cortex (Brodmann's Area 6; c1 in Fig. 5B) exhibited stronger iFC in ADHD relative to LNCG (Fig. 5C), while a second region in right dorsal prefrontal cortex (c2 in Fig. 5B) exhibited weaker connectivity in ADHD relative to LNCG (Fig. 5C).

Finally, within the right hemisphere-based frontoparietal network (N8; Fig. 6A), iFC in the right inferior frontal junction (Fig. 6B) was weaker in ADHD relative to LNCG (Fig. 6C).

3.2. Main effects of CAN

Significant main effects of cannabis use history were detected in 2 ICNs.

Within the default network (N1; Fig. 6A), iFC in the right superior temporal sulcus (STS; Fig. 7B) exhibited stronger iFC in CAN relative to NU (Fig. 7C). Within the lateral visual network (N7; Fig. 8A), left fusiform gyrus (Fig. 8B) also exhibited stronger iFC in CAN relative to NU (Fig. 8C).

3.3. Interactions

No significant interactions between ADHD diagnosis and cannabis use status were observed.

3.4. Post-hoc exploratory brain-behavior analyses

To explore the behavioral significance of our findings, we examined the relationship between iFC in regions exhibiting significant effects of diagnosis or cannabis use and a set of targeted EF measures. The effects of diagnosis and cannabis use on the EF measures themselves have been described in Tamm et al. (2013). In brief, Tamm et al. found that while ADHD diagnosis was associated with significant impairment across a range of executive function indices, there were few effects of cannabis use status. Here, we focused on a subset of the indices examined by Tamm et al., namely, (1) motor response inhibition (percent Go/NoGo commission errors), (2) cognitive interference (time to complete the

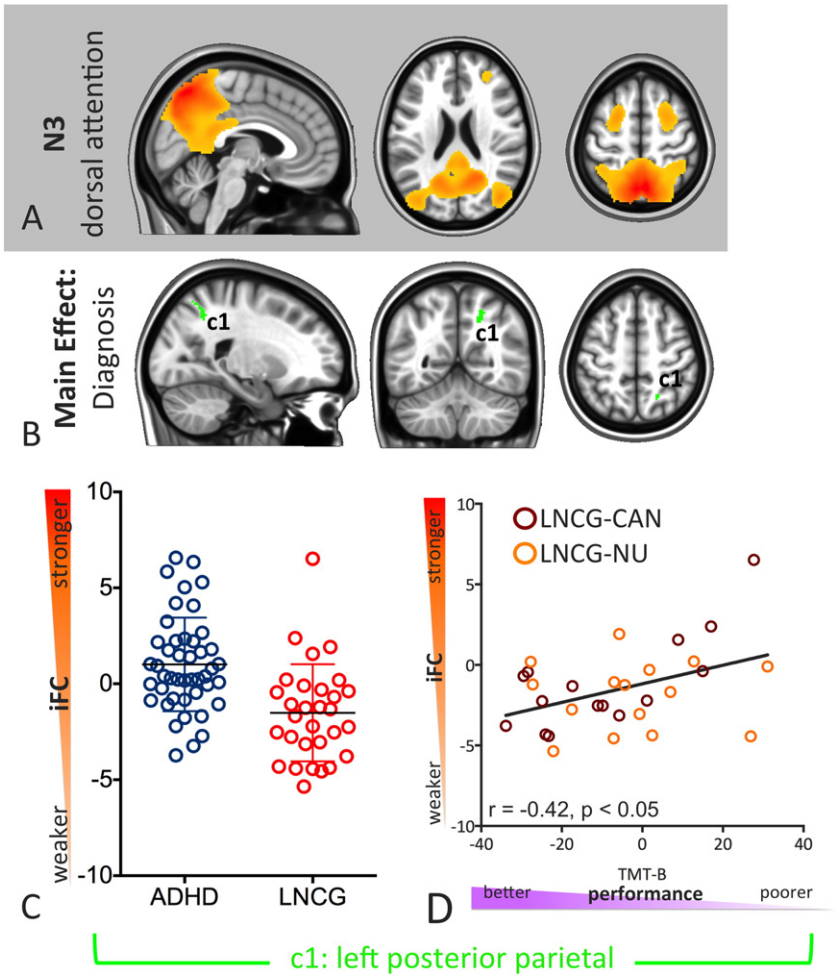

Fig. 4. Significant main effects of ADHD diagnosis and brain-behavior relationships for N3, the dorsal attention network. Panel (A) displays N3. (B) shows the posterior intraparietal sulcus cluster that exhibited a main effect of ADHD diagnosis (ADHD > LNCG; C). Panel D displays the brain-behavior relationship observed for the region shown in (B): iFC within this region was positively correlated with processing speed amongst LNCG participants only (Fig. 3D), indicating that stronger iFC within this region was associated with slower processing speed.

Inhibition condition of the D-KEFS-CWI), (3) processing speed (time to complete TMT-B), (4) risky behavior (IGT net score), and (5) HVLT delayed recall. Across these indices, the effects and trends associated with diagnostic group and cannabis status were the same as those observed by Tamm et al., albeit sometimes weaker due to the more limited sample size examined here (75 participants rather than 128). These examinations of brain-behavior relationships were exploratory; we have therefore reported findings that were significant at an uncorrected $p < 0.05$, as well as those significant when corrected for the number of associations explored for each cluster (6; $p < 0.0083$).

3.4.1. Exploratory brain-behavior relationships in regions exhibiting an effect of diagnosis

Within the somatomotor network (N2), the right hemisphere lateral/medial motor region that exhibited a significant effect of diagnosis (ADHD < LNCG) also exhibited an effect of ADHD persistence (Fig. 3C; $t(2,44) = 2.13$; $p < 0.05$), such that individuals with persistent ADHD exhibited the weakest iFC, while desisters exhibited iFC that was intermediate between those with persistent ADHD and LNCG participants, though still significantly weaker than LNCG [$t(2,44) = 2.40$; $p < 0.05$]. Additionally, for both somatomotor regions that exhibited a diagnostic effect (Fig. 3B, C), iFC was negatively correlated with processing speed (time to complete TMT-B): weaker iFC within these regions was associated with slower processing speed.

Within the dorsal attention network (N3), iFC in right posterior parietal cortex (ADHD > LNCG; Fig. 4B) was positively correlated with processing speed amongst LNCG participants only (Fig. 4D), indicating stronger iFC within this region was associated with slower processing speed.

Within the cingulo-opercular network (N4), iFC in left inferior premotor region (ADHD > LNCG; Fig. 5B) was negatively correlated with D-KEFS-CWI Inhibition Time, across all participants as well as within the ADHD group alone (Fig. 5D), indicating stronger iFC in this region was associated with less cognitive interference.

