King's Research Portal

DOI:

[10.1016/j.neubiorev.2018.03.008](https://doi.org/10.1016/j.neubiorev.2018.03.008)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Blest-Hopley, G., Giampietro, V., & Bhattacharyya, S. (2018). Residual effects of cannabis use in adolescent and adult brains – a meta-analysis of fMRI studies. *Neuroscience and Biobehavioral Reviews*.
<https://doi.org/10.1016/j.neubiorev.2018.03.008>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Accepted Manuscript

Title: Residual effects of cannabis use in adolescent and adult brains – a meta-analysis of fMRI studies

Authors: Grace Blest-Hopley, Vincent Giampietro, Sagnik Bhattacharyya

PII: S0149-7634(17)30739-X
DOI: <https://doi.org/10.1016/j.neubiorev.2018.03.008>
Reference: NBR 3066

To appear in:

Received date: 6-10-2017
Revised date: 30-1-2018
Accepted date: 9-3-2018

Please cite this article as: Blest-Hopley G, Giampietro V, Bhattacharyya S, Residual effects of cannabis use in adolescent and adult brains – a meta-analysis of fMRI studies, *Neuroscience and Biobehavioral Reviews* (2010), <https://doi.org/10.1016/j.neubiorev.2018.03.008>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Residual effects of cannabis use in adolescent and adult brains – a meta-analysis of fMRI studies

Authorline: Grace Blest-Hopley¹, Vincent Giampietro², Sagnik Bhattacharyya^{1, 3*}

¹ Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK.

² Department of Neuroimaging, Centre for Neuroimaging Sciences, PO Box 089, Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK.

³ South London and Maudsley NHS Foundation Trust, Denmark Hill, Camberwell, London, UK

*Corresponding author

Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, De Crespigny Park, London SE5 8AF, UK, Tel +44 207 848 0955, Fax +44 207 848 0976, Email: sagnik.2.bhattacharyya@kcl.ac.uk

Figures: 2

Tables: 3

Supplementary Materials – Supplementary materials; sub-group and meta-regression analysis, tables and figures.

1.1.1.1 Highlights

- Brain activation alterations associated with cannabis use was examined
- Changes in adults and adolescents were examined separately
- Studies using fMRI to measure brain activation were combined meta-analytically
- Adult cannabis users had increased activation in frontal and temporal regions.
- They also had decreased activation in striate area, insula and middle temporal gyrus.
- Adolescent cannabis users had increased activation in inferior parietal gyrus and putamen.

1. Abstract

While numerous studies have investigated the residual effects of cannabis use on human brain function, results of these studies have been inconsistent. Using meta-analytic approaches we summarize the effects of prolonged cannabis exposure on human brain function as measured using task-based functional MRI (fMRI) across studies employing a range of cognitive activation tasks comparing regular cannabis users with non-users. Separate meta-analyses were carried out for studies investigating adult and adolescent cannabis users. Systematic literature search identified 20 manuscripts (13 adult and 7 adolescent studies) meeting study inclusion criteria. Adult analyses compared 530 cannabis users to

580 healthy controls while adolescent analyses compared 219 cannabis users to 224 healthy controls.

In adult cannabis users brain activation was increased in the superior and posterior transverse temporal and inferior frontal gyri and decreased in the striate area, insula and middle temporal gyrus. In adolescent cannabis users, activation was increased in the inferior parietal gyrus and putamen compared to healthy controls. Functional alteration in these areas may reflect compensatory neuroadaptive changes in cannabis users.

2. Keywords: Cannabis, THC, Functional magnetic resonance imaging, Meta-analysis.

3. Introduction

Cannabis has been used recreationally for thousands of years (Russo, 2007) and is currently the world's most used illicit drug, with around 183 million users globally (Unodc, 2017). Cannabis use has been associated with a number of adverse mental, psychological and social outcomes (Appiah-Kusi et al., 2016; Crippa et al., 2009; Gage et al., 2016; Goldenberg et al., 2017; Marconi et al., 2016; Meier et al., 2012; Moore et al., 2007; Patel et al., 2016; Schoeler et al., 2016a; Schoeler et al., 2016b; Schoeler et al., 2016c; Schoeler et al., 2016d). Consistent with this, acute challenge studies in humans have shown that delta-9-tetrahydrocannabinol (THC) can induce transient psychotic and anxiety symptoms (Bhattacharyya et al., 2017; D'Souza et al., 2004) , as well as changes

to cognitive task performance (Curran et al., 2002; D'Souza et al., 2004) and functional brain activation during cognitive and emotional activation tasks (Bhattacharyya et al., 2015; Bhattacharyya et al., 2012a; Bhattacharyya et al., 2012c; Bhattacharyya et al., 2009; Bhattacharyya et al., 2010; Bossong et al., 2012a; Bossong et al., 2012b; Morrison et al., 2011; Phan et al., 2008; van Hell et al., 2011; van Hell et al., 2012; Winton-Brown et al., 2011). Hence, the residual effects of cannabis use on brain function that persist beyond the immediate acute intoxication effects (typically lasting for a few hours (Grotenhermen, 2003)) and may underlie its adverse mental, psychological and social effects are of particular interest.

Animal studies have found morphological as well as neurochemical changes in areas rich in cannabinoid type 1 (CB1) receptors following THC exposure during adulthood (Colizzi et al., 2016; Heath et al., 1980; Landfield et al., 1988; Scallet et al., 1987), as well as changes in cognitive function following prolonged exposure to cannabis (Imam et al., 2017). Human studies have shown impaired cognition that persist beyond the acute intoxication period in both adult and adolescent cannabis users, particularly in the performance of memory, attention, executive function and learning tasks (Crane et al., 2013; Crean et al., 2011; Ganzer et al., 2016; Lundqvist, 2005; Schoeler and Bhattacharyya, 2013; Schoeler et al., 2016a; Solowij et al., 2002). Human studies have also shown impaired cognition (executive functioning, processing speed, attention and memory) in adolescent cannabis users when compared to controls (Jacobus et al., 2009; Jacobus and Tapert, 2014), with suggestion of this impairment being greater than in adult users particularly in the domains of learning and memory (Schweinsburg et al.,

2008a). Meta-analysis of cognitive task performance in current users found a significant negative effect on global cognitive task performance as well as in most cognitive domains tested (executive functioning, attention, memory, motor control, reaction time) while an analysis of currently abstinent users found no significant effect either on global cognitive task performance or the specific domains assessed (Schreiner and Dunn, 2012). Consistent with these results, studies investigating structural changes in whole-brain architecture have reported both changes in grey and white matter density as well as lack of differences when compared to control groups as reviewed here (Batalla et al., 2013). In contrast, studies employing a region of interest (ROI) analysis approach have reported decreased volume in the hippocampus (Matochik et al., 2005) that appeared to correlate with cannabis use levels (Cousijn et al., 2012; Yücel et al., 2008) and persisted even after a prolonged period of abstinence (Ashtari et al., 2011). However, reduced hippocampal volume has not been consistently reported in adult (Tzilos et al., 2005) or adolescent (Silveri et al., 2016) cannabis users.

Several systematic (Batalla et al., 2013; Martin-Santos et al., 2010) and narrative (Bhattacharyya et al., 2012b; Bhattacharyya and Sendt, 2012; Chang and Chronicle, 2007; Gonzalez, 2007; Quickfall and Crockford, 2006) reviews have summarized the effects of regular cannabis use on human brain function using data from functional magnetic resonance imaging (fMRI) studies. Collectively, these results suggest a wide pattern of brain function alteration associated with cannabis use in humans. However, the results of these studies have been inconsistent and no clear picture has emerged as yet. A number of different

methodological factors may underlie the heterogeneity in these results, such as small sample sizes, heterogeneous populations including in their length of cannabis exposure as well as neuroimaging methods employed. Meta-analytic approaches allow the statistical integration of results from multiple individual studies that on their own may be insufficiently powered to detect the effect of cannabis exposure on brain function. To our knowledge, such an approach has not been applied as yet to investigate the effects of cannabis exposure on human brain function, but collectively have greater statistical power to reliably and robustly detect group differences.

Another important consideration is that previous fMRI studies have employed a wide range of cognitive activation paradigms that engage various cognitive processes (Batalla et al., 2013; Martin-Santos et al., 2010) shown to be affected by cannabis use. Studies employing specific cognitive paradigms in conjunction with fMRI are likely to demonstrate altered function in brain substrates or networks that play a central role in the cognitive processes engaged by the paradigm being used. However, the effects of cannabis are not likely to be limited to only those cognitive processes or brain regions that subserve those processes that are being investigated in a particular study. Instead, the effects of cannabis use on brain function are very likely to depend on (among a number of other factors) distribution of the main receptor targets (for example the CB1 receptor) (Pertwee, 2006) for the cannabinoids present in cannabis such as delta-9-tetrahydrocannabinol. It is well-recognised that one of the main cannabinoid receptors, the CB1 receptor, is fairly ubiquitous in distribution in the brain (Iversen, 2003). Therefore, brain function alterations associated with cannabis

use are likely to be distributed throughout the brain, consistent with the distribution of CB1 in the brain, as shown by the association between acute effects of THC and central CB1 availability (Bhattacharyya et al., 2017). By allowing us to quantitatively summarize whole-brain analysis fMRI data from studies employing a diverse array of cognitive activation paradigms, the meta-analytic approach provides a robust method to address the broader question as to where in the brain are there robust functional alterations associated with cannabis use, that are independent of specific cognitive processes of interest?

To our knowledge, such an approach has not been applied as yet to investigate the effects of cannabis exposure on human brain function. Hence, we have investigated this focusing specifically on the non-acute or residual effects of repeated cannabis exposure on human brain function. Articulation of a precise definition of the timescale beyond which any effects of cannabis that persist may be described as non-acute effects and one that is consistently used by studies in the field is challenging. However previous reviews in the field have sought to define non-acute effects as those that persist after several hours of abstinence (Crane et al., 2013; Crean et al., 2011) . Consistent with this approach and mindful of the fact that acute intoxication effects following use of cannabis by the inhalation route (often the typical route of use) lasts usually around 3 hours (Grotenhermen, 2003) , for the purpose of this meta-analysis we have defined non-acute effects as those that last beyond several hours of abstinence and are not observed following experimental cannabinoid challenge. However, as an overarching strategy, we have adopted a pragmatic approach in this regard in order to optimize the number of studies that are suitable for inclusion in our

analyses, given that not all studies have consistently reported this. We aimed to quantify effects across studies employing a diverse array of cognitive tasks, rather than a narrow set of conceptually related tasks, with a view to identifying the distributed network of brain regions showing significant neurophysiological alteration in those regularly exposed to cannabis compared to non-users. In order to summarize the current literature and identify convergent findings, we therefore conducted a systematic literature search to identify studies that have investigated the effects of long-term cannabis use on human brain function using fMRI techniques.

Previous studies have shown that cannabis use is generally associated with an attenuation of activation in the brain regions typically engaged by the cognitive paradigm employed (Martin-Santos et al., 2010). On the other hand, cannabis use has also been associated with increased engagement of brain regions such as the posterior cingulate, medial prefrontal and the inferior parietal cortex (Abdullaev et al., 2010; Chang and Chronicle, 2007; Chang et al., 2006; Gruber et al., 2012; Kanayama et al., 2004; Martin-Santos et al., 2010; Nestor et al., 2008), which together with the medial temporal cortex are part of the default mode network (DMN) (Buckner et al., 2008). In healthy individuals, regions within this network are deactivated or have an attenuation of activation while performing a cognitive task that involves focusing of attention (Fox et al., 2009b; Raichle et al., 2001) and activation in this network is anti-correlated with task-positive activation (Fox et al., 2006). Cannabis use has also been associated with altered activation of brain regions such as the dorsolateral prefrontal and posterior parietal cortex and intraparietal sulcus/ superior parietal lobule (Bolla et al., 2005; Eldreth et

al., 2004; Jager et al., 2006; Schweinsburg et al., 2008a; Sevy et al., 2008; Tapert et al., 2007). Collectively, these regions are also known as the central executive network (CEN) and that are thought to subserve higher order cognitive functions such as the control of attention, working memory, executive function (Seeley et al., 2007; Sridharan et al., 2008). Altered activation have also been reported in cannabis users commonly in the amygdala, caudate, insula, orbitofrontal and anterior cingulate cortices (Block et al., 2000; Gruber et al., 2009; Harding et al., 2012; Hester et al., 2009; van Hell et al., 2010) that are part of the salience network (SN) (Menon, 2011; Seeley et al., 2007). All of these regions also have a high density of the main central CB1 receptor (Elphick and Egertova, 2001; Glass et al., 1997). Although, cannabinoid challenge has been found to modulate various components of these networks (Batalla et al., 2014; Bhattacharyya et al., 2012b) and their connectivity (Bhattacharyya et al., 2015; Gorka et al., 2016) acutely, the precise association of regular cannabis use with altered functioning of these large-scale brain networks is much less clear (Batalla et al., 2013; Wijayendran et al., 2016).

