Supplement

Non-Acute Effects of Cannabis on Neuropsychological Functioning in Clinical Populations

Two meta-analyses (with significant overlap in studies included) found that adult patients with Schizophrenia who have a history of cannabis use (but no recent cannabis use) had better neuropsychological functioning across all domains with small to medium effect sizes compared to non-cannabis-using patients (Rabin, Zakzanis, & George, 2011; Yucel et al., 2012). On the other hand, another meta-analysis found that young adult patients (<25 years old) with psychotic-spectrum disorders and comorbid current cannabis use performed more poorly across most domains (i.e., IQ, verbal learning, working memory, inhibitory control) than patients without cannabis use, with small to medium effect sizes (Bogaty, Lee, Hickie, & Hermens, 2018). One possible explanation for the discrepancy in these findings is that individuals who are able to remain abstinent demonstrate better neuropsychological functioning than those individuals who are current users. There is also some evidence that among first-episode psychosis patients diagnosed with schizophrenia-spectrum disorders, those with early onset cannabis use had superior performance compared to those who began using cannabis later (i.e., after 16 years old) (Stirling, Lewis, Hopkins, & White, 2005; Yucel et al., 2012). Therefore, it is possible that early cannabis use contributes to the development of Schizophrenia Spectrum disorders among a subgroup of less neuropsychologically impaired and vulnerable individuals, who in the absence of cannabis use may never have developed a Schizophrenia Spectrum disorder (Yucel et al., 2012). On neuropsychological testing, early cannabis users may perform better than non-cannabis users or late cannabis users, especially if they were able to stop using cannabis after a psychotic episode or Schizophrenia Spectrum diagnosis.

Few studies have examined neuropsychological functioning in cannabis users with other comorbid psychopathology. Among patients with Bipolar Disorder, there is some evidence that history of cannabis use has been associated with increased symptoms of psychosis, but better neuropsychological functioning on measures of attention, processing speed, working memory, and executive functioning among those with history of cannabis use (Braga, Burdick, Derosse, & Malhotra, 2012; Ringen et al., 2010), although some studies do not find differences between cannabis users and non-users (Sagar et al., 2016). It is important to note that some of these studies did not measure last cannabis use, so it is unclear if neuropsychological performance reflects the effects of chronic use or the effects of acute use among users. Among patients with Major Depressive Disorder (MDD), there is some evidence of an additive adverse effect of marijuana use and MDD on verbal learning and memory performance (Radoman, Hoeppner, Schuster, Evins, & Gilman, 2019), but other studies have found no effects of cannabis use (Roebke, Vadhan, Brooks, & Levin, 2014; Secora et al., 2010). Among patients with ADHD, verbal memory, processing speed, cognitive interference, decision-making, working memory, and inhibitory control do not seem to differ between ADHD patients with and without a history of cannabis use (Rasmussen et al., 2016; Tamm et al., 2013), although ADHD patients with earlier initiated cannabis use (i.e., < 16 years old) may have poorer decision-making, working memory, and inhibitory control than those who began using later (Tamm et al., 2013).

Neuroimaging Findings

Acute Neuroimaging Findings

Task-Based fMRI. A recent review by Bloomfield and colleagues (Bloomfield et al., 2019) of the acute effects of THC on neural responses during cognitive tasks found that about half to two-thirds of participants administered cannabis or THC exhibited behavioral deficits.

Neural activation patterns depended on task and cannabis use history. For example, mixed results were found for reward-based tasks based on cannabis use history. Attention and inhibition tasks varied with both increases and decreases across cortical and subcortical regions. Learning and memory tasks were associated with increased activity in frontal, hippocampal, and cuneus and precuneus regions, with decreases largely task-specific in regions such as the insula, occipital gyrus, or visual-motor areas. Emotional processing tasks were associated with increases and decreases in frontal, temporal, and amygdala regions, as well as broad-based decreases in connectivity with the amygdala. Across tasks, aberrant neural activation was generally associated with decreased performance. Thus, cannabis users may be less able to recruit necessary neural resources to accomplish goals, or even if they utilize broader neural networks than non-users, this does not correspond to an increase in performance. Importantly, THC and CBD are suggested to have opposing actions during fMRI tasks (Bhattacharyya et al., 2012; Bhattacharyya et al., 2010), further underscoring the importance of specific cannabinoid content.

Non-Acute Neuroimaging Findings

Gray Matter. A meta-analysis from 2013 (Rocchetti et al., 2013) revealed that bilateral hippocampi were smaller in cannabis users than non-users (but not related to duration of use). In looking at individual studies, smaller OFC and amygdala volumes have been noted (e.g., (Battistella et al., 2014; Price et al., 2015; Yucel et al., 2008), but inconsistently (e.g., (Cousijn et al., 2012; Koenders et al., 2016). A pilot study of older adult cannabis users found larger gray matter volumes in left putamen, lingual cortex, and rostral middle frontal cortex, though this did not correspond to cognitive changes (Thayer, YorkWilliams, Hutchison, & Bryan, 2019).

White Matter. A few studies found that cannabis users show lower fractional anisotropy (FA) in the corpus callosum, forceps minor and uncinate fasciculus (Gruber, Dahlgren, Sagar,

Gonenc, & Lukas, 2014; Jakabek, Yucel, Lorenzetti, & Solowij, 2016; Shollenbarger, Price, Wieser, & Lisdahl, 2015), but others have found no FA differences between cannabis users and non-users (Cousijn et al., 2012; Orr, Paschall, & Banich, 2016; Thayer et al., 2017). A longitudinal 2-year study suggested young adult cannabis users demonstrated lower FA across a number of tracts (Becker, Collins, Lim, Muetzel, & Luciana, 2015). Developmentally, age of onset is an important predictor of white matter outcomes, with earlier onset related to poorer integrity (Gruber et al., 2014; Orr et al., 2016). One study revealed younger users exhibited lower axial diffusivity (AD) and radial diffusivity (RD), indicating more axonal damage and greater myelination, respectively, while older users (above age 32) had higher AD and RD across frontal, parietal, and motor tracts (Jakabek et al., 2016). In older adults (>60 years), the only known study of white matter revealed no difference in white matter volume by cannabis user status (Thayer et al., 2019).

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