Finally, within the right frontoparietal network (N8), iFC within the right inferior frontal junction (ADHD < LNCG; Fig. 6B) exhibited several significant relationships. Across all participants and within LNCG alone, a positive correlation was observed with IGT net score (Fig. 6D), indicating that weaker iFC was associated with more risky choices. Within LNCG, a negative correlation between iFC and processing speed (TMT-B) was also observed, indicating weaker iFC was associated with slower information processing (Fig. 6E). Last, across all participants, a negative correlation was observed between iFC and D-KEFS-CWI Inhibition Time (Fig. 6F), indicating weaker iFC in this region was also associated with greater cognitive interference.

3.4.2. Exploratory brain-behavior relationships in regions exhibiting a main effect of cannabis use

Within the default network (N1), iFC in the right STS (CAN > NU; Fig. 7B) exhibited a positive correlation with HVLT delayed recall, both across all participants and in the NU group alone (Fig. 7D), indicating

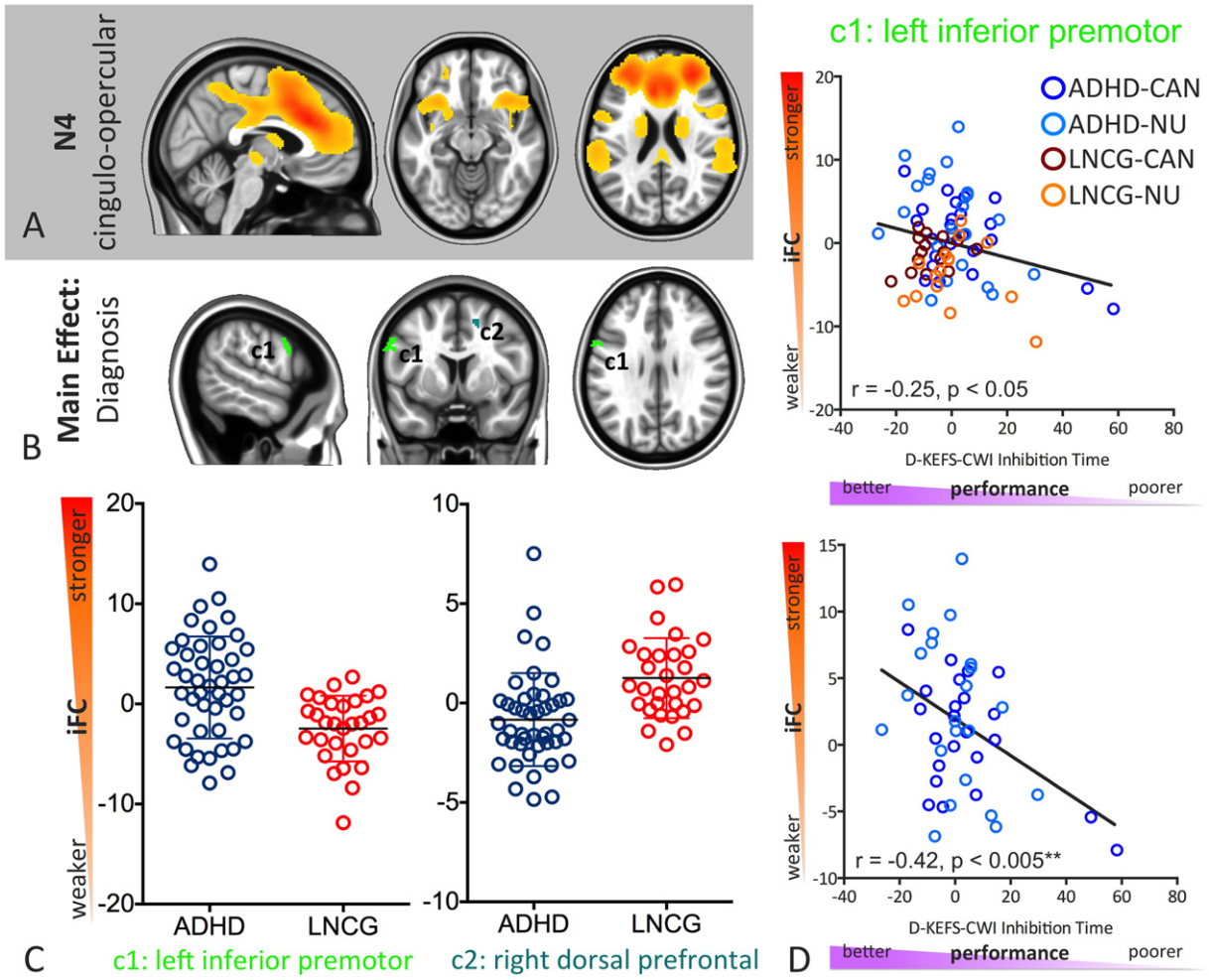

Fig. 5. Significant main effects of ADHD diagnosis and brain-behavior relationships for N4, the cingulo-opercular network. Panel (A) displays N4. (B) shows the two clusters within N4 that exhibited a main effect of ADHD diagnosis: c1, in left inferior premotor cortex (Brodmann's Area 6) exhibited stronger iFC in ADHD relative to LNCG (C, left), while c2, in right dorsal prefrontal cortex exhibited weaker connectivity in ADHD relative to LNCG (C, right). Panel D displays the brain-behavior relationship observed for c1: iFC within this region was negatively correlated with D-KEFS-CWI Inhibition Time, across all participants (D, upper) as well as within the ADHD group alone (D, lower). This relationship indicates that stronger iFC in this region was associated with less cognitive interference. **Indicates a brain-behavior relationship significant at $p < 0.0083$ (i.e., corrected for the number of associations explored for each cluster).

that those with stronger iFC in this network exhibited the best delayed recall performance.

Within the lateral visual network (N7), iFC in left fusiform gyrus (CAN > NU; Fig. 8B) exhibited a significant negative correlation with Go/NoGo commission errors (Fig. 8D) amongst CAN, suggesting that stronger iFC was associated with better inhibitory control. The same region also exhibited a significant negative relationship with D-KEFS-CWI Inhibition Time, indicating stronger iFC in this region was also associated with less cognitive interference, across all participants and amongst NU (Fig. 8E).

4. Discussion

We examined whether frequent cannabis use interacts with a childhood diagnosis of ADHD to affect the integrity of large-scale functional networks. Consistent with our primary hypothesis, we observed predominantly weaker iFC in ADHD relative to comparisons in networks supporting somatomotor and executive function (EF). Contrary to expectations, the effects of cannabis use were distinct from those of diagnostic group; there were no interacting effects, and the relatively restricted main effects of cannabis use were observed in different functional networks (the default and lateral visual networks). These findings are in line with those of Tamm et al. (2013), who examined neurocognitive performance in an overlapping sample – while individuals with a childhood diagnosis of ADHD exhibited decrements in EFs such as response inhibition and decision-making, there were no significant effects of recent cannabis use and no interactions between ADHD history and cannabis use. Task-based fMRI data collected from an overlapping sample of participants while they performed a Go/NoGo task revealed a similar pattern (Rasmussen et al., 2015), as did an analysis of cortical thickness (Lisdahl et al., 2016). Taken together, these data suggest that weekly cannabis use does not exacerbate underlying neuronal vulnerabilities in individuals with a childhood diagnosis of ADHD. However, this conclusion must be viewed in the context of several limitations, as discussed below.