As we pooled data from studies employing a diverse array of cognitive tasks that may differentially engage cognitive processes and brain regions, we hypothesized that the present meta-analysis would specifically identify a core network of brain regions as being differentially activated in cannabis users compared to controls. We specifically hypothesized that robust differences in activation between cannabis users and controls would be detected in brain regions that are part of the CEN, SN and DMN networks.

Adolescence represents a critical period of vulnerability to exogenous insults when many developmental processes including brain development and binding affinity of CB1 receptors, the main target of cannabinoids, are in a state of flux before attaining maturity in early adulthood (Andersen, 2003; Belue et al., 1995; Rice and Barone, 2000; Spear, 2007). Both animal (Belue et al., 1995; Verduran et al., 2011) and human (Biegon and Kerman, 2001; Glass et al., 1997; Mato et al., 2003), studies indicate a progressive increase in CB1 receptor density from early life into adolescence, before stabilising in adulthood (Belue et al., 1995). Furthermore, evidence from animal studies has also emerged that exposure to the effects of THC during adolescence may be associated with altered maturation of the endocannabinoid system leading to impairments in endocannabinoid signaling and long-term depression as well as cognition in adulthood (Rubino et al., 2015), consistent with independent evidence of reduced compensatory CB1 downregulation in adolescent compared to adult rodents following experimentally induced cannabinoid exposure (Dalton and Zavitsanou, 2010). Preclinical research has also shown adolescence to be a period of greater sensitivity to cannabinoids compared to adults in terms of greater impairment in certain cognitive tasks (object recognition memory, spatial memory, prepulse inhibition, operant behavioural task) as well as altered hippocampal protein expression profile (Quinn et al., 2008; Schneider and Koch, 2003), though other studies have shown greater impairment (in spatial learning and novel object recognition) in adults (Acheson et al., 2011; Fox et al., 2009a). In line with this preclinical evidence of differential sensitivity, a human study has also demonstrated age-related differential sensitivity to the subjective, cognitive (memory and inhibitory processing), physiological and psychotomimetic effects

of a single dose of cannabis under experimental conditions in male cannabis users, without a clear pattern emerging of greater vulnerability of either adolescent or adult users (Mokrysz et al., 2016). Nevertheless, as available evidence broadly suggests differential sensitivity of adolescent versus adult users, we have carried out separate meta-analyses focusing on studies in adult and adolescent cannabis users. Meta-analyses based on coordinates from altered brain activation results and their associated statistical values were used to determine changes in activation across all studies that meet our criteria. We hypothesized that adult and adolescent cannabis users would show distinctly different patterns of functional brain activation compared to healthy controls.

4. Methods

4.1 Search strategy and selection of studies.

We conducted a systematic search of published literature in the publication database Pubmed following the Cochrane Handbook (JPT, 2011) and the MOOSE guidelines (Stroup et al., 2000) employing two categories of search terms: 1) Cannabis: cannabis, marijuana, marihuana, THC, tetrahydrocannabinol and 2) Neuroimaging technique: fMRI, imaging, functional activation, BOLD. Boolean Operators were used to combine the two categories. The search was limited to human studies and run through the titles and abstracts. An initial Pubmed search was completed on the 21/10/2015, which was finally repeated again on the 13/12/2017.. To identify further relevant publications, reference lists were screened from included manuscripts and published reviews.

Only published peer-reviewed manuscripts reported in English language journals that satisfied the following inclusion criteria were selected:

- Original peer-reviewed data-based publication.
- Compared habitual otherwise healthy cannabis users (>50 times of lifetime use, as indexed by self-reported number of occasions of cannabis use over the person's lifetime), to healthy controls who were not habitual cannabis-users (with < 50 times of lifetime cannabis use).
- Reported results using whole-brain imaging analysis.
- Used a cognitive or emotional activation task that did not involve cannabis-related stimuli.

The initial search in October 2015 identified 598 manuscripts which were screened for inclusion into the study (figure 1). No additional studies meeting study inclusion criteria were identified in a final repeat search performed on the 13/12/2017.

4.2 Data Extraction

Data was extracted in to a database with the variables of interest retrieved from the included studies after establishing that whole brain analysis results were reported. Coordinates of significant peaks were extracted along with their t-statistic. If a t-statistic was not reported, this was computed from a z-value or p-value, using a converter (www.sdmproject.com/utilities/?show=Statistics) provided with the software used for meta-analysis, Seed based d- Mapping (SDM,

formally signed differential mapping) (Sdmproject.com, 2017). If no statistic value was reported a positive or negative peak was indicated with a 'p' or 'n' respectively as per established approaches (Radua et al., 2012). Studies that had no significant peaks were also included.

Each separately reported contrast of interest relative to a control condition within a published manuscript was treated as a separate study. For example, a study comparing cannabis users with non-users while performing a gambling task during fMRI might have reported both the 'win' and 'lose' conditions each compared separately with the control condition. In this case, the 'win' and 'lose' conditions would have been considered as two separate studies for the purposes of the meta-analysis. Hereafter, each of these separate contrasts of interest included in the meta-analysis as a separate study are referred to as such within the methods section. As per established protocol (Radua et al., 2012) a text file was created for each study, including the coordinates reported, t-value (positive or negative, such that activation increased in cannabis users was reported as positive and increased in healthy controls as negative), and the number of participants for each group. Information as to the specific brain template e.g. Montreal Neurological Institute (MNI) or Talairach template used in reporting the brain activation coordinates in the study was included with this study specific text file.

Quality assessment of each study was completed using criteria previously used for fMRI studies (Radua et al., 2015). However, we did not exclude any of the studies based on this quality assessment, but have reported the results of the quality assessment as part of supplementary material (supplementary table 4).

4.3 Data Analysis

Meta-analysis was carried out using seed-based d mapping (SDM) (Sdmproject.com, 2017), the methods of which have been describe in detail elsewhere (Radua et al., 2014) and applied in a number of meta-analyses of fMRI data (Alegria et al., 2016; Norman et al., 2016; Rubia et al., 2014; Scognamiglio and Houenou, 2014). For voxels containing a peak, the unbiased effect-size and variance was computed using standard formulae (Hedges and Olkin, 1985). For the rest of the voxels, the effect-size was estimated by assigning an effect-size to each voxel based on its distance to nearby peaks using a 20 mm full-width-at-half-maximum non-normalized Gaussian kernel (Radua and Mataix-Cols, 2009). In this method, the kernel was multiplied by the effect-size of the peak. When a voxel was assigned a value from more than one coordinate, the value was averaged weighting by the square of the distance to each close peak. Bias from one study reporting many close coordinates was limited by employing a study value maximum. Both positive and negative activations were modelled on the same map. If the t values of the peak coordinates were unknown, SDM conducted a threshold-based imputation of effect-size, which consisted of estimating the mean-effect-size of peaks from studies reporting t values, separately for each type of significance threshold. These processes were fully automated within the SDM software. SDM uses peak coordinates and their associated statistical values to create individual effect-size brain maps for each study and implements a random-effects model to meta-analytically combine the data from each study, by weighting each study with the inverse of the sum of its variance plus the between-study variance as obtained by the DerSimonian-Laird estimator

(DerSimonian and Laird, 1986), which is statistically comparable to the restricted maximum likelihood (Viechtbauer, 2005). Heterogeneity Q statistic is assessed in terms of a chi-square distribution and reported after conversion to standard z values.

For the present meta-analyses, all maps created as above from each study were then included in a meta-analytic Seed-based d map. A null distribution of the meta-analytic values was created to test which voxels had more studies reporting difference of activation around them than by chance, performed by monte-carlo randomizations of coordinates. Twenty permutations have been used, as this number has been shown to yield highly stable results (Radua et al., 2012). Results have been thresholded to ensure voxel threshold = $p < 0.005$, peak height threshold: peak SDM-Z < 1 , and a cluster-size threshold of clusters ≥ 10 voxels.

Heterogeneity Q statistic was assessed in terms of a chi-square distribution and reported after conversion to standard z values. Jack-knife sensitivity analysis was completed on both analyses, and visually inspected to assess heterogeneity. This method repeats the meta-analysis as many times as the number of studies removing each study in turn from one run of the analysis. Funnel plots were created for each cluster, in order to perform Egger's test and assess publication bias (Sedgwick and Marston, 2015) as a result of a greater likelihood of publication (and therefore of inclusion in the meta-analysis) of studies with statistically significant results than those with non-significant results.

Co-ordinates of cluster peaks and cluster extent were then reported using MNI coordinates. Each cluster peak was examined using a human brain atlas in order to visually inspect the peak region (Mai et al., 2008).

4.4 Sub-group and regression analysis

To investigate whether differential task performance was influencing group differences in brain activation, we performed a sub-group analysis, including only studies that reported no significant group difference in task performance. Sub-group analysis for adult studies to investigate the effect of differential task performance included all studies from the main analysis excluding three studies (Abdullaev et al., 2010; Sneider et al., 2013; Wesley et al., 2011), making up a total of six comparisons. The equivalent sub-group analysis for adolescent studies excluded only one study from the main analysis (Behan et al., 2014).

Effect of comorbid tobacco, alcohol or other drug use on group differences between the cannabis user and control groups was investigated by carrying out a sub-group analysis, including only studies which had matched groups for use of these substances. This was only completed for adult studies as all of the adolescent studies reported some difference in alcohol, tobacco or drug use between groups. Five studies, with 17 different comparisons were used in the sub-group analysis of adult studies (Abdullaev et al., 2010; Heitzeg et al., 2015; Nestor et al., 2010; Nestor et al., 2008; Smith et al., 2011) to investigate the effect of comorbid tobacco, alcohol or other drug use. All other studies reported significant difference in at least one of the substances of interest to the sub-group analysis, except one which was not included in sub-group analysis as it did

not provide any information on difference in tobacco use (Kanayama et al., 2004).

A further sub-group analysis, including only studies that employed a memory task as a cognitive activation paradigm for fMRI, was carried out using identical approaches as in the main data analysis, to investigate the effects of cannabis use over tasks engaging similar cognitive processes. Due to the limited number of studies that employed related cognitive activation tasks that could be grouped in a meaningful way as being related, we were only able to carry this out for studies employing paradigms involving memory processing in adults. For adolescent studies, a similar search led to only 2 studies (Schweinsburg et al., 2008b; Schweinsburg et al., 2011), which was not deemed enough for a meta-analysis.

Meta-regression analyses were carried out using approaches described previously (Radua and Mataix-Cols, 2009) to investigate association with level of life-time cannabis use and gender, in light of considerable variation in both cannabis use and gender distribution across the included studies. We quantified life-time cannabis use employing reported data to arrive at a cannabis use measure that was broadly comparable across studies. Where no life-time cannabis data was reported, this was estimated using information on number of instances of use per week/ month and multiplying that with lifetime duration of use reported in the study. Where any of these measures have been reported in the published manuscript as a range for the group, the median value was used. Results of all meta-regression and sub-group analyses have been thresholded to ensure voxel threshold = $p < 0.005$, peak height threshold: peak SDM-Z < 1, and a cluster-size threshold of clusters ≥ 10 voxels.

A further meta-regression was carried out to investigate the association with age of onset of cannabis use in the studies in adults. As information on age of onset of cannabis use was not available for all studies that were included (8 out of 13 studies reported age of onset), for this meta-regression we only included studies with this information. Meta-regression was completed using the mean values for age of cannabis use onset taken from the manuscript or computed using available data. If the means were reported separately for males and females, these were recalculated to arrive at one mean for the study.

