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# Recommendation to reconsider examining cannabis subtypes together due to opposing effects on brain, cognition and behavior

**Kristine Rømer Thomsen**[a,*], **Mette Buhl Callesen**[a], and **Sarah W. Feldstein Ewing**[b]

[a]Centre for Alcohol and Drug Research, Department of Psychology and Behavioural Sciences, Aarhus University, Bartholins Allé 10, 8000 Aarhus C, Denmark

[b]Department of Child and Adolescent Psychiatry, Oregon Health and Science University, Mail Code: DC7, 3181 SW Sam Jackson Park Rd, Portland, OR 97239-3098, USA

## Abstract

Cannabis use represents a major public health issue throughout the globe. Yet, we still lack the most fundamental knowledge on long-term effects of cannabis on neural, cognitive, and behavioral function. Part of this stems from how cannabis has been measured historically. To this end, most empirical examinations of cannabis have consolidated all types of cannabis collectively. However, this approach obscures differences in how cannabinoids operate. In this commentary, we address the contrasting properties of tetrahydrocannabinol (THC) and cannabidiol (CBD) and their opposing effects on cognitive function. In addition, we address the increase in cannabis potency throughout the past two decades and how that impacts generalizability of early data to evaluations of contemporary public health. We underscore the urgent need for future research to disaggregate examination of THC from CBD, along with the importance of measuring cannabis potency to more effectively unravel its influence on cognitive function and other health issues.

### Keywords

Cannabis; Delta-9-tetrahydrocannabinol; Cannabidiol; Potency; Cognition; Memory; Learning

This paper is a commentary on the review "A systematic review of the effect of cannabidiol on cognitive function: Relevance to schizophrenia" that evaluated preclinical and clinical literature on the effects of cannabidiol (CBD) on cognitive domains relevant to schizophrenia, and points to the ability of CBD to improve cognition across multiple disorders (Osborne et al., 2017). We seek to use the opportunity of this commentary to extend the implications of these findings to the field of addiction, where the convention in empirical examination is to consolidate all types of cannabis use collectively, despite

*Corresponding author. krt.crf@psy.au.dk (K. Rømer Thomsen).

Contributors

KRT conceptualized the commentary and wrote the first draft of the commentary. KRT and SWFE performed the literary searches. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors declare no conflict of interest.

considerable variations in nature of delta-9-tetrahydrocannabinol (THC) and CBD. The timeliness of this is further supported by the increase in cannabis potency over the past two decades (Dujourdy and Besacier, 2017), which challenges generalizability of data gathered more than 20 years ago on contemporary estimates of the effects of cannabis on cognitive function.

For most quantitative brain and behavioral studies of cannabis, the standard empirical approach within addiction neuroscience and treatment is to collapse all types of cannabis use in collective examinations (National Academies of Sciences, 2017). Thus, individuals who use a wide range of products with varying levels of THC/CBD and across a vast range of potency are assessed together, and outcomes are reported without disaggregating effects for these different types of active ingredients, and/or levels of potency. Importantly, at this time, it is these *collective* outcomes that are guiding scientific debate and public policy decision-making throughout the globe regarding how cannabis affects brain, cognition, and behavior.

However, this approach obscures real-world differences in how cannabinoids operate. In actuality, cannabis use includes a range of subtypes that vary considerably in potency. This has become particularly evident with the introduction of high potency cannabis types to the market such as sinsemilla or “skunk” that contain high levels of THC (20%) and low levels of CBD (< 0.5%) (Osborne et al., 2017). Cannabis contains more than 80 different cannabinoid compounds, and growing evidence suggests that two of the main cannabinoids, THC and CBD (Fig. 1), display opposing neural, cognitive, and behavioral effects, as reflected in recent comprehensive systematic reviews of CBD’s antipsychotic properties (Iseger and Bossong, 2015) and ability to restore cognitive function (Osborne et al., 2017). While THC is a $CB^1$ and $CB^2$ receptor partial agonist (Pertwee, 2008), CBD is a negative allosteric modulator of the cannabinoid $CB^1$ receptor (Laprairie et al., 2015). Further, THC induces psychotic symptoms and anxiety in healthy volunteers (D’Souza et al., 2004; Morrison et al., 2009), whereas CBD demonstrates antipsychotic and anxiolytic effects (Leweke et al., 2012; Zuardi et al., 2009; Zuardi et al., 2006; Zuardi et al., 1995). Evidence from clinical studies indicates that THC impairs learning and memory (including working memory) in healthy volunteers and cannabis users (D’Souza et al., 2004; Morgan et al., 2012; Morrison et al., 2009), whereas CBD enhances learning and memory and inhibits THC-elicited decline in learning and memory (including working memory) (Das et al., 2013; Englund et al., 2013; Morgan et al., 2012). Moreover, a recent study of cannabis users implicates THC in impaired facial emotional recognition, while CBD improves facial emotional recognition and attenuates THC-induced impairment (Hindocha et al., 2015). These effects are mirrored in functional imaging studies, which reveal opposing acute effects of THC and CBD in areas pivotal to queried cognitive processes including emotional processing (amygdala); salience processing (striatum, hippocampus, prefrontal cortex); and processing of auditory and visual information (auditory and visual cortex) (Bhattacharyya et al., 2010; Borgwardt et al., 2008; Fusar-Poli et al., 2009; Winton-Brown et al., 2011). It is relevant to note however, that research investigating the impact of CBD on human functioning is still sparse and suffers from limitations. For instance, Morgan et al. (2012) base their conclusions on hair samples from users with varying levels of THC and CBD, and Das et al. (2013) only assessed CBD and not its effects on THC. In general, double-blind placebo controlled assessments are needed to improve our knowledge on the impact of THC