4.1. Childhood diagnosis of ADHD and iFC

A key phenotypic feature of ADHD is motor dysregulation; deficits in motor control, such as impaired motor inhibition and increased response time variability, are the most consistently observed neurocognitve deficits across studies (Rasmussen et al., 2015). Here, the most salient effect of a childhood diagnosis of ADHD was weakened iFC within the somatomotor network. This agrees with a previous effort that aimed to identify iFC-based signatures of ADHD, which found that abnormalities in sensorimotor cortex iFC were common to both Combined and Inattentive subtypes (Fair et al., 2012). Strikingly, we found that iFC within the somatomotor network was also related to performance on the TMT-B,

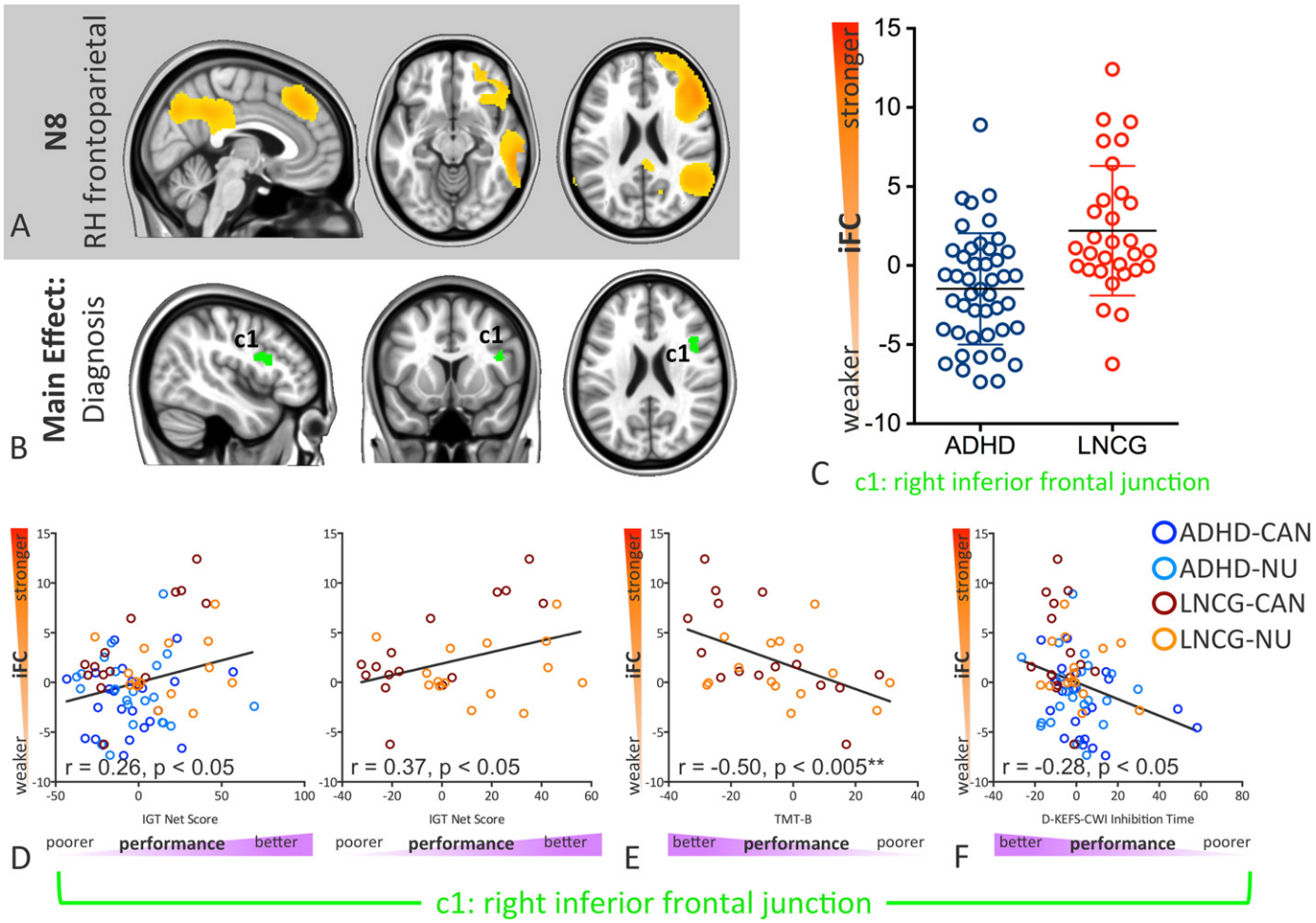

Fig. 6. Significant main effects of ADHD diagnosis and brain-behavior relationships for N8, the right-hemisphere frontoparietal network. Panel (A) displays N8. (B) shows the right inferior frontal junction region that exhibited weaker iFC in ADHD relative to LNCG (C). Functional connectivity within this cluster exhibited several brain-behavior relationships. Panel (D) shows the significant positive relationship obtained across all participants (D, left) and within LNCG alone (D, right) between iFC and IGT net score, indicating that stronger iFC in this region was associated with less risky choice on the IGT. Panel (E) shows a negative correlation between iFC and processing speed (TMT-B) within LNCG, indicating that stronger iFC was associated with more rapid information processing. Panel (F) shows a negative correlation observed across all participants between iFC and D-KEFS-CWI Inhibition Time, indicating that stronger iFC in this region was also associated with less cognitive interference. **Indicates a brain-behavior relationship significant at $p < 0.0083$ (i.e., corrected for the number of associations explored for each cluster).

such that those with the slowest processing speeds exhibited the weakest iFC. The areas implicated overlap with regions activated in an fMRI study of a computerized analogue of the TMT-B task (Jacobson et al., 2011). Finally, iFC within the somatomotor network was weakest in those with persistent ADHD. This suggests that ADHD-related deficits in somatomotor network integrity may ameliorate for those whose symptoms decrease. Importantly, however, iFC in remitters was still significantly weaker than in LNCG. This finding is consistent with observations, primarily from structural imaging, that although some neuronal effects of ADHD may reflect neurodevelopmental delays that "normalize" with remission (Shaw et al., 2013, 2015), others persist (e.g., Cortese et al., 2013; Proal et al., 2011). Our data thus support the suggestion that ADHD-related reductions in the integrity of the somatomotor network are central to the neuronal phenotype of ADHD and are a good candidate for imaging-based prediction of ADHD diagnosis (Fair et al., 2012).