5. Results

5.1 Publications

A final list of 20 manuscripts employing task-based fMRI were found to meet study inclusion criteria (Abdullaev et al., 2010; Acheson et al., 2015; Behan et al., 2014; Chang et al., 2006; Cousijn et al., 2013; Gruber et al., 2009; Heitzeg et al., 2015; Jager et al., 2013; Kanayama et al., 2004; King et al., 2011; Lopez-Larson et al., 2012; Nestor et al., 2010; Nestor et al., 2008; Schweinsburg et al., 2008b; Schweinsburg et al., 2011; Smith et al., 2011; Sneider et al., 2013; Tapert et al., 2007; van Hell et al., 2010; Wesley et al., 2011). Figure 1 shows the PRISMA flowchart (Moher et al., 2009), with reasons for exclusion of studies. Thirteen of these investigated adults, (Table 1), and seven investigated adolescent cannabis users, (Table 2). Each separate contrast of interest that was reported comparing users to controls within these 20 manuscripts was considered as a separate

study for the purposes of the meta-analysis (as described earlier in the Methods section), giving a total of 43 studies (of which 10 reported no significant results), 31 investigating adults (seven with no significant results), and 11 investigating adolescents (three with no significant results). Adult studies included participants between the age range of 17-55 years (based on 7 out of a total of 13 studies), while adolescent studies had a participant age range of 13-19 years. The adult analysis compared 530 cannabis users to 580 healthy controls. The adolescent analysis compared 219 cannabis users to 224 healthy controls.

Studies in adults included cognitive paradigms that engaged memory (n=3), attentional processing (n=2), monetary incentive delay (n=2), emotional processing (n=2), gambling (n=2), inhibitory processing (n=1) and checker board (n=1) tasks. Studies in adolescents included cognitive paradigms that engaged memory (n=2), inhibitory processing (n=2), gambling (n=1), monetary incentive (n=1) and finger tapping (n=1) tasks.

5.2 Effects on the adult brain

All cannabis-using groups were reported to have used cannabis between at least one day per week to 6-7 days per week. Controls included in these studies reported cannabis use as not greater than 50 times over life-time (Table 1).

In adult cannabis users there were three areas of significantly greater activation in cannabis users compared to controls (Figure 2 and Table 1): left superior temporal gyrus (extending to the angular gyrus and middle temporal gyrus), right inferior frontal gyrus (extending to both opercular and triangular parts) and left posterior transverse temporal gyrus (extending to the superior temporal

gyrus). Four clusters showed significantly decreased activation in cannabis users compared to controls: left striate area (extending to the inferior, superior, and middle occipital gyrus, calcarine fissure, lingual gyrus and cuneus), left area piriformis insulae (extending to the insula, lenticular nucleus and putamen) and two clusters in the right middle frontal gyrus (including the precentral gyrus, middle and superior frontal gyrus) (Table 3).

5.3 Effects on the adolescent brain

In adolescent studies there were two clusters of significantly greater activation in cannabis users compared to controls: the right inferior parietal gyrus, (extending to the superior parietal gyrus and angular gyrus), and right putamen (extending to the striatum and insula) (Figure 2, Table 3).

5.4 Sensitivity, Heterogeneity and Publication bias

Jack-knife sensitivity analyses for both meta-analyses were completed and inspected. For the adult meta-analysis, inspection of the jack-knife sensitivity analyses showed that all seven clusters survived in the 74% of the repeat analyses. However, a small number of studies did appear to be having a large influence on different positive clusters, suggesting heterogeneity in the analyses. Funnel plots were created and examined for each cluster and Egger's tests performed to look for publication bias. All but one was found to show no sign of significance for bias. The activation cluster (cannabis users > controls) in the

superior temporal gyrus (-52, -60, 30) had a strong trend toward significance ($p=0.054$) in the Egger's test suggesting potential publication bias.

For the adolescent meta-analysis, inspection of the jack-knife sensitivity analyses showed that for 64% of outputs there was no change in the clusters reported in the overall results. However, two pairs of studies each appeared to be contributing to the two positive clusters, respectively. While this may suggest heterogeneity in the analyses, this may also be due to only a limited number of studies being available for use in the analysis. Funnel plots were created and examined for significant clusters, and Egger's test was performed which was non-significant for one peak (right inferior parietal gyrus, 46, -46, 50; $p=0.283$), and significant at trend level for the second peak (right putamen, 28, 14, -2; $p=0.072$) suggesting potential publication bias.

5.5 Sub-group analyses

As stated before, we investigated whether differential task performance was influencing group differences in brain activation by performing a sub-group analysis including only studies that reported no significant group difference in task performance. Results from this analysis including only adult studies (Supplementary Table 1), showed that cannabis users had significantly greater activation compared to controls in the posterior transverse temporal gyrus and the anterior lobe of the cerebellum, but less activation than controls in the middle occipital gyrus, postcentral gyrus, insula and middle frontal gyrus. This indicated that when only studies that reported no significant group difference in task performance were considered, of the 3 clusters of greater activation in our

meta-analysis of all adult studies of cannabis users compared to controls (reported in 3.2), the posterior transverse temporal gyrus was still significant, while the two clusters in the superior temporal and inferior frontal gyri, were no longer significant. In contrast, all four clusters of decreased activation in cannabis users that were present in the meta-analysis of all adult studies (reported in 3.2) persisted in the sub-group analysis.

For the equivalent sub-group analysis of adolescent studies including only studies with no difference in task performance, clusters of significantly greater activation in cannabis users from the complete group analysis (reported in 3.3) were essentially unchanged (Supplementary Table 2).

For the sub-group analysis focusing on the effects of tobacco, alcohol and other drug use as possible confounders, we carried out analyses including only studies, which had matched groups for use of these substances. Results of this analysis for the adult studies (Supplementary Table 3) revealed that cannabis users had significantly greater activation compared to controls in the inferior and superior frontal gyri. This indicated that of the three clusters showing significantly greater activation in cannabis users compared to controls in the meta-analysis of all adult studies (reported in 3.2), only the inferior frontal gyrus remained significant in the sub-group analysis. For the opposing contrast, a superior temporal gyrus cluster on the right side showed decreased activation in cannabis users relative to controls. Therefore, none of the four clusters of decreased activation in cannabis users compared to controls that were present in the meta-analysis of all adult studies (reported in 3.2) persisted in the sub-group analysis.

An equivalent sub-group analysis was not completed for adolescent studies as all the studies reported some difference in other substance use.

A further sub-group analysis investigating adult studies using only memory-based fMRI tasks included 3 manuscripts investigating adult participants (Kanayama et al., 2004; Nestor et al., 2008; Sneider et al., 2013). The total number of separate contrasts of interest from all manuscripts was five and compared 46 cannabis users to 45 healthy controls. This analysis revealed decreased activation in cannabis users compared to controls in the right precentral, postcentral and inferior frontal gyri and in the precuneus.

5.6 Meta-regression analyses

Meta-regression analysis with lifetime cannabis use levels suggested an association between level of cannabis use and activation across a network of brain regions. In the lingual and superior temporal gyri, hippocampus and precuneus, higher levels of cannabis use was associated with greater activation, while in the insula, cingulate and cerebellum, lower levels of use was associated with greater activation levels in adult cannabis users. In contrast, in adolescent cannabis users, higher level of use was associated with greater activation in the caudate nucleus.

Meta-regression analysis with gender suggested an association between the number of female users and activation across a network of brain regions. In the superior temporal, superior and inferior frontal gyri as well as in the caudate

nucleus, higher number of female participants in the cannabis user group was associated with greater activation, while lower number of female participants was associated with greater activation bilaterally in the middle frontal gyrus in adult cannabis users. In contrast, in adolescent cannabis users, lower number of females was associated with greater activation in the caudate nucleus.

For the meta-regression analyses to examine the association with age of onset of cannabis use in adult users, out of 8 studies (Abdullaev et al., 2010; Chang et al., 2006; Gruber et al., 2009; King et al., 2011; Nestor et al., 2010; Nestor et al., 2008; Sneider et al., 2013; Wesley et al., 2011) where it was possible to obtain a mean age of onset of cannabis use, there were a total of 22 separate contrasts of interest. A total of 322 adult cannabis users were compared to 339 healthy controls for the meta-regression (Supplementary Table 6). Activation was increased in later cannabis use onset users compared to earlier onset cannabis users in the posterior lobe of cerebellum and middle frontal gyrus on the right side and in the left superior parietal lobule. Earlier onset cannabis users had increased activation compared to later onset cannabis users in the right medial frontal gyrus and the left posterior lobe of cerebellum.

6. Discussion

We carried out two complementary meta-analyses of all fMRI studies that compared cannabis users with non-using controls separately in adolescents and adults using a whole-brain analysis image analysis approach. We investigated

adult and adolescent users separately to eliminate developmental differences and in light of evidence that adolescence is a time of greater vulnerability to the effects of cannabis use.

Our results show that adult users had greater functional brain activation in three regions, the left superior temporal gyrus (STG) extending to the angular gyrus and middle temporal gyrus, right inferior frontal gyrus (IFG) extending to both opercular and triangular parts and left posterior transverse temporal gyrus (PTTG) extending to the superior temporal gyrus. Jack-knife sensitivity analyses showed that two of these clusters of altered brain function in adult cannabis users with peaks in the right IFG and the left PPTG were fairly robust and also were not susceptible to publication bias, as evident from the results of Egger's test. On the other hand, post-analysis assessment of peak stability and reliability revealed that the largest cluster of difference with peak in the left STG, was produced by a limited number of studies, such that this difference was likely to reflect publication bias. Adult cannabis users showed lower functional brain activation compared to controls in four regions, the left striate area extending to the inferior, superior, and middle occipital gyrus, calcarine fissure, lingual gyrus and cuneus, the left area piriformis insulae extending to the insula, lenticular nucleus and putamen, and two adjacent clusters in the right middle frontal gyrus one extending to the precentral gyrus, and the other extending to the superior frontal gyrus, one a bit more anterior to the other. Jack-knife sensitivity analyses suggested that all four clusters were reasonably stable and were also not susceptible to publication bias. Consistent with our hypotheses, we observed changes in brain activation associated with cannabis use in regions that are part

of the DMN, CEN and SN. Meta-analysis of the studies in adolescents showed only greater activation in adolescent cannabis users compared to controls, in components of the DMN and SN. Although, the larger cluster of altered activation in the right inferior parietal gyrus extending to the superior parietal gyrus and angular gyrus was found to be not susceptible to publication bias, jack-knife analysis suggested that this cluster was produced by a limited number of studies reflecting considerable heterogeneity. In contrast, the second cluster of altered activation with peak in the right putamen extending to the striatum and insula had a similar result in the jack-knife analysis as well as the parietal cluster, but Egger's test results approaching significance. Results of sub-group analyses, where this was possible, to account for the effects of differential task performance and use of other drugs and alcohol suggested that perhaps the adolescent meta-analysis results may have been less affected by these confounders. The relatively modest number of studies used in this analysis, as well as heterogeneity in the study paradigms employed in these studies may underlie instability in these results. Although we carried out sub-group analysis using only studies that used memory tasks for cognitive activation, this did not identify differences between adult cannabis users and controls. This may reflect limited power to detect differences as there were only 3 studies that met inclusion criteria for this analysis. A similar sub-group analysis with studies in adolescents was not possible as only two studies were available that used comparable cognitive paradigms. While one needs to be cautious in terms of interpretation of the results of the meta-regression analyses, they give an indication as to the brain regions where the effects of cannabis use may indicate dose-responsiveness as well as differential sensitivity moderated by gender and

age of onset of cannabis use. In particular, in the right middle frontal gyrus where adult cannabis users had lower functional activation compared to healthy controls, earlier onset of cannabis use in adults seems to be associated with a greater reduction in activation compared to later onset cannabis users. Collectively, our results are consistent with a recent systematic review of neurofunctional effects of cannabis use following a period of abstinence from cannabis use of a least 14 days, wherein the authors reported consistent change in prefrontal, temporal and occipital regions, (Ganzer et al., 2016).