and CBD, as well as cannabis with and without CBD, on cognition and behavior. Nevertheless, the available studies still reflect critical and relevant cognitive differences that should be further explored in future studies.

At the same time, possible long-term detrimental effects of cannabis on cognitive function continue to be at the center of scientific debate (National Academies of Sciences, 2017). Recent prospective studies (Jackson et al., 2016; Mokrysz et al., 2016) and systematic reviews (Broyd et al., 2016; Curran et al., 2016; National Academies of Sciences, 2017) show limited to mixed findings on the impact of cannabis on cognitive processing, that contrast with highly-cited findings from Meier et al. (2012) linking heavy cannabis use with IQ decline. Importantly, none of these empirical studies disentangled the role of THC from CBD, and/or examined the role of potency (Feldstein Ewing et al., 2017). These types of examinations have yet to be carefully scrutinized in prospective designs to investigate possible long-term effects of cannabis on cognitive functioning. Similarly, an increased focus on disaggregating the role of THC from CBD, and/or the role of potency in studies of acute effects of cannabis, also promises more robust and consistent findings (National Academies of Sciences, 2017).

When examined on a subtype level, cannabis has historically been assigned to two predominant types: herbal cannabis and cannabis resin. These categories contain even more subtypes, which at a minimum, vary considerably in potency (e.g., cannabis plant; shatter). Further, the most comprehensive study available (Dujourdy and Besacier, 2017), which examined cannabis samples from five French forensic police laboratories over 25 years, reflects that during the past two decades, there has been a gradual increase in potency in both subtypes, documented through increases in THC levels as well as calculation of THC/CBD ratios. In herbal cannabis, mean THC content rose from 2% in 1995–13% in 2016; and in the past four years, the increase in potency in cannabis resin has been dramatic (10% mean THC content in 2009–23% in mid-2016) (Dujourdy and Besacier, 2017). This escalation in cannabis potency is comparable to findings in other European countries (Niesink et al., 2015; Zamengo et al., 2015) and the US (National Academies of Sciences, 2017).

The dramatic increase in potency also presents scientific and public health challenges in the generalizability and extension of early cannabis data on current evaluations of the implication of cannabis use on brain, cognition, and behavior. For example, the dramatic increase in potency in cannabis resin the past four years poses specific challenges in the generalizability of cannabis resin data gathered prior to 2012. We propose that these nuances are, in fact, critical health issues that must be carefully examined and addressed in order to truly begin to co-ordinate and interpret early data on public health from data collected today. At a minimum, these data underscore the urgent need to disaggregate examination of THC from CBD, along with the importance of measuring potency in future studies of cannabis and its impact on cognitive function and other health related issues across the globe.

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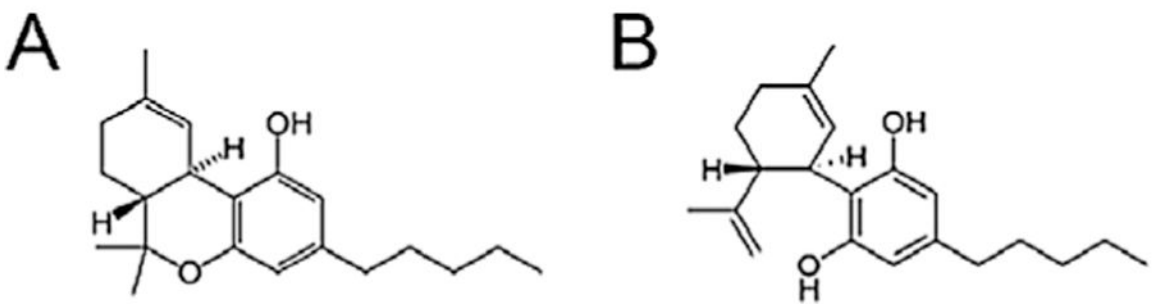


**Fig. 1.**

Chemical structure of delta-9-tetrahydrocannabinol (A) and cannabidiol (B). Printed with permission from Hayakawa K, Mishima K, Fujiwara M. − Pharmaceuticals. 2010 Jul;3(7): 2197–212. http://dx.doi.org/10.3390/ph3072197, CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=40172369