Deficits in EF represent a second key neurocognitive dimension of impairment in ADHD. Consistent with this, ADHD-related reductions in iFC were also observed within the frontoparietal network – specifically, within the right inferior frontal junction (IFJ). Examining an overlapping sample of participants, Rasmussen et al. (2015) detected weaker task-related activation during a Go/NoGo task in primarily right-lateralized frontoparietal regions, including IFJ. These observations are in line with a meta-analysis of 55 fMRI studies of ADHD, which found that virtually all regions of reported ADHD-related hypoactivity in adults were located in the frontoparietal network (Fair et al., 2012). Studies of iFC have also repeatedly highlighted ADHD-related frontoparietal network dysconnectivity (Rasmussen et al., 2015). These ADHD-related alterations in frontoparietal iFC have been linked with both symptoms and EF (Lin et al., 2015). Here, we found that iFC within the IFJ was significantly correlated with several EF indices, including risky choice (Fig. 6D), visuomotor processing speed (Fig. 6E), and cognitive interference (Fig. 6F), consistent with a hypothesized role for the IFJ as a nexus in the executive control of behavior (e.g., Brass et al., 2005; Derrfuss et al., 2005; Levy and Wagner, 2011),

Although individuals with childhood ADHD predominantly exhibited weakened iFC relative to LNCG, they exhibited strengthened iFC in two networks. The brain-behavior relationship observed for the dorsal attention network (Fig. 4B) suggests that stronger integration of right posterior parietal cortex within that network is maladaptive, as it was associated with slower processing speed in LNCG participants. In contrast, stronger integration of left inferior premotor region within the cingulo-opercular network was associated with less cognitive interference (Fig. 5D), suggesting that ADHD-related strengthening of iFC within the cingulo-opercular network may reflect a compensatory

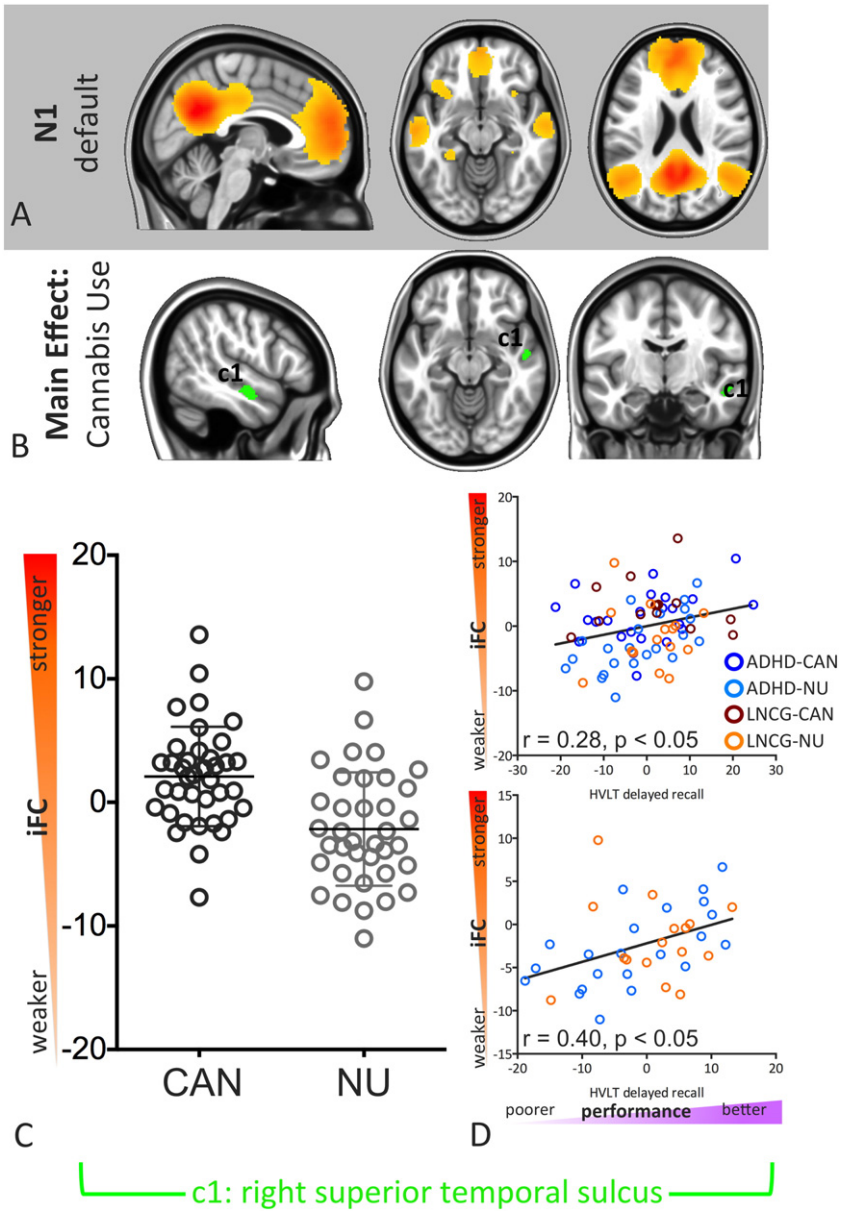

Fig. 7. Significant main effects of cannabis use and brain-behavior relationships for N1, the default network. Panel (A) displays N1. (B) shows the right STS cluster that exhibited a main effect of cannabis use (CAN > NU; C). Panel D displays the brain-behavior relationship observed for the region shown in (B): iFC within this region was positively correlated with HVLT delayed recall, both across all participants (D, upper) and in the NU group alone (D, lower). This relationship suggests that those with stronger iFC in this region exhibited the best delayed recall performance.

adaptation - the strengthening of connections or recruitment of additional brain regions in the service of maintaining normal cognitive performance.

4.2. Effects of frequent cannabis use on iFC

We expected that weekly cannabis use would be associated with deficits in iFC, particularly when combined with a childhood diagnosis of ADHD. This hypothesis was not confirmed, however, and the pattern of brain-behavior relationships observed for the two loci of cannabis use-related alterations in iFC are suggestive of neuroadaptive processes in CAN. Within right STS, which was more strongly integrated within the default network in CAN, stronger iFC was associated with superior delayed recall (Fig. 7). Similarly, within left fusiform gyrus, which was more strongly integrated within the lateral visual network in CAN, stronger iFC was associated with (a) better response inhibition performance and (b) reduced cognitive interference (Fig. 8). These observations may be viewed as consistent with a recent systematic review of functional and structural MRI studies of chronic cannabis users (Batalla et al., 2013), which reported a pattern of predominantly *increased* task-related activation in cannabis users, relative to controls, across studies. The authors attributed this pattern to compensatory neuroadapation. Our observations are also in line with the near-absence of EF deficits associated with recent cannabis exposure in an overlapping sample (Tamm et al., 2013). It is important to note that this set of findings does not mean that negative effects of cannabis use on brain function are not observed, however. Indeed, analyses examining the impact of age of onset suggest that early age of regular cannabis use onset in participants with ADHD is associated with additional structural abnormalities (Lisdahl et al., 2016) and executive function deficits (Tamm et al., 2013). As emphasized by Batalla et al. (2013), large-scale, prospective, longitudinal studies are required to fully delineate the evolution of such effects and the long-term impact of cannabis use on cognitive function and behavior, particularly when use is initiated in adolescence and in the context of