These results are to be considered in light of a number of limitations. We were unable to include a substantial number of identified studies as they had only reported the results of region of interest (ROI) analyses (Carey et al., 2015; Gruber et al., 2012; Harding et al., 2012; Hester et al., 2009; Jager et al., 2010; Jager et al., 2006; Jager et al., 2007; Pillay et al., 2008; Pillay et al., 2004; Roser et al., 2012; Sagar et al., 2015; Spechler et al., 2015; Zimmermann et al., 2017), focusing on areas relevant to the specific task used or of interest in light of previously hypothesized change in cannabis users. Of the results reported in these manuscripts, the two studies focusing on changes in adolescent cannabis users reported greater activation in cannabis users in task-related areas (left superior parietal cortex; inferior frontal gyrus; dorsolateral prefrontal cortex; anterior cingulate cortex; right and left amygdala; right middle temporal gyrus) and no areas of decreased activation (Jager et al., 2010; Spechler et al., 2015), in line with our findings. In the two studies that investigated the effect of age of initiation of cannabis use which we were unable to include in our analyses, onset of use before the age of 16 was shown to be associated with a greater difference

in brain activity in the left anterior cingulate (Sagar et al., 2015) compared with controls and increased activation in the middle part of the right cingulate gyrus compared to those with a later onset of use (Gruber et al., 2012). While consistent with the idea that cannabis use during early adolescence is associated with greater effect on brain function than later use, this may also reflect differences due to higher total use in those who started use earlier compared to those who started later, as both of these studies investigated adult populations. In contrast, we found earlier onset of cannabis use in adults being associated with differential activation compared to later onset users in a different set of brain regions than those identified by these studies (Gruber et al., 2012; Sagar et al., 2015) . However, it is worth noting that our study was not designed to systematically investigate this issue.

In the meta-analysis in adults, we found decreased activation in the cuneus in cannabis users consistent with results of the study by Roser and colleagues (Roser et al., 2012) who employed an ROI analysis approach. Some other ROI-based studies have reported increased activation in the cingulate (Gruber et al., 2012; Roser et al., 2012), while others reported an opposite effect (Carey et al., 2015). Greater functional brain activation (in the left superior parietal cortex; inferior frontal gyrus; medial orbitofrontal cortex; precentral/ dorsolateral prefrontal cortex; striatum; hippocampus; cuneus and anterior cingulate cortex) was found by a number of the ROI-based studies (Gruber et al., 2012; Hester et al., 2009; Jager et al., 2010; Roser et al., 2012; Zimmermann et al., 2017). Some found no significant differences between groups (Cousijn et al., 2014; Harding et al., 2012; Jager et al., 2010; Jager et al., 2006; Spechler et al., 2015) while others

found only decreased activation (in the hippocampus and parahippocampal gyrus; inferior temporal gyrus; anterior and mid-cingulate cortex; thalamus; inferior and superior parietal lobule; putamen; postcentral gyrus and supramarginal gyrus) compared to controls, (Carey et al., 2015; Jager et al., 2007; Pillay et al., 2008; Pillay et al., 2004; Sagar et al., 2015). However, as these studies restricted their analyses to only certain brain regions, they were very likely to have missed any alterations in brain activation in cannabis users outside of those brain regions. Task performance by cannabis users was found to be not significantly different to control participants in the majority of the studies, with only 5 studies (Abdullaev et al., 2010; Behan et al., 2014; Nestor et al., 2010; Sneider et al., 2013; Wesley et al., 2011) reporting any difference during a range of different tasks (attention, Go/NoGo, monetary incentive delay, water maze and gambling tasks). Hence, observed differences in brain activation could arguably suggest neuroadaptive changes to maintain normal function. However, greater differences were reported in activation between groups performing the same task at two levels of difficulty, such that greater difference was seen in the more difficult version of the task (King et al., 2011).

One important issue that needs to be highlighted is that the results of our separate meta-analyses in adults and adolescents are not directly comparable in terms of differences in the pattern of altered activation associated with cannabis use in these two age groups, distinct though they are. This is because we did not directly compare these two groups in light of the limited number of studies that have compared these two age groups directly to allow a meaningful integration of data using a meta-analytic approach. Another caveat relates to the modest

number of studies using similar or comparable cognitive activation paradigms in the two age groups, which further limits firm inferences from being drawn from any comparison. Nevertheless, it is worth pointing out some of the similarities and differences between the adult and adolescent meta-analyses. We found no areas of decreased activation in adolescent cannabis users compared to healthy controls, while a number of regions of decreased activation were found in the adult cannabis users relative to the healthy controls. While this may reflect greater total dose of cannabis that adult users may have been exposed to compared to adolescent users, whether they may also relate to differences in alcohol, nicotine and other drug use, differences in the duration of abstinence before image acquisition or a reflection of sample power issues (with fewer studies in the adolescent meta-analysis) is unclear. However, one cannot rule out that these differences also reflect differences in the distribution of cognitive paradigms that were employed in the studies included in the adult and adolescent meta-analyses. However, it is worth noting that one common region of altered activation in relation to cannabis exposure that has emerged in both the adult and adolescent meta-analyses is a region that maps close to the angular gyrus region an area within the DMN (Andrews-Hanna et al., 2014). This region has also been reported to be involved in a number of cognitive processes and is thought to serve as a cross-modal hub involved in the integration of information from multiple modalities, reorienting attention and retrieving stored information in the context of giving meaning to new experiences and problem-solving (Seghier, 2013). This may reflect the multitude of cognitive tasks employed by the various studies included in these meta-analyses, all of which involved performing a task thereby requiring the participant to reorient their

attention and attempt to solve the problem at hand and suggest that greater engagement of this region indicates less efficient cognitive performance in cannabis users in general, irrespective of their age. On the other hand, perhaps it may also reflect an alteration in the attribution of meaning or significance that has been well recognised in the context of cannabis use and experimental cannabinoid challenge studies (Bhattacharyya et al., 2015; Bhattacharyya et al., 2012c; Wijayendran et al., 2016) and in the context of psychotic disorders (Kapur, 2003) that are sometimes associated with heavy and long-term use in a small proportion of cannabis users (Appiah-Kusi et al., 2016; Moore et al., 2007). It is particularly noteworthy that across both the adult and adolescent meta-analyses, components of the SN showed altered activation, albeit in different direction. While in adults, this reflected lesser activation in cannabis users relative to controls in particular in the insula, in adolescent cannabis users there was an opposite pattern of insular engagement relative to controls. The insula is a core node within the SN and plays a central role in the switching of engagement between the task positive (CEN) and the task negative (DMN) states, thereby allowing the detection of a salient event (Menon, 2011; Sridharan et al., 2008). Whether this reflects greater developmental sensitivity of adolescent cannabis users leading to a more impaired functioning of the network switching process that normally allows efficient allocation of cognitive resources in adolescents and the same network switching process going on overdrive in adults, as a compensatory mechanism, warrants investigation in future studies.

Some of the other regions where there was altered activation in cannabis users in these meta-analyses also overlap with meta-analytic evidence of altered

functional brain activation as indexed using fMRI while performing a number of cognitive activation tasks in patients with schizophrenia compared to healthy controls. Decreased activation was found in patients with schizophrenia compared to controls in MFG and the occipital lobe, as well as increased activation in the IFG, STG and SFG, consistent with results reported here. Increased activation reported by Minzenberg and colleagues in the insula, an area that is part of the SN (Menon, 2015), in patients with schizophrenia is however in contrast to the findings from our adult analysis (Minzenberg et al., 2009) while a similar change as patients was observed in the insula in adolescent cannabis users. The STG has been shown to have increased activation in patients with schizophrenia and those at high clinical risk of psychosis compared to controls, similar to that found in our analysis (Crossley et al., 2009). However, it is worth noting that this region does not appear to be reliably found in all studies included in the meta-analysis.

There are certain limitations that are inherent to the meta-analytic integration of data, especially in the context of neuroimaging studies. For example, use of only reported coordinates as opposed to contrast maps renders neuroimaging meta-analyses subject to bias as only coordinates significant at a certain threshold (e.g. $p < 0.05$) are reported in most published studies. This results in clusters of activation with p values that are slightly over the threshold being excluded from the meta-analysis. However, we tried to mitigate this issue by also including published studies that did not include any significant results. While the use of activation maps allow better group comparisons of true activation and avoid the limitations of coordinate-based meta-analyses, they are much more challenging

in terms of having access to activation maps. Another limitation stems from heterogeneity in the studies included. There are many sources of heterogeneity in the present meta-analyses, from differences in the duration and severity of exposure to cannabis and in length of abstinence prior to scan acquisition as well as in comorbid exposure to alcohol, nicotine and other drugs between samples included in the various studies, to the different cognitive tasks employed as activation paradigms during fMRI. While we carried out sub-group analysis focusing on studies employing similar or related cognitive tasks, this was possible to only a limited extent and only in adult studies because of lack of enough studies investigating a particular cognitive process for any statistical integration through meta-analysis to be really meaningful. Further limitations relate to differences in methods of data analysis that generated the coordinate data and statistical values used for meta-analysis as well as scanner differences between studies. Use of other drugs have been controlled for by the majority of the studies and a number have made efforts to match participants for tobacco use, helping to minimize confounding effects. We also carried out sub-group and meta-regression analyses to inform the extent to which some of these potential confounders influence the results of the complete group meta-analyses. Notwithstanding these limitations, the results of this study have shown stable differences in brain activation between cannabis users and controls in both adult and adolescent analyses. However, it is worth noting that as the studies included in the present meta-analyses did not employ longitudinal multi-point assessments, the results of the present meta-analysis are unable to inform the extent to which observed group differences are a cause or consequence of exposure to cannabis. Future studies need to employ longitudinal design and

multi-point assessment in conjunction with detailed matching and accounting for potential confounders to allow accurate delineation of the effects of cannabis on the human brain in adolescent and adult users. Furthermore, future meta-analytic endeavours in this area should also investigate using a set of conceptually related task-based studies to investigate task-specific regional differences, once enough of a body of literature has accumulated to allow meaningfully powered analysis.

Acknowledgements

SB has been funded by the National Institute for Health Research (NIHR), UK through a Clinician Scientist award (NIHR-CS-11-001) and also supported by the NIHR Biomedical Research Centre for Mental Health at the South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, Psychology and Neuroscience, King's College London jointly funded by the Guy's and St Thomas' Trustees and the South London and Maudsley Trustees.

Role of the funding source

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript;

and decision to submit the manuscript for publication. All authors have approved the final version of the paper.

Financial Disclosures

None.

ACCEPTED MANUSCRIPT

References

- Abdullaev, Y., Posner, M.I., Nunnally, R., Dishion, T.J., 2010. Functional MRI evidence for inefficient attentional control in adolescent chronic cannabis abuse. *Behav Brain Res* 215, 45-57.
- Acheson, A., Ray, K.L., Hines, C.S., Li, K., Dawes, M.A., Mathias, C.W., Dougherty, D.M., Laird, A.R., 2015. Functional activation and effective connectivity differences in adolescent marijuana users performing a simulated gambling task. *J Addict* 2015, 783106.
- Acheson, S.K., Moore, N.L., Kuhn, C.M., Wilson, W.A., Swartzwelder, H.S., 2011. The synthetic cannabinoid WIN 55212-2 differentially modulates thigmotaxis but not spatial learning in adolescent and adult animals. *Neurosci Lett* 487, 411-414.
- Alegria, A.A., Radua, J., Rubia, K., 2016. Meta-Analysis of fMRI Studies of Disruptive Behavior Disorders. *Am J Psychiatry* 173, 1119-1130.
- Andersen, S.L., 2003. Trajectories of brain development: point of vulnerability or window of opportunity? *Neurosci Biobehav Rev* 27, 3-18.
- Andrews-Hanna, J.R., Smallwood, J., Spreng, R.N., 2014. The default network and self-generated thought: component processes, dynamic control, and clinical relevance. *Annals of the New York Academy of Sciences* 1316, 29-52.
- Appiah-Kusi, E., Leyden, E., Parmar, S., Mondelli, V., McGuire, P., Bhattacharyya, S., 2016. Abnormalities in neuroendocrine stress response in psychosis: the role of endocannabinoids. *Psychological medicine* 46, 27-45.
- 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, 1055-1066.
- Batalla, A., Bhattacharyya, S., Yucel, M., Fusar-Poli, P., Crippa, J.A., Nogue, S., Torrens, M., Pujol, J., Farre, M., Martin-Santos, R., 2013. Structural and functional imaging studies in chronic cannabis users: a systematic review of adolescent and adult findings. *PLoS One* 8, e55821.
- Batalla, A., Crippa, J.A., Busatto, G.F., Guimaraes, F.S., Zuardi, A.W., Valverde, O., Atakan, Z., McGuire, P.K., Bhattacharyya, S., Martin-Santos, R., 2014. Neuroimaging studies of acute effects of THC and CBD in humans and animals: a systematic review. *Curr Pharm Des* 20, 2168-2185.
- Behan, B., Connolly, C.G., Datwani, S., Doucet, M., Ivanovic, J., Morioka, R., Stone, A., Watts, R., Smyth, B., Garavan, H., 2014. Response inhibition and elevated parietal-cerebellar correlations in chronic adolescent cannabis users. *Neuropharmacology* 84, 131-137.

Belue, R.C., Howlett, A.C., Westlake, T.M., Hutchings, D.E., 1995. The ontogeny of cannabinoid receptors in the brain of postnatal and aging rats. *Neurotoxicol Teratol* 17, 25-30.

Bhattacharyya, S., Atakan, Z., Martin-Santos, R., Crippa, J.A., Kambeitz, J., Malhi, S., Giampietro, V., Williams, S., Brammer, M., Rubia, K., Collier, D.A., McGuire, P.K., 2015. Impairment of inhibitory control processing related to acute psychotomimetic effects of cannabis. *Eur Neuropsychopharmacol* 25, 26-37.

Bhattacharyya, S., Atakan, Z., Martin-Santos, R., Crippa, J.A., Kambeitz, J., Prata, D., Williams, S., Brammer, M., Collier, D.A., McGuire, P.K., 2012a. Preliminary report of biological basis of sensitivity to the effects of cannabis on psychosis: AKT1 and DAT1 genotype modulates the effects of δ -9-tetrahydrocannabinol on midbrain and striatal function. *Mol Psychiatry* 17, 1152-1155.

Bhattacharyya, S., Atakan, Z., Martin-Santos, R., Crippa, J.A., McGuire, P.K., 2012b. Neural mechanisms for the cannabinoid modulation of cognition and affect in man: a critical review of neuroimaging studies. *Curr Pharm Des* 18, 5045-5054.

Bhattacharyya, S., Crippa, J.A., Allen, P., Martin-Santos, R., Borgwardt, S., Fusar-Poli, P., Rubia, K., Kambeitz, J., O'Carroll, C., Seal, M.L., Giampietro, V., Brammer, M., Zuardi, A.W., Atakan, Z., McGuire, P.K., 2012c. Induction of psychosis by Δ 9-tetrahydrocannabinol reflects modulation of prefrontal and striatal function during attentional salience processing. *Arch Gen Psychiatry* 69, 27-36.

Bhattacharyya, S., Egerton, A., Kim, E., Rosso, L., Riano Barros, D., Hammers, A., Brammer, M., Turkheimer, F.E., Howes, O.D., McGuire, P., 2017. Acute induction of anxiety in humans by delta-9-tetrahydrocannabinol related to amygdalar cannabinoid-1 (CB1) receptors. *Sci Rep* 7, 15025.

Bhattacharyya, S., Fusar-Poli, P., Borgwardt, S., Martin-Santos, R., Nosarti, C., O'Carroll, C., Allen, P., Seal, M.L., Fletcher, P.C., Crippa, J.A., Giampietro, V., Mechelli, A., Atakan, Z., McGuire, P., 2009. Modulation of mediotemporal and ventrostriatal function in humans by Delta9-tetrahydrocannabinol: a neural basis for the effects of Cannabis sativa on learning and psychosis. *Arch Gen Psychiatry* 66, 442-451.

Bhattacharyya, S., Morrison, P.D., Fusar-Poli, P., Martin-Santos, R., Borgwardt, S., Winton-Brown, T., Nosarti, C., CM, O.C., Seal, M., Allen, P., Mehta, M.A., Stone, J.M., Tunstall, N., Giampietro, V., Kapur, S., Murray, R.M., Zuardi, A.W., Crippa, J.A., Atakan, Z., McGuire, P.K., 2010. Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 35, 764-774.

Bhattacharyya, S., Sendt, K.V., 2012. Neuroimaging evidence for cannabinoid modulation of cognition and affect in man. *Front Behav Neurosci* 6, 22.

- Biegon, A., Kerman, I.A., 2001. Autoradiographic study of pre- and postnatal distribution of cannabinoid receptors in human brain. *Neuroimage* 14, 1463-1468.
- Block, R.I., O'Leary, D.S., Hichwa, R.D., Augustinack, J.C., Ponto, L.L., Ghoneim, M.M., Arndt, S., Ehrhardt, J.C., Hurtig, R.R., Watkins, G.L., Hall, J.A., Nathan, P.E., Andreasen, N.C., 2000. Cerebellar hypoactivity in frequent marijuana users. *Neuroreport* 11, 749-753.
- Bolla, K.I., Eldreth, D.A., Matochik, J.A., Cadet, J.L., 2005. Neural substrates of faulty decision-making in abstinent marijuana users. *Neuroimage* 26, 480-492.
- Bossong, M.G., Jager, G., van Hell, H.H., Zuurman, L., Jansma, J.M., Mehta, M.A., van Gerven, J.M., Kahn, R.S., Ramsey, N.F., 2012a. Effects of Delta9-tetrahydrocannabinol administration on human encoding and recall memory function: a pharmacological fMRI study. *J Cogn Neurosci* 24, 588-599.
- Bossong, M.G., Jansma, J.M., van Hell, H.H., Jager, G., Oudman, E., Saliasi, E., Kahn, R.S., Ramsey, N.F., 2012b. Effects of delta9-tetrahydrocannabinol on human working memory function. *Biol Psychiatry* 71, 693-699.
- Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain's default network: anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences* 1124, 1-38.
- Carey, S.E., Nestor, L., Jones, J., Garavan, H., Hester, R., 2015. Impaired learning from errors in cannabis users: Dorsal anterior cingulate cortex and hippocampus hypoactivity. *Drug Alcohol Depend* 155, 175-182.
- Chang, L., Chronicle, E.P., 2007. Functional imaging studies in cannabis users. *Neuroscientist* 13, 422-432.
- Chang, L., Yakupov, R., Cloak, C., Ernst, T., 2006. Marijuana use is associated with a reorganized visual-attention network and cerebellar hypoactivation. *Brain* 129, 1096-1112.
- Colizzi, M., McGuire, P., Pertwee, R.G., Bhattacharyya, S., 2016. Effect of cannabis on glutamate signalling in the brain: A systematic review of human and animal evidence. *Neurosci Biobehav Rev* 64, 359-381.
- Cousijn, J., Vingerhoets, W.A., Koenders, L., de Haan, L., van den Brink, W., Wiers, R.W., Goudriaan, A.E., 2014. Relationship between working-memory network function and substance use: a 3-year longitudinal fMRI study in heavy cannabis users and controls. *Addict Biol* 19, 282-293.
- Cousijn, J., Wiers, R.W., Ridderinkhof, K.R., van den Brink, W., Veltman, D.J., Goudriaan, A.E., 2012. Grey matter alterations associated with cannabis use: results of a VBM study in heavy cannabis users and healthy controls. *Neuroimage* 59, 3845-3851.

Cousijn, J., Wiers, R.W., Ridderinkhof, K.R., van den Brink, W., Veltman, D.J., Porrino, L.J., Goudriaan, A.E., 2013. Individual differences in decision making and reward processing predict changes in cannabis use: a prospective functional magnetic resonance imaging study. *Addict Biol* 18, 1013-1023.

Crane, N.A., Schuster, R.M., Fusar-Poli, P., Gonzalez, R., 2013. Effects of cannabis on neurocognitive functioning: recent advances, neurodevelopmental influences, and sex differences. *Neuropsychol Rev* 23, 117-137.

Crean, R.D., Crane, N.A., Mason, B.J., 2011. An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. *J Addict Med* 5, 1-8.

Crippa, J.A., Zuardi, A.W., Martin-Santos, R., Bhattacharyya, S., Atakan, Z., McGuire, P., Fusar-Poli, P., 2009. Cannabis and anxiety: a critical review of the evidence. *Hum Psychopharmacol* 24, 515-523.

Crossley, N.A., Mechelli, A., Fusar-Poli, P., Broome, M.R., Matthiasson, P., Johns, L.C., Bramon, E., Valmaggia, L., Williams, S.C., McGuire, P.K., 2009. Superior temporal lobe dysfunction and frontotemporal dysconnectivity in subjects at risk of psychosis and in first-episode psychosis. *Hum Brain Mapp* 30, 4129-4137.

Curran, H.V., Brignell, C., Fletcher, S., Middleton, P., Henry, J., 2002. Cognitive and subjective dose-response effects of acute oral Delta 9-tetrahydrocannabinol (THC) in infrequent cannabis users. *Psychopharmacology (Berl)* 164, 61-70.

D'Souza, D.C., Perry, E., MacDougall, L., Ammerman, Y., Cooper, T., Wu, Y.T., Braley, G., Gueorguieva, R., Krystal, J.H., 2004. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 29, 1558-1572.

Dalton, V.S., Zavitsanou, K., 2010. Cannabinoid effects on CB1 receptor density in the adolescent brain: an autoradiographic study using the synthetic cannabinoid HU210. *Synapse* 64, 845-854.

DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. *Control Clin Trials* 7, 177-188.

Eldreth, D.A., Matochik, J.A., Cadet, J.L., Bolla, K.I., 2004. Abnormal brain activity in prefrontal brain regions in abstinent marijuana users. *Neuroimage* 23, 914-920.

Elphick, M.R., Egertova, M., 2001. The neurobiology and evolution of cannabinoid signalling. *Philos Trans R Soc Lond B Biol Sci* 356, 381-408.

Fox, K.M., Sterling, R.C., Van Bockstaele, E.J., 2009a. Cannabinoids and novelty investigation: influence of age and duration of exposure. *Behav Brain Res* 196, 248-253.

Fox, M.D., Corbetta, M., Snyder, A.Z., Vincent, J.L., Raichle, M.E., 2006. Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. *Proc Natl Acad Sci U S A* 103, 10046-10051.

Fox, M.D., Zhang, D., Snyder, A.Z., Raichle, M.E., 2009b. The global signal and observed anticorrelated resting state brain networks. *J Neurophysiol* 101, 3270-3283.

Gage, S.H., Hickman, M., Zammit, S., 2016. Association Between Cannabis and Psychosis: Epidemiologic Evidence. *Biol Psychiatry* 79, 549-556.

Ganzer, F., Bröning, S., Kraft, S., Sack, P.M., Thomasius, R., 2016. Weighing the Evidence: A Systematic Review on Long-Term Neurocognitive Effects of Cannabis Use in Abstinent Adolescents and Adults. *Neuropsychol Rev* 26, 186-222.

Glass, M., Dragunow, M., Faull, R.L., 1997. Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. *Neuroscience* 77, 299-318.

Goldenberg, M., IsHak, W.W., Danovitch, I., 2017. Quality of life and recreational cannabis use. *Am J Addict* 26, 8-25.

Gonzalez, R., 2007. Acute and non-acute effects of cannabis on brain functioning and neuropsychological performance. *Neuropsychol Rev* 17, 347-361.

Gorka, S.M., Phan, K.L., Lyons, M., Mori, S., Angstadt, M., Rabinak, C.A., 2016. Cannabinoid Modulation of Frontolimbic Activation and Connectivity During Volitional Regulation of Negative Affect. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 41, 1888-1896.

Grotenhermen, F., 2003. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet* 42, 327-360.

Gruber, S.A., Dahlgren, M.K., Sagar, K.A., Gönenc, A., Killgore, W.D., 2012. Age of onset of marijuana use impacts inhibitory processing. *Neurosci Lett* 511, 89-94.

Gruber, S.A., Rogowska, J., Yurgelun-Todd, D.A., 2009. Altered affective response in marijuana smokers: an fMRI study. *Drug Alcohol Depend* 105, 139-153.

Harding, I.H., Solowij, N., Harrison, B.J., Takagi, M., Lorenzetti, V., Lubman, D.I., Seal, M.L., Pantelis, C., Yücel, M., 2012. Functional connectivity in brain networks underlying cognitive control in chronic cannabis users. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 37, 1923-1933.