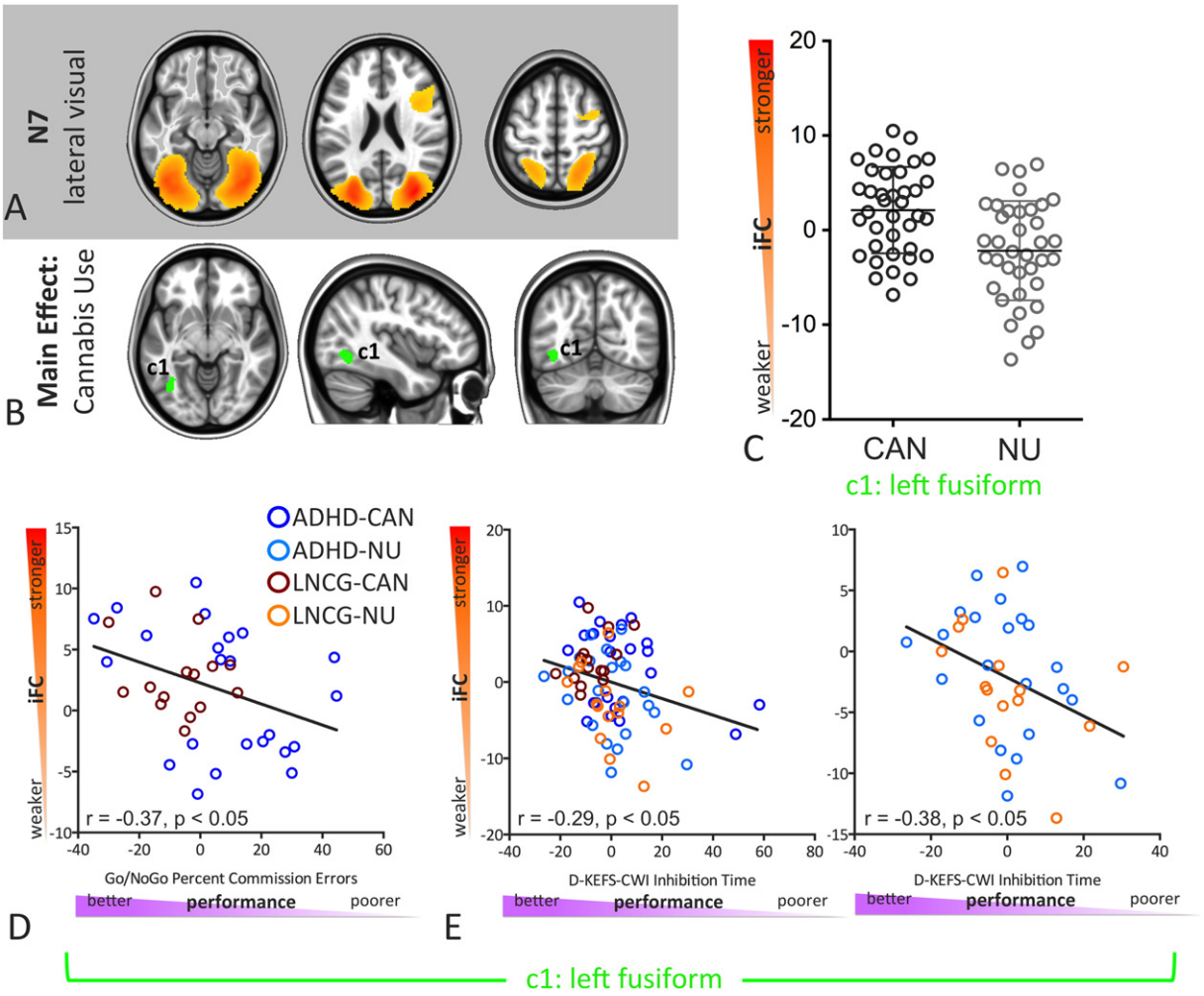

Fig. 8. Significant main effects of cannabis use and brain-behavior relationships for N7, the lateral visual network. Panel (A) displays N7. (B) shows the left fusiform gyrus cluster that exhibited a main effect of cannabis use (CAN > NU; C). Two brain-behavior relationships were observed for the region shown in (B): iFC exhibited a significant negative correlation with inhibitory control (Go/NoGo commission errors) amongst CAN, suggesting that stronger iFC was associated with better inhibitory control (D). This region also exhibited a significant negative relationship with D-KEFS-CWI Inhibition Time, indicating that stronger iFC in this region was also associated with less cognitive interference, both across all participants (E, left) and amongst NU (E, right).

neurodevelopmental disorders such as ADHD. Current societal movements toward legalization of cannabis use render such studies all the more urgent.

4.3. Limitations

Our findings should be viewed in the context of several limitations. First is that while recruiting from the MTA sample provided a unique and invaluable opportunity to assess brain functional architecture in individuals with childhood ADHD who have been followed longitudinally since middle childhood, our final sample, once divided into 4 groups, was relatively small. Consequently, even though studies have shown that acute (An et al., 2013; Cary et al., 2016; Hong et al., 2015; Yang et al., 2016) and long-term (Battel et al., 2016) stimulant treatment can alter network functional connectivity in ADHD, we were unable to leverage the rich longitudinal phenotypic data available for MTA participants (e.g., treatment received, symptom trajectories) due to the prohibitively small samples remaining once participants were stratified accordingly. Future analyses of data collected as part of the larger MTA study will examine important questions related to the effects of cumulative exposure to ADHD medications over time on neurocognitive performance and brain function; unfortunately such questions could not be addressed in the current study.

Small sample size may have proved particularly problematic for detecting the effects of cannabis use, and impaired our ability to explore brain-behavior relationships in depth. Though similarly few effects were seen in an examination of neurocognitive data collected from an overlapping sample of participants, exploratory analyses of the effects of age of onset of use suggested that younger age of onset was associated with poorer neurocognitive performance (Tamm et al., 2013). Given evidence (e.g., Batalla et al., 2013) of compensatory neuroadaptation to cannabis use, as well as evidence of greater effects with greater chronicity of use (Lisdahl et al., 2014), studies in larger longitudinal samples are required before we can conclude that cannabis use in the context of a childhood diagnosis of ADHD does not have a negative impact on brain functional organization.