Heath, R.G., Fitzjarrell, A.T., Fontana, C.J., Garey, R.E., 1980. Cannabis sativa: effects on brain function and ultrastructure in rhesus monkeys. *Biol Psychiatry* 15, 657-690.

Hedges, L.V., Olkin, I., 1985. *Statistical Methods for Meta-Analysis*. Academic Press, San Diego, pp. 1-14.

Heitzeg, M.M., Cope, L.M., Martz, M.E., Hardee, J.E., Zucker, R.A., 2015. Brain activation to negative stimuli mediates a relationship between adolescent marijuana use and later emotional functioning. *Dev Cogn Neurosci* 16, 71-83.

Hester, R., Nestor, L., Garavan, H., 2009. Impaired error awareness and anterior cingulate cortex hypoactivity in chronic cannabis users. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 34, 2450-2458.

Imam, A., Ajao, M.S., Akinola, O.B., Ajibola, M.I., Ibrahim, A., Amin, A., Abdulmajeed, W.I., Lawal, Z.A., Ali-Oluwafuyi, A., 2017. Repeated Acute Oral Exposure to Cannabis sativa Impaired Neurocognitive Behaviours and Cortico-hippocampal Architectonics in Wistar Rats. *Niger J Physiol Sci* 31, 153-159.

Iversen, L., 2003. Cannabis and the brain. *Brain* 126, 1252-1270.

Jacobus, J., Bava, S., Cohen-Zion, M., Mahmood, O., Tapert, S.F., 2009. Functional consequences of marijuana use in adolescents. *Pharmacol Biochem Behav* 92, 559-565.

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

Jager, G., Block, R.I., Luijten, M., Ramsey, N.F., 2010. Cannabis use and memory brain function in adolescent boys: a cross-sectional multicenter functional magnetic resonance imaging study. *J Am Acad Child Adolesc Psychiatry* 49, 561-572. e561-563.

Jager, G., Block, R.I., Luijten, M., Ramsey, N.F., 2013. Tentative evidence for striatal hyperactivity in adolescent cannabis-using boys: a cross-sectional multicenter fMRI study. *J Psychoactive Drugs* 45, 156-167.

Jager, G., Kahn, R.S., Van Den Brink, W., Van Ree, J.M., Ramsey, N.F., 2006. Long-term effects of frequent cannabis use on working memory and attention: an fMRI study. *Psychopharmacology (Berl)* 185, 358-368.

Jager, G., Van Hell, H.H., De Win, M.M., Kahn, R.S., Van Den Brink, W., Van Ree, J.M., Ramsey, N.F., 2007. Effects of frequent cannabis use on hippocampal activity during an associative memory task. *Eur Neuropsychopharmacol* 17, 289-297.

JPT, H., 2011. *Cochrane Handbook for Systematic Reviews of Interventions* in: S, G. (Ed.). The Cochrane Collaboration.

Kanayama, G., Rogowska, J., Pope, H.G., Gruber, S.A., Yurgelun-Todd, D.A., 2004. Spatial working memory in heavy cannabis users: a functional magnetic resonance imaging study. *Psychopharmacology (Berl)* 176, 239-247.

Kapur, S., 2003. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry* 160, 13-23.

King, G.R., Ernst, T., Deng, W., Stenger, A., Gonzales, R.M., Nakama, H., Chang, L., 2011. Altered brain activation during visuomotor integration in chronic active cannabis users: relationship to cortisol levels. *J Neurosci* 31, 17923-17931.

Landfield, P.W., Cadwallader, L.B., Vinsant, S., 1988. Quantitative changes in hippocampal structure following long-term exposure to delta 9-tetrahydrocannabinol: possible mediation by glucocorticoid systems. *Brain Res* 443, 47-62.

Lopez-Larson, M.P., Rogowska, J., Bogorodzki, P., Bueler, C.E., McGlade, E.C., Yurgelun-Todd, D.A., 2012. Cortico-cerebellar abnormalities in adolescents with heavy marijuana use. *Psychiatry Res* 202, 224-232.

Lundqvist, T., 2005. Cognitive consequences of cannabis use: comparison with abuse of stimulants and heroin with regard to attention, memory and executive functions. *Pharmacol Biochem Behav* 81, 319-330.

Mai, J.K., Voss, T., Paxinos, G., 2008. *Atlas of the human brain*, 3rd ed. Elsevier Academic Press, Amsterdam.

Marconi, A., Di Forti, M., Lewis, C.M., Murray, R.M., Vassos, E., 2016. Meta-analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis. *Schizophrenia bulletin*.

Martin-Santos, R., Fagundo, A.B., Crippa, J.A., Atakan, Z., Bhattacharyya, S., Allen, P., Fusar-Poli, P., Borgwardt, S., Seal, M., Busatto, G.F., McGuire, P., 2010. Neuroimaging in cannabis use: a systematic review of the literature. *Psychological medicine* 40, 383-398.

Mato, S., Del Olmo, E., Pazos, A., 2003. Ontogenetic development of cannabinoid receptor expression and signal transduction functionality in the human brain. *Eur J Neurosci* 17, 1747-1754.

Matochik, J.A., Eldreth, D.A., Cadet, J.L., Bolla, K.I., 2005. Altered brain tissue composition in heavy marijuana users. *Drug Alcohol Depend* 77, 23-30.

Meier, M.H., Caspi, A., Ambler, A., Harrington, H., Houts, R., Keefe, R.S., McDonald, K., Ward, A., Poulton, R., Moffitt, T.E., 2012. Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proc Natl Acad Sci U S A* 109, E2657-2664.

Menon, V., 2011. Large-scale brain networks and psychopathology: a unifying triple network model. *Trends in cognitive sciences* 15, 483-506.

Menon, V., 2015. Salience Network, in: Toga, A.W. (Ed.), *Brain Mapping: An Encyclopedic Reference*. Academic Press: Elsevier, pp. 597-611.

Minzenberg, M.J., Laird, A.R., Thelen, S., Carter, C.S., Glahn, D.C., 2009. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. *Arch Gen Psychiatry* 66, 811-822.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Group, P., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 339, b2535.

Mokrysz, C., Freeman, T.P., Korkki, S., Griffiths, K., Curran, H.V., 2016. Are adolescents more vulnerable to the harmful effects of cannabis than adults? A placebo-controlled study in human males. *Transl Psychiatry* 6, e961.

Moore, T.H., Zammit, S., Lingford-Hughes, A., Barnes, T.R., Jones, P.B., Burke, M., Lewis, G., 2007. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet* 370, 319-328.

Morrison, P.D., Nottage, J., Stone, J.M., Bhattacharyya, S., Tunstall, N., Brenneisen, R., Holt, D., Wilson, D., Sumich, A., McGuire, P., Murray, R.M., Kapur, S., Ffytche, D.H., 2011. Disruption of frontal theta coherence by Delta9-tetrahydrocannabinol is associated with positive psychotic symptoms. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 36, 827-836.

Nestor, L., Hester, R., Garavan, H., 2010. Increased ventral striatal BOLD activity during non-drug reward anticipation in cannabis users. *Neuroimage* 49, 1133-1143.

Nestor, L., Roberts, G., Garavan, H., Hester, R., 2008. Deficits in learning and memory: parahippocampal hyperactivity and frontocortical hypoactivity in cannabis users. *Neuroimage* 40, 1328-1339.

Norman, L.J., Carlisi, C., Lukito, S., Hart, H., Mataix-Cols, D., Radua, J., Rubia, K., 2016. Structural and Functional Brain Abnormalities in Attention-Deficit/Hyperactivity Disorder and Obsessive-Compulsive Disorder: A Comparative Meta-analysis. *JAMA Psychiatry* 73, 815-825.

Patel, R., Wilson, R., Jackson, R., Ball, M., Shetty, H., Broadbent, M., Stewart, R., McGuire, P., Bhattacharyya, S., 2016. Association of cannabis use with hospital admission and antipsychotic treatment failure in first episode psychosis: an observational study. *BMJ open* 6, e009888.

Pertwee, R.G., 2006. The pharmacology of cannabinoid receptors and their ligands: an overview. *Int J Obes (Lond)* 30 Suppl 1, S13-18.

Phan, K.L., Angstadt, M., Golden, J., Onyewuenyi, I., Popovska, A., de Wit, H., 2008. Cannabinoid modulation of amygdala reactivity to social signals of threat in humans. *J Neurosci* 28, 2313-2319.

Pillay, S.S., Rogowska, J., Kanayama, G., Gruber, S., Simpson, N., Pope, H.G., Yurgelun-Todd, D.A., 2008. Cannabis and motor function: fMRI changes following 28 days of discontinuation. *Exp Clin Psychopharmacol* 16, 22-32.

Pillay, S.S., Rogowska, J., Kanayama, G., Jon, D.I., Gruber, S., Simpson, N., Cherayil, M., Pope, H.G., Yurgelun-Todd, D.A., 2004. Neurophysiology of motor function following cannabis discontinuation in chronic cannabis smokers: an fMRI study. *Drug Alcohol Depend* 76, 261-271.

Quickfall, J., Crockford, D., 2006. Brain neuroimaging in cannabis use: a review. *J Neuropsychiatry Clin Neurosci* 18, 318-332.

Quinn, H.R., Matsumoto, I., Callaghan, P.D., Long, L.E., Arnold, J.C., Gunasekaran, N., Thompson, M.R., Dawson, B., Mallet, P.E., Kashem, M.A., Matsuda-Matsumoto, H., Iwazaki, T., McGregor, I.S., 2008. Adolescent rats find repeated Delta(9)-THC less aversive than adult rats but display greater residual cognitive deficits and changes in hippocampal protein expression following exposure. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 33, 1113-1126.

Radua, J., Mataix-Cols, D., 2009. Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. *Br J Psychiatry* 195, 393-402.

Radua, J., Mataix-Cols, D., Phillips, M.L., El-Hage, W., Kronhaus, D.M., Cardoner, N., Surguladze, S., 2012. A new meta-analytic method for neuroimaging studies that combines reported peak coordinates and statistical parametric maps. *Eur Psychiatry* 27, 605-611.

Radua, J., Rubia, K., Canales-Rodríguez, E.J., Pomarol-Clotet, E., Fusar-Poli, P., Mataix-Cols, D., 2014. Anisotropic kernels for coordinate-based meta-analyses of neuroimaging studies. *Front Psychiatry* 5, 13.

Radua, J., Schmidt, A., Borgwardt, S., Heinz, A., Schlagenhauf, F., McGuire, P., Fusar-Poli, P., 2015. Ventral Striatal Activation During Reward Processing in Psychosis: A Neurofunctional Meta-Analysis. *JAMA Psychiatry* 72, 1243-1251.

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 2001. A default mode of brain function. *Proc Natl Acad Sci U S A* 98, 676-682.

Rice, D., Barone, S., Jr., 2000. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. *Environ Health Perspect* 108 Suppl 3, 511-533.

Roser, P., Lissek, S., Tegenthoff, M., Nicolas, V., Juckel, G., Brüne, M., 2012. Alterations of theory of mind network activation in chronic cannabis users. *Schizophr Res* 139, 19-26.

Rubia, K., Alegria, A.A., Cubillo, A.I., Smith, A.B., Brammer, M.J., Radua, J., 2014. Effects of stimulants on brain function in attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *Biol Psychiatry* 76, 616-628.

Rubino, T., Prini, P., Piscitelli, F., Zamberletti, E., Trusel, M., Melis, M., Sagheddu, C., Ligresti, A., Tonini, R., Di Marzo, V., Parolaro, D., 2015. Adolescent exposure to THC in female rats disrupts developmental changes in the prefrontal cortex. *Neurobiol Dis* 73, 60-69.

Russo, E.B., 2007. History of cannabis and its preparations in saga, science, and sobriquet. *Chem Biodivers* 4, 1614-1648.

Sagar, K.A., Dahlgren, M.K., Gönenç, A., Racine, M.T., Dreman, M.W., Gruber, S.A., 2015. The impact of initiation: Early onset marijuana smokers demonstrate altered Stroop performance and brain activation. *Dev Cogn Neurosci* 16, 84-92.

Scallet, A.C., Uemura, E., Andrews, A., Ali, S.F., McMillan, D.E., Paule, M.G., Brown, R.M., Slikker, W., 1987. Morphometric studies of the rat hippocampus following chronic delta-9-tetrahydrocannabinol (THC). *Brain Res* 436, 193-198.

Schneider, M., Koch, M., 2003. Chronic pubertal, but not adult chronic cannabinoid treatment impairs sensorimotor gating, recognition memory, and the performance in a progressive ratio task in adult rats. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 28, 1760-1769.

Schoeler, T., Bhattacharyya, S., 2013. The effect of cannabis use on memory function: an update. *Substance abuse and rehabilitation* 4, 11-27.

Schoeler, T., Kambeitz, J., Behlke, I., Murray, R., Bhattacharyya, S., 2016a. The effects of cannabis on memory function in users with and without a psychotic disorder: findings from a combined meta-analysis. *Psychological medicine* 46, 177-188.

Schoeler, T., Monk, A., Sami, M.B., Klamerus, E., Foglia, E., Brown, R., Camuri, G., Altamura, A.C., Murray, R., Bhattacharyya, S., 2016b. Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis. *The lancet. Psychiatry* 3, 215-225.

Schoeler, T., Petros, N., Di Forti, M., Klamerus, E., Foglia, E., Ajnakina, O., Gayer-Anderson, C., Colizzi, M., Quattrone, D., Behlke, I., Shetty, S., McGuire, P., David, A.S., Murray, R., Bhattacharyya, S., 2016c. Effects of continuation, frequency, and type of cannabis use on relapse in the first 2 years after onset of psychosis: an observational study. *The lancet. Psychiatry* 3, 947-953.

Schoeler, T., Petros, N., Di Forti, M., Pingault, J.B., Klamerus, E., Foglia, E., Small, A., Murray, R., Bhattacharyya, S., 2016d. Association Between Continued Cannabis Use and Risk of Relapse in First-Episode Psychosis: A Quasi-Experimental Investigation Within an Observational Study. *JAMA Psychiatry* 73, 1173-1179.

Schreiner, A.M., Dunn, M.E., 2012. Residual effects of cannabis use on neurocognitive performance after prolonged abstinence: a meta-analysis. *Exp Clin Psychopharmacol* 20, 420-429.

Schweinsburg, A.D., Brown, S.A., Tapert, S.F., 2008a. The influence of marijuana use on neurocognitive functioning in adolescents. *Curr Drug Abuse Rev* 1, 99-111.

Schweinsburg, A.D., Nagel, B.J., Schweinsburg, B.C., Park, A., Theilmann, R.J., Tapert, S.F., 2008b. Abstinent adolescent marijuana users show altered fMRI response during spatial working memory. *Psychiatry Res* 163, 40-51.

Schweinsburg, A.D., Schweinsburg, B.C., Nagel, B.J., Eyler, L.T., Tapert, S.F., 2011. Neural correlates of verbal learning in adolescent alcohol and marijuana users. *Addiction* 106, 564-573.

Scognamiglio, C., Houenou, J., 2014. A meta-analysis of fMRI studies in healthy relatives of patients with schizophrenia. *Aust N Z J Psychiatry* 48, 907-916.

Sdmproject.com, 2017. Seed-based d Mapping (formerly Signed Differential Mapping) - Meta-analyses of neuroimaging data.

Sedgwick, P., Marston, L., 2015. How to read a funnel plot in a meta-analysis. *BMJ* 351, h4718.

Seeley, W.W., Menon, V., Schatzberg, A.F., Keller, J., Glover, G.H., Kenna, H., Reiss, A.L., Greicius, M.D., 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci* 27, 2349-2356.

Seghier, M.L., 2013. The angular gyrus: multiple functions and multiple subdivisions. *Neuroscientist* 19, 43-61.

Sevy, S., Smith, G.S., Ma, Y., Dhawan, V., Chaly, T., Kingsley, P.B., Kumra, S., Abdelmessih, S., Eidelberg, D., 2008. Cerebral glucose metabolism and D2/D3 receptor availability in young adults with cannabis dependence measured with positron emission tomography. *Psychopharmacology (Berl)* 197, 549-556.

Silveri, M.M., Dager, A.D., Cohen-Gilbert, J.E., Sneider, J.T., 2016. Neurobiological signatures associated with alcohol and drug use in the human adolescent brain. *Neurosci Biobehav Rev* 70, 244-259.

Smith, A.M., López, Z.R.A., D., A.C., A., L.C., Ian, C., J., H.M., A., F.P., 2011. Impact of Marijuana on Response Inhibition: an fMRI Study in Young Adults. *Journal of Behavioral and Brain Science* 01, 124-133.

Sneider, J.T., Gruber, S.A., Rogowska, J., Silveri, M.M., Yurgelun-Todd, D.A., 2013. A preliminary study of functional brain activation among marijuana users during performance of a virtual water maze task. *J Addict* 2013, 461029.

Solowij, N., Stephens, R.S., Roffman, R.A., Babor, T., Kadden, R., Miller, M., Christiansen, K., McRee, B., Vendetti, J., Marijuana Treatment Project Research, G.,

2002. Cognitive functioning of long-term heavy cannabis users seeking treatment. *JAMA* 287, 1123-1131.

Spear, L.P., 2007. Assessment of adolescent neurotoxicity: rationale and methodological considerations. *Neurotoxicol Teratol* 29, 1-9.

Spechler, P.A., Orr, C.A., Chaarani, B., Kan, K.J., Mackey, S., Morton, A., Snowe, M.P., Hudson, K.E., Althoff, R.R., Higgins, S.T., Cattrell, A., Flor, H., Nees, F., Banaschewski, T., Bokde, A.L., Whelan, R., Büchel, C., Bromberg, U., Conrod, P., Frouin, V., Papadopoulos, D., Gallinat, J., Heinz, A., Walter, H., Ittermann, B., Gowland, P., Paus, T., Poustka, L., Martinot, J.L., Artiges, E., Smolka, M.N., Schumann, G., Garavan, H., Consortium, I., 2015. Cannabis use in early adolescence: Evidence of amygdala hypersensitivity to signals of threat. *Dev Cogn Neurosci* 16, 63-70.

Sridharan, D., Levitin, D.J., Menon, V., 2008. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proc Natl Acad Sci U S A* 105, 12569-12574.

Stroup, D.F., Berlin, J.A., Morton, S.C., Olkin, I., Williamson, G.D., Rennie, D., Moher, D., Becker, B.J., Sipe, T.A., Thacker, S.B., 2000. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 283, 2008-2012.

Tapert, S.F., Schweinsburg, A.D., Drummond, S.P., Paulus, M.P., Brown, S.A., Yang, T.T., Frank, L.R., 2007. Functional MRI of inhibitory processing in abstinent adolescent marijuana users. *Psychopharmacology (Berl)* 194, 173-183.

Tzilos, G.K., Cintron, C.B., Wood, J.B., Simpson, N.S., Young, A.D., Pope, H.G., Jr., Yurgelun-Todd, D.A., 2005. Lack of hippocampal volume change in long-term heavy cannabis users. *Am J Addict* 14, 64-72.

Unodc, 2017. Market analysis of plant-based drugs., *World Drug Report 2017* ed. United Nations

van Hell, H.H., Bossong, M.G., Jager, G., Kristo, G., van Osch, M.J., Zelaya, F., Kahn, R.S., Ramsey, N.F., 2011. Evidence for involvement of the insula in the psychotropic effects of THC in humans: a double-blind, randomized pharmacological MRI study. *Int J Neuropsychopharmacol* 14, 1377-1388.

van Hell, H.H., Jager, G., Bossong, M.G., Brouwer, A., Jansma, J.M., Zuurman, L., van Gerven, J., Kahn, R.S., Ramsey, N.F., 2012. Involvement of the endocannabinoid system in reward processing in the human brain. *Psychopharmacology (Berl)* 219, 981-990.

van Hell, H.H., Vink, M., Ossewaarde, L., Jager, G., Kahn, R.S., Ramsey, N.F., 2010. Chronic effects of cannabis use on the human reward system: an fMRI study. *Eur Neuropsychopharmacol* 20, 153-163.

Verdurand, M., Nguyen, V., Stark, D., Zahra, D., Gregoire, M.C., Greguric, I., Zavitsanou, K., 2011. Comparison of Cannabinoid CB(1) Receptor Binding in Adolescent and Adult Rats: A Positron Emission Tomography Study Using [F]MK-9470. *Int J Mol Imaging* 2011, 548123.

Viechtbauer, W., 2005. Bias and efficiency of meta-analytic variance estimators in the random-effects model. *Journal of Educational and Behavioral Statistics* 30, 261-293.

Wesley, M.J., Hanlon, C.A., Porrino, L.J., 2011. Poor decision-making by chronic marijuana users is associated with decreased functional responsiveness to negative consequences. *Psychiatry Res* 191, 51-59.

Wijayendran, S.B., O'Neill, A., Bhattacharyya, S., 2016. The effects of cannabis use on salience attribution: a systematic review. *Acta neuropsychiatrica*, 1-15.

Winton-Brown, T.T., Allen, P., Bhattacharyya, S., Borgwardt, S.J., Fusar-Poli, P., Crippa, J.A., Seal, M.L., Martin-Santos, R., Ffytche, D., Zuardi, A.W., Atakan, Z., McGuire, P.K., 2011. Modulation of auditory and visual processing by delta-9-tetrahydrocannabinol and cannabidiol: an FMRI study. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 36, 1340-1348.

Yücel, M., Solowij, N., Respondek, C., Whittle, S., Fornito, A., Pantelis, C., Lubman, D.I., 2008. Regional brain abnormalities associated with long-term heavy cannabis use. *Arch Gen Psychiatry* 65, 694-701.

Zimmermann, K., Yao, S., Heinz, M., Zhou, F., Dau, W., Banger, M., Weber, B., Hürlemann, R., Becker, B., 2017. Altered orbitofrontal activity and dorsal striatal connectivity during emotion processing in dependent marijuana users after 28 days of abstinence. *Psychopharmacology (Berl)*.

7. Figures and Tables

Figure 1; PRISMA flowchart of search strategy for adult and adolescent meta-analysis.

Figure 2; Maps of statistically significant differences in activation between cannabis users and healthy controls (Voxel threshold = $p < 0.005$, peak height threshold: peak SDM-Z < 1, clusters ≥ 10). Areas of increased activation in cannabis users compared to controls are depicted in red and areas of decreased activation in cannabis users compared to controls are depicted in blue. Left side of the brain is shown on the left side of the images.

A = Adult meta-analysis results

B = Adolescent meta-analysis results

Table 1; Functional magnetic resonance imaging studies involving adult cannabis users and healthy controls included in the meta-analysis.