Our investigation of the effects of cannabis use may also have been subject to other limitations. First, cannabis usage was obtained via self-report; some users may not have admitted to use or may have inaccurately reported frequency or age of initiation. Second, although we focused on those reporting *at least* weekly use, this may still not have been sufficient to be associated with detectable effect sizes, particularly given the sample size. Third, duration of cannabis use was unknown, though the mean reported age of onset of monthly use was approximately 16 years (see Fig. 1) and the mean age of the participants when they took part in this imaging study was approximately 25 years. Finally, the effects of other substances (alcohol, nicotine) may be larger or

more widespread than those of cannabis (Weiland et al., 2015); controlling for these confounds may have further weakened our ability to detect cannabis effects.

4.4. Conclusions

Reduced integrity of large-scale functional networks, particularly those supporting executive function and somatomotor control, appears to be a persistent correlate of a childhood diagnosis of ADHD. While cannabis use does not appear to reflect a strong confound in iFC studies of ADHD, replication of our observations in larger-scale longitudinal studies is required. Longitudinal neuroimaging studies are demanding, costly, and complex. However such studies are absolutely essential to our ability to unravel and ultimately intervene in the neurodevelopmental cascade that culminates in positive and negative long-term outcomes for those diagnosed with ADHD in childhood.

Financial disclosures

None.

Acknowledgements

Data collection and sharing for this project was funded by the NIDA MTA Neuroimaging Study (National Institute on Drug Abuse Grant Contract #: HHSN271200800009C). MTA data analysis was supported by NIDA (R01 DA039881, PI: Molina). Manuscript preparation and publication was supported by a grant from the National Institute of Mental Health (R03MH104334, PI: Kelly) and a Pathfinder award from Trinity College Dublin (PI: Kelly).

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2016.09.012.

References

An, L., Cao, X.-H., Cao, Q.-J., Sun, L., Yang, L., Zou, Q.-H., Katya, R., Zang, Y.-F., Wang, Y.-F., 2013. Methylphenidate normalizes resting-state brain dysfunction in boys with attention deficit hyperactivity disorder. Neuropsychopharmacology 38:1286–1294. http://dx.doi.org/10.1038/npp.2013.27.

Arnone, D., Barrick, T.R., Chengappa, S., Mackay, C.E., Clark, C.A., Abou-Saleh, M.T., 2008. Corpus callosum damage in heavy marijuana use: preliminary evidence from diffusion tensor tractography and tract-based spatial statistics. NeuroImage 41: 1067–1074. http://dx.doi.org/10.1016/j.neuroimage.2008.02.064.

Baker, S.T.E., Yücel, M., Fornito, A., Allen, N.B., Lubman, D.I., 2013. A systematic review of diffusion weighted MRI studies of white matter microstructure in adolescent substance users. Neurosci. Biobehav. Rev. 37:1713–1723. http://dx.doi.org/10.1016/j.neubiorev.2013.06.015.

Batalla, A., Bhattacharyya, S., Yücel, M., Fusar-Poli, P., Crippa, J.A., Nogué, S., Torrens, M., Pujol, J., Farré, M., Martín-Santos, R., 2013. Structural and functional imaging studies in chronic cannabis users: a systematic review of adolescent and adult findings. PLoS One 8, e55821. http://dx.doi.org/10.1371/journal.pone.0055821.

Battel, L., Kieling, R.R., Kieling, C., Anés, M., Aurich, N.K., da Costa, J.C., Rohde, L.A., Franco, A.R., 2016. Intrinsic brain connectivity following long-term treatment with methylphenidate in children with attention-deficit/hyperactivity disorder. J. Child Adolesc. Psychopharmacol. 26:555–561. http://dx.doi.org/10.1089/cap.2015.0221.

Battistella, G., Fornari, E., Annoni, J.-M., Chtioui, H., Dao, K., Fabritius, M., Favrat, B., Mall, J.-F., Maeder, P., Giroud, C., 2014. Long-term effects of cannabis on brain structure. Neuropsychopharmacology 39:2041–2048. http://dx.doi.org/10.1038/npp.2014.67.

Behan, B., Connolly, C.G., Datwani, S., Doucet, M., Ivanovic, J., Morioka, R., Stone, A., Watts, R., Smyth, B., Garavan, H., 2013. Response inhibition and elevated parietal-cerebellar correlations in chronic adolescent cannabis users. Neuropharmacology 84:131–137. http://dx.doi.org/10.1016/j.neuropharm.2013.05.027.

Bossong, M.G., Niesink, R.J.M., 2010. Adolescent brain maturation, the endogenous cannabinoid system and the neurobiology of cannabis-induced schizophrenia. Prog. Neurobiol. 92:370–385. http://dx.doi.org/10.1016/j.pneurobio.2010.06.010.

Brass, M., Derrfuss, J., Forstmann, B., von Cramon, D.Y., 2005. The role of the inferior frontal junction area in cognitive control. Trends Cogn. Sci. 9:314–316. http://dx.doi.org/10.1016/j.tics.2005.05.001 Regul Ed.

Brown, T.T., Kuperman, J.M., Chung, Y., Erhart, M., McCabe, C., Hagler, D.J., Venkatraman, V.K., Akshoomoff, N., Amaral, D.G., Bloss, C.S., Casey, B.J., Chang, L., Ernst, T.M., Frazier, J.A., Gruen, J.R., Kaufmann, W.E., Kenet, T., Kennedy, D.N., Murray, S.S., Sowell, E.R., Jernigan, T.L., Dale, A.M., 2012. Neuroanatomical assessment of biological maturity. Curr. Biol. 22:1693–1698. http://dx.doi.org/10.1016/j.cub.2012.07.002.

Cary, R.P., Ray, S., Grayson, D.S., Painter, J., Carpenter, S., Maron, L., Sporns, O., Stevens, A.A., Nigg, J.T., Fair, D.A., 2016. Network structure among brain systems in adult ADHD is uniquely modified by stimulant administration. Cereb. Cortex http://dx.doi.org/10.1093/cercor/bhw209.

Castellanos, F.X., Aoki, Y., 2016. Intrinsic functional connectivity in attention-deficit/hyperactivity disorder: a science in development. Biol. Psychiatry 1:253–261. http://dx.doi.org/10.1016/j.bpsc.2016.03.004.

Castellanos, F.X., Proal, E., 2012. Large-scale brain systems in ADHD: beyond the prefrontal-striatal model. Trends Cogn. Sci. 16:17–26. http://dx.doi.org/10.1016/j.tics.2011.11.007.

Charach, A., Yeung, E., Climans, T., Lillie, E., 2011. Childhood attention-deficit/hyperactivity disorder and future substance use disorders: comparative meta-analyses. J. Am. Acad. Child Adolesc. Psychiatry 50:9–21. http://dx.doi.org/10.1016/j.jaac.2010.09.019.

Cortese, S., Kelly, C., Chabernaud, C., Proal, E., Di Martino, A., Milham, M.P., Castellanos, F.X., 2012. Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. Am. J. Psychiatry 169:1038–1055. http://dx.doi.org/10.1176/appi.ajp.2012.11101521.

Cortese, S., Imperati, D., Zhou, J., Proal, E., Klein, R.G., Mannuzza, S., Ramos-Olazagasti, M.A., Milham, M.P., Kelly, C., Castellanos, F.X., 2013. White matter alterations at 33-year follow-up in adults with childhood attention-deficit/hyperactivity disorder. Biol. Psychiatry 74:591–598. http://dx.doi.org/10.1016/j.biopsych.2013.02.025.

Cubillo, A., Halari, R., Smith, A., Taylor, E., Rubia, K., 2012. A review of fronto-striatal and fronto-cortical brain abnormalities in children and adults with attention deficit hyperactivity disorder (ADHD) and new evidence for dysfunction in adults with ADHD during motivation and attention. Cortex 48:194–215. http://dx.doi.org/10.1016/j.cortex.2011.04.007.

Derrfuss, J., Brass, M., Neumann, J., von Cramon, D.Y., 2005. Involvement of the inferior frontal junction in cognitive control: meta-analyses of switching and Stroop studies. Hum. Brain Mapp. 25:22–34. http://dx.doi.org/10.1002/hbm.20127.

Di Martino, A., Fair, D.A., Kelly, C., Satterthwaite, T.D., Castellanos, F.X., Thomason, M.E., Craddock, R.C., Luna, B., Leventhal, B.L., Zuo, X.-N., Milham, M.P., 2014. Unraveling the miswired connectome: a developmental perspective. Neuron 83:1335–1353. http://dx.doi.org/10.1016/j.neuron.2014.08.050.

Downer, E.J., Campbell, V.A., 2010. Phytocannabinoids, CNS cells and development: a dead issue? Drug Alcohol Rev. 29:91–98. http://dx.doi.org/10.1111/j.1465-3362.2009.00102.x.

Fair, D.A., Nigg, J.T., Iyer, S., Bathula, D., Mills, K.L., Dosenbach, N.U.F., Schlaggar, B.L., Mennes, M., Gutman, D., Bangaru, S., Buitelaar, J.K., Dickstein, D.P., Di Martino, A., Kennedy, D.N., Kelly, C., Luna, B., Schweitzer, J.B., Velanova, K., Wang, Y.-F., Mostofsky, S., Castellanos, F.X., Milham, M.P., 2012. Distinct neural signatures detected for ADHD subtypes after controlling for micro-movements in resting state functional connectivity MRI data. Front. Syst. Neurosci. 6:80. http://dx.doi.org/10.3389/fnsys.2012.00080.

Faraone, S.V., Asherson, P., Banaschewski, T., Biederman, J., Buitelaar, J.K., Ramos-Quiroga, J.A., Rohde, L.A., Sonuga-Barke, E.J.S., Tannock, R., Franke, B., 2015. Attention-deficit/hyperactivity disorder. Nat. Rev. Dis. Primers:15020–15023 http://dx.doi.org/10.1038/nrdp.2015.20.

Filbey, F.M., Aslan, S., Calhoun, V.D., Spence, J.S., Damaraju, E., Caprihan, A., Segall, J., 2014. Long-term effects of marijuana use on the brain. Proc. Natl. Acad. Sci. U. S. A. 111: 16913–16918. http://dx.doi.org/10.1073/pnas.1415297111.

Fowler, C.J., Rojo, M.L., Rodriguez-Gaztelumendi, A., 2010. Modulation of the endocannabinoid system: neuroprotection or neurotoxicity? Exp. Neurol. 224: 37–47. http://dx.doi.org/10.1016/j.expneurol.2010.03.021.

Friedman, L.A., Rapoport, J.L., 2015. Brain development in ADHD. Curr. Opin. Neurobiol. 30:106–111. http://dx.doi.org/10.1016/j.conb.2014.11.007.

Greve, D.N., Fischl, B., 2009. Accurate and robust brain image alignment using boundary-based registration. NeuroImage 48:63–72. http://dx.doi.org/10.1016/j.neuroimage.2009.06.060.

Hart, H., Radua, J., Nakao, T., Mataix-Cols, D., Rubia, K., 2013. Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: exploring task-specific, stimulant medication, and age effects. JAMA Psychiatry 70:185–198. http://dx.doi.org/10.1001/jamapsychiatry.2013.277.

Hong, S.-B., Harrison, B.J., Fornito, A., Sohn, C.-H., Song, I.-C., Kim, J.-W., 2015. Functional dysconnectivity of corticostriatal circuitry and differential response to methylphenidate in youth with attention-deficit/hyperactivity disorder. J. Psychiatry Neurosci. 40:46–57. http://dx.doi.org/10.1503/jpn.130290.

Houck, J.M., Bryan, A.D., Feldstein Ewing, S.W., 2013. Functional connectivity and cannabis use in high-risk adolescents. The American journal of drug and alcohol abuse 39: 414–423. http://dx.doi.org/10.3109/00952990.2013.837914.

Jacobson, S.C., Blanchard, M., Connolly, C.C., Cannon, M., Garavan, H., 2011. An fMRI investigation of a novel analogue to the trail-making test. Brain Cogn. 77:60–70. http://dx.doi.org/10.1016/j.bandc.2011.06.001.

Jacobus, J., Tapert, S.F., 2014. Effects of cannabis on the adolescent brain. Curr. Pharm. Des. 20, 2186–2193.

Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. NeuroImage 17, 825–841.

Klein, R.G., Mannuzza, S., Olazagasti, M.A.R., Roizen, E., Hutchison, J.A., Lashua, E.C., Castellanos, F.X., 2012. Clinical and functional outcome of childhood attention-deficit/hyperactivity disorder 33 years later. Arch. Gen. Psychiatry 69:1295–1303. http://dx.doi.org/10.1001/archgenpsychiatry.2012.271.

Lee, S.S., Humphreys, K.L., Flory, K., Liu, R., Glass, K., 2011. Prospective association of childhood attention-deficit/hyperactivity disorder (ADHD) and substance use and abuse/