Study	Task	CU M/F	HC M/F	Age of CU (years)	Age of HC (years)	Quantity of cannabis used by CU	Quantity of cannabis used by HC	Time between scan and last smoke	Age of onset of cannabis use for CU (years)	Mean years of cannabis use by CU	fMRI activation paradigms (tasks)	Results of Whole Brain Analysis	Task Performance	Number of task comparisons	Tesla	fMRI method
(Abdullaev et al., 2010)	Attention Network Task	10/4	10/4	19.5 (0.8) (SD)	19.7 (1.4) (SD)	71-196 days per year	0	48 hours	12-16	N/A	Executive task; Alerting task; Orienting task.	CU>HC RLPFC, Supplementary motor cortex, Lateral parietal cortex; No difference for Alerting & Orientation task.	Longer reaction time for CU. More errors made for executive task.	3	3T	FSL
	Use Generation Task	5/2	5/2	19.6 (0.9)	20 (0.2) (SD)	71-196 days per year	0	48 Hours	12-16	N/A	Generating nouns versus reading nouns; difficult words versus easy words.	CU>HC RVPFC. HC>CU ACG to LPFC, L temporo-parietal cortex; CU>HC ACC, R fordital cortex, L Frontal Pole & L precuneus.	N/A	2	3T	FSL
(Smith et al., 2011)	Go/NoGo Task	6/4	9/5	19-21	19-21	> 1 joints per week	<4 x per year	>3 hours	N/A	4.55 years	Press all but X; Press X	No significant differences in both tasks after including covariates.	No Significant difference	2	1.5T	SPM

(Chang et al., 2006)	Visual-Attention Task	9/3	11/8	27.91 6 3.13 (SEM)	30.57 6 1.83 (SEM)	≥5 days per week	N/A	4-24 hours	9-20	36-448 months	Visual attention	CU>HC Small clusters of L precuneus, LOLG & L limbic uncus. HC>CU RFC, R & L dorsal parietal and R cerebella.	No Significant difference	1	4T	SPM
	Visual-Attention Task	6/6	11/8	29.63 6 2.50 (SEM)	30.57 6 1.83 (SEM)	≥5 days per week	N/A	0.5 - 156 months	12-16	48-276 months	Visual attention	CU>HC Small clusters in the frontal, parital, temporal and occipital regions. HC>CU MFG, SFG, IFG, R dorsal MPL & declive.	No Significant Difference	1	4T	SPM
(Cousijn et al., 2012)	Iowa Gambling Task	21/1 1	26/1 5	21.4 (2.3) (SD) 18-25	22.2 (2.4) (SD) 18-25	> 10 days per month	<50 lifetime use	24 hours	N/A	2.5 (1.9) (SD)	Win>Loss; Loss>Win	CU>HC ROFC, R insula, LSTG; No activation difference.	No Significant difference	2	3T	FEAT
(Gruber, Rogowska and Yurgelun-Todd, 2009)	Facial affect task	14/1	14/1	25 (±8.8)	26 (±9.0)	4-7 days per week	N/A	12 hours	14.9 (±2.50)	N/A	Viewing Angry Faces; Viewing Happy Faces	CU>HC IFG, R precuneus, RF paracetrar lobe, LSTG, cerebellar, RMTG, HC>CU LSPL, interhemispheric precuneus, L cingulate Gyrus; CU>HC cerebella, HC>CU STG & sub.lobular space.	No Performance data	2	3T	SPM
(Heitzeg et al., 2015)	Emotional arousal word task	12/8	14/6	19.84 (1.45) (SD) 17-22	20.51 (1.26) (SD) 17-22	>100 time (average 618.12)	<10 lifetime use	48 hours	N/A	13.4 (2.7) (SD)	Negative words; Positive words.	HC>CU RME, Dorsolateral SFT, RMTG, RSTG, R calcarine fissure & Insula; CU>HC R Dorsolateral SFG, HC>CU RIPL.	No Significant difference	2	3T	SPM

(King et al., 2011)	Checker-board task	16/14	16/14	M = 21 F = 22.5 18-45	M = 23 F = 24.5 18-45	6-7 days per week	N/A	12 hours	M = 14.5 F = 16 (years)	M = 78 F = 63 (months)	2HZ frequency; 4HZ frequency	CU>HC SFG, HC>CU LG & cuneus; L postcentral gyrus, Bi. MFG, RSPG, R frontal pole, HC>CU R postcentral gyrus, R precentral gyrus & L LG.	None Taken	2	3T	FMRIB
(Kanayama et al., 2004)	Spatial working memory Task	10/2	6/4	37.9 (7.4) (SD) 30-55	27.8 (7.9) (SD)	5100-54000 life time use	0	6-36 hours	N/A	>5000 lifetime use	Short- delay task minus perception task.	CU>HC SFG, MFG, IFG, RSTG, Bi. ACG. R. precentral gyrus, caudate & putamen. HC>CU MFC.	No Significant difference	1	1.5T	SPM
(Nestor, Hester and Garavan, 2010)	Monetary incentive delay task	12/2	11/3	22.1 ± 1.2 (SEM) 18-40	23.1 ± 1.2 (SEM) 18-40	5-7 days per week	3.0 ± 0.6 lifetime use	12-505 hours	16.1 ± 0.4 (SEM)	6.1 ± 1.1 (SEM)	Neutral lose; Neutral win; Lose 50 cent; Save 50 cent; Miss 50 cent; Win 50 cent.	CU>HC neutral lose & win in no. of regions inc. caudate nucleus, inferior cingulate, & parahippocampal gyri. HC>CU in L insula during lose outcome and save 50.	No Significant difference	6	3T	AFNI
(Nestor et al., 2008)	Face-Name pairs task	32/3	29/9	22.3 ± 0.5 (SEM)	22.0 ± 0.4 (SEM)	5-7 days per week	< 10 lifetimes use	3-686 hours	16.5 ± 0.4 (SEM)	5.7 ± 0.6 (SEM)	Learning phase; Recall phase.	HC>CU in RSTG, RSFG, LSFG; No difference in recall.	No Significant difference	2	3T	AFNI
(van Hell et al., 2010)	Monetary reward task	13/1	11/2	24 (± 4.4) (SEM)	24 (± 2.7) (SEM)	1500-9700 life time use range	N/A	1 week	N/A	N/A	Anticipation; Reward.	CU>HC Bi. MTG, R cuneus & R parahippocampal gyrus. HC>CU Bi. nucleus accumbens, caudate nucleus, SFG, L putamen, RIFG, R medial FG & L cingulate	No Significant difference	2	1.5T	SPM

												gyrus; CU>HC Bi. putamen, R caudate nucleus.				
(Wesley, Hanlon and Porrino, 2011)	Iowa Gambling Task	9/7	6/10	26.4 (3.6) (SD)	26.6 (6.1) (SD)	Mean 29.4 days per month	<50 lifetime use	None from 12am	16.3 (2.1) (SD)	9.6 (4.1) (SD)	Win; Lose	No difference in Win; HC>CU Bi. MFG, R ACC, Precuneus & superior parietal lobe, L declive.	More loss events for CU	2	1.5T	SPM
(Sneider et al., 2013)	Virtual Water Maze Task	8/2	11/7	18-30	18-33	≥5 days per week	<5 lifetime use	12 hours	15.6 ± 1.2 (SD)	4.0 ± 2.4 (SD) (years)	Retrieval - motor control	HC>CU Bi. IF pars triangularis, IF par opercularis, MFG. LSFG, LSF par orbitalis, R pallidum & putamen.	Longer path length, same time taken. User group significantly less time to move.	1	3T	SPM

CU = Cannabis Users, HC = Healthy Controls, M = Male, F = Female, WBA = Whole Brain Analysis, T = Tesla R = Right, L = Left, Bi. = Bilateral, (V)PFC = (Ventral) Prefrontal Cortex, ACG = Anterior Cingulate Gyrus, (O)LG = (Occipital) Lingual Gyrus, FC = Frontal Cortex, MFG = Middle Frontal Gyrus, SFG = Superior Frontal Gyrus, IFG = Inferior Frontal Gyrus, OFC, Orbitofrontal Cortex, STG = Superior Temporal Gyrus, MTG = Medial Temporal Gyrus, ACC = Anterior Cingulate Cortex, IF = Inferior Frontal, SPL = Superior Parietal Lobe, MPL = Medial Parietal Lobe, SPG = Superior Parietal Gyrus, IPL = Inferior Parietal Lobe, N/A = Quantity not reported in paper, SD = Standard Deviation SEM = Standard error of the mean.

Table 2; Functional magnetic resonance imaging studies involving adolescent cannabis users and healthy controls; used in the meta-analysis.

Study	Task	CU M/F	HC M/F	Age of CU (years)	Age of HC (years)	Quantity of cannabis used by CU	Quantity of cannabis used by HC	Time between scan and last smoke	Age onset of cannabis use for CU (years)	Average years of cannabis use by CU	fMRI activation paradigm s (tasks)	Results WBA	Task Performance results	Number of task comparisons	Tesla	fMRI method
(Acheson et al., 2015)	Win/Lose Gambling Task	11/3	11/3	17.3 (1.3) (SEM)	17.6 (1.0) (SEM)	>5 uses per week	0	None from 12am	N/A	N/A	Win ; Loss	CU>HC MFG, Caudate 7 Claustrum; CU>HC RMFG, R post. & ant. Cingulate, L Insula, Bi. Claustrum & declive.	Not Reported	2	3T	FSL
(Behan et al., 2014)	Go/NoGo Task	16/1	17/1	16.5 (0.2) (SEM)	16.1 (0.4) (SEM)	42.9 mean joints per week	13 mean lifetime use	None from 12am	13 (0.2) (SEM)	N/A	Successful inhibition	HC>CU Bi. white matter adjacent to anterior cingulate.	CU significantly worse at inhibition task.	1	3T	AFNI
(Jager et al., 2013)	Monetary incentive delay task	21	24	17.2 (1.0) (SD)	16.8 (1.3) (SD)	224-32,850 Joints	<15 lifetime use	24 hours (Average 5.1 weeks)	13.2 (2.3) (SD)	N/A	Anticipation; feedback	No WBA differences found.	No Significant Difference	2	3T	SPM

(Lopez-Larson et al., 2012)	Finger Tapping	22/12	17/7	18.2 (0.7) (SD)	18.0 (1.9) (SD)	Mean use of joints per week	N/A	No set abstinence period (20 participants used within 24 hours)	15.3 (1.4) (SD)	N/A	Finger taping	HC>CU R Cingulate Gyrus	Not Reported	1	3T	SPM
(Schweinsburg et al., 2011)	Verbal Encoding Task	27/9	29/9	18.1 (0.9) (SD)	17.6 (0.8) (SD)	480.7 (277.2 SD) life time use	1.50 (4.68) lifetime use	(two groups added) 117.6 (153.9) days + 43.4 (37.1)	14.5 (2.5) (SD)	N/A	Novel encoding	No significant difference.	No Significant Difference	1	3T	AFNI
(Schweinsburg et al., 2008)	Spatial working memory Task	11/4	12/5	18.1 (0.7) (SD)	17.9 (1.0) (SD)	480.7 (277.2 SD) life time use	0.5 (1.3) lifetime use	At least 28 days	N/A	4.0 (1.6) (SD)	SWM> Vigilance; Vigilance> SWM.	CU>HC R superior parietal lobe, HC>CU R dorsolateral PFC; CU>HC Inferior cuneus.	No Significant Difference	2	1.5T	AFNI
(Tapert, Schweinsburg and Brown, 2008)	Go/NoGo Task	12/4	12/5	18.1 (0.7) (SD)	17.9 (1.0) (SD)	475.6 (268.5 SD) life time use	<5 lifetime use	28 days	14.0 (1.6)	N/A	Inhibition; Go	CU>HC Bi.SFG, Bi.MFG, R Insula, Bi. MFC, Bi. IPL, Bi. SPL, R lingual OG, R middle OG; CU>HC RIFG, R insula, RSFG, RMFG, RSPL, RIPL, R medial Precuneus.	No Significant Difference	2	1.5T	AFNI

CU = Cannabis Users, HC = Healthy Controls, M = Male, F = Female, WBA = Whole Brain Analysis, T = Tesla R = Right, L = Left, Bi. = Bilateral, SFG = Superior Frontal Gyrus, MFG = Middle Frontal Gyrus, IFG = Inferior Frontal Gyrus, MFC = Medial Frontal Cortex, IPL = Inferior Parietal Lobe, SPL = Superior Parietal Lobe, OG = Lingual Occipital Gyrus, N/A = Quantity not reported in paper; SD = Standard Deviation SEM = Standard error of the mean

Table 3; Functional magnetic resonance imaging of adults and adolescent, meta-analysis results.

Adults	MNI coordinate			SDM-Z	P	Voxels	Area	Egger's Test p value
	x	y	z					
CU>HC								
	-52	-60	30	1.561	0.00144732	260	L. Superior Temporal Gyrus	0.054
	54	14	20	1.568	0.001376152	128	R. Inferior Frontal Gyrus	0.141
	-52	-32	14	1.479	0.002391756	90	L. Posterior Transverse Temporal Gyrus	0.542
HC>CU								
	-8	-100	-8	-1.843	0.000071228	789	L. Striate area/ Occipital Gyrus	0.989
	-32	12	-2	-1.637	0.000325918	386	L. Area Piriformis Insulae	0.198

	34	-4	54	-1.341	0.002040088	147	R. Middle Frontal Gyrus	0.383
	32	8	44	-1.278	0.002825022	29	R. Middle frontal Gyrus.	0.232
Adolescents	MNI coordinate			SDM-Z	P	Voxels	Label	Eggert's Test p value
	x	y	z					
CU>HC								
	46	-46	50	1.06	0.00055349	397	R. Inferior Parietal Gyrus	0.283
	28	14	-2	1.008	0.00083428	348	R. Putamen	0.072

CU = Cannabis Users, HC = Healthy Controls, R = Right hemisphere, L = Left Hemisphere, SDM = Seed-based D Mapping.

ACCEPTED MANUSCRIPT