dependence: a meta-analytic review. Clin. Psychol. Rev. 31:328–341. http://dx.doi.org/10.1016/j.cpr.2011.01.006.
Levy, B.J., Wagner, A.D., 2011. Cognitive control and right ventrolateral prefrontal cortex: reflexive reorienting, motor inhibition, and action updating. Ann. N. Y. Acad. Sci. 1224:40–62. http://dx.doi.org/10.1111/j.1749-6632.2011.05958.x.
Lin, H.-Y., Tseng, W.-Y.I., Lai, M.-C., Matsuo, K., Gau, S.S.-F., 2015. Altered resting-state frontoparietal control network in children with attention-deficit/hyperactivity disorder. J. Int. Neuropsychol. Soc. 21:271–284. http://dx.doi.org/10.1017/S135561771500020X.
Lisdahl, K.M., Wright, N.E., Kirchner-Medina, C., Maple, K.E., Shollenbarger, S., 2014. Considering cannabis: the effects of regular cannabis use on neurocognition in adolescents and young adults. Curr. Addict. Rep. 1:144–156. http://dx.doi.org/10.1007/s40429-014-0019-6.
Lisdahl, K.M., Tamm, L., Epstein, J.N., Jernigan, T., Molina, B.S.G., Hinshaw, S.P., Swanson, J.M., Newman, E., Kelly, C., Bjork, J.M., MTA Neuroimaging Group, 2016. The impact of ADHD persistence, recent cannabis use, and age of regular cannabis use onset on subcortical volume and cortical thickness in young adults. Drug Alcohol Depend. 161:135–146. http://dx.doi.org/10.1016/j.drugalcdep.2016.01.032.
Lorenzetti, V., Solowij, N., Fornito, A., Lubman, D.I., Yücel, M., 2014. The association between regular cannabis exposure and alterations of human brain morphology: an updated review of the literature. Curr. Pharm. Des. 20, 2138–2167.
Lubman, D.I., Cheetham, A., Yücel, M., 2015. Cannabis and adolescent brain development. Pharmacol. Ther. 148:1–16. http://dx.doi.org/10.1016/j.pharmthera.2014.11.009.
Medina, K.L., Nagel, B.J., Tapert, S.F., 2010. Abnormal cerebellar morphometry in abstinent adolescent marijuana users. Psychiatry Res. 182:152–159. http://dx.doi.org/10.1016/j.pscychresns.2009.12.004.
Molina, B.S.G., Pelham, W.E., 2003. Childhood predictors of adolescent substance use in a longitudinal study of children with ADHD. J. Abnorm. Psychol. 112, 497–507.
Molina, B.S.G., Hinshaw, S.P., Eugene Arnold, L., Swanson, J.M., Pelham, W.E., Hechtman, L., Hoza, B., Epstein, J.N., Wigal, T., Abikoff, H.B., Greenhill, L.L., Jensen, P.S., Wells, K.C., Vitiello, B., Gibbons, R.D., Howard, A., Houck, P.R., Hur, K., Lu, B., Marcus, S., Cooperative Group, M.T.A., 2013. Adolescent substance use in the multimodal treatment study of attention-deficit/hyperactivity disorder (ADHD) (MTA) as a function of childhood ADHD, random assignment to childhood treatments, and subsequent medication. J. Am. Acad. Child Adolesc. Psychiatry 52:250–263. http://dx.doi.org/10.1016/j.jaac.2012.12.014.
Orr, C., Morioka, R., Behan, B., Datwani, S., Doucet, M., Ivanovic, J., Kelly, C., Weierstall, K., Watts, R., Smyth, B., Garavan, H., 2013. Altered resting-state connectivity in adolescent cannabis users. Am. J. Drug Alcohol Abuse 39:372–381. http://dx.doi.org/10.3109/00952990.2013.848213.
Posner, J., Park, C., Wang, Z., 2014. Connecting the dots: a review of resting connectivity MRI studies in attention-deficit/hyperactivity disorder. Neuropsychol. Rev. 24:3–15. http://dx.doi.org/10.1007/s11065-014-9251-z.
Proal, E., Reiss, P.T., Klein, R.G., Mannuzza, S., Gotimer, K., Ramos-Olazagasti, M.A., Lerch, J.P., He, Y., Zijdenbos, A., Kelly, C., Milham, M.P., Castellanos, F.X., 2011. Brain gray matter deficits at 33-year follow-up in adults with attention-deficit/hyperactivity disorder established in childhood. Arch. Gen. Psychiatry 68:1122–1134. http://dx.doi.org/10.1001/archgenpsychiatry.2011.117.
Rasmussen, J., Casey, B.J., Van Erp, T.G.M., Tamm, L., Epstein, J.N., Buss, C., Bjork, J.M., Molina, B.S.G., Velanova, K., Mathalon, D.H., Somerville, L., Swanson, J.M., Wigal, T., Arnold, L.E., Potkin, S.G., MTA Neuroimaging Group, 2015. ADHD and cannabis use in young adults examined using fMRI of a Go/NoGo task. Brain Imaging Behav.: 1–11 http://dx.doi.org/10.1007/s11682-015-9438-9.
Sarne, Y., Asaf, F., Fishbein, M., Gafni, M., Keren, O., 2011. The dual neuroprotective-neurotoxic profile of cannabinoid drugs. Br. J. Pharmacol. 163:1391–1401. http://dx.doi.org/10.1111/j.1476-5381.2011.01280.x.
Shaw, P., Malek, M., Watson, B., Greenstein, D., de Rossi, P., Sharp, W., 2013. Trajectories of cerebral cortical development in childhood and adolescence and adult attention-deficit/hyperactivity disorder. Biol. Psychiatry 74:599–606. http://dx.doi.org/10.1016/j.biopsych.2013.04.007.
Shaw, P., Sudre, G., Wharton, A., Weingart, D., Sharp, W., Sarlls, J., 2015. White matter microstructure and the variable adult outcome of childhood attention deficit hyperactivity disorder. Neuropsychopharmacology 40:746–754. http://dx.doi.org/10.1038/npp.2014.241.
Tamm, L., Epstein, J.N., Lisdahl, K.M., Molina, B., Tapert, S., Hinshaw, S.P., Arnold, L.E., Velanova, K., Abikoff, H., Swanson, J.M., MTA Neuroimaging Group, 2013. Impact of ADHD and cannabis use on executive functioning in young adults. Drug Alcohol Depend. 133:607–614. http://dx.doi.org/10.1016/j.drugalcdep.2013.08.001.
The MTA Cooperative Group, 1999. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. The MTA Cooperative Group. Multimodal Treatment Study of Children with ADHD. Arch. Gen. Psychiatry 56, 1073–1086.
Weiland, B.J., Thayer, R.E., Depue, B.E., Sabbineni, A., Bryan, A.D., Hutchison, K.E., 2015. Daily marijuana use is not associated with brain morphometric measures in adolescents or adults. J. Neurosci. 35:1505–1512. http://dx.doi.org/10.1523/JNEUROSCI.2946-14.2015.
Yang, Z., Kelly, C., Castellanos, F.X., Leon, T., Milham, M.P., Adler, L.A., 2016. Neural correlates of symptom improvement following stimulant treatment in Adults with Attention-Deficit/Hyperactivity Disorder. Journal of child and adolescent psychopharmacology http://dx.doi.org/10.1089/cap.2015.0243 cap.2015.0243.
Zalesky, A., Solowij, N., Yücel, M., Lubman, D.I., Takagi, M., Harding, I.H., Lorenzetti, V., Wang, R., Searle, K., Pantelis, C., Seal, M., 2012. Effect of long-term cannabis use on axonal fibre connectivity. Brain 135:2245–2255. http://dx.doi.org/10.1093/brain/aws136.