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MYOCARDIAL DISEASE (A ABBATE AND G SINAGRA, SECTION EDITORS)

Cannabis Use as a Risk Factor for Takotsubo (Stress) Cardiomyopathy: Exploring the Evidence from Brain-Heart Link

Liangsuo Ma[1,2] · Marco Giuseppe Del Buono[3,4,5] · F. Gerard Moeller[1,6,7,8]

Abstract

Purpose of Review Recently, an association between cannabis use and Takotsubo (stress) cardiomyopathy (TTC) has been shown. With the current trend of legalization of cannabis, it is important to understand brain effects of cannabis use that could lead to cardiac disease, such as TTC. Here we review recent brain imaging studies in order to search for the evidence supporting the association between cannabis use, stress, and TTC.

Recent Findings There exist brain imaging studies showing similar findings across TTC, stress, and cannabis use. These similar findings are mainly centered on a key central autonomic network region amygdala, i.e., amygdala hyperactivity/hyperconnectivity when exposed to challenge, stress, or negative stimuli.

Summary This similarity supports a close association among cannabis use, stress, and TTC. Amygdala-centered neuronal circuits could underlie cannabis use as risk factor to TTC. Based on the findings, several directions for future studies are proposed.

Keywords Takotsubo cardiomyopathy · Stress · Cannabis use · Brain-heart link · Central autonomic network · Amygdala

Introduction

Takotsubo cardiomyopathy (TTC) [1] is a clinical syndrome characterized by an acute and reversible myocardial dysfunction, often precipitated by an emotional or physical stress, not explained by an obstruction in an epicardial coronary artery [1, 2]. Cardiac dysfunction in TTC is unlikely to be a manifestation of circulating cardiac depressant factors (i.e., cytokines) [3] but rather represents a form of neurogenic stunned myocardium mediated by a catecholaminergic spillover from the sympathetic nerves at myocardial level [4–9]. Female sex, postmenopausal status, schizophrenia, anxiety/depression, asthma/chronic obstructive pulmonary disease, diabetes, chronic medications, and substance use disorders are some potential risk factors for TTC [1].

Accumulating evidence shows an association between cannabis (marijuana) use and adverse cardiovascular events [10, 11]. Recently, an association between cannabis use and TTC

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✉ Liangsuo Ma
Liangsuo.ma@vcuhealth.org

Marco Giuseppe Del Buono
marcodelbuono@hotmail.it

F. Gerard Moeller
frederick.moeller@vcuhealth.org

[1] Institute for Drug and Alcohol Studies, Virginia Commonwealth University (VCU), 203 East Cary Street, Suite 202, Richmond, VA 23219, USA

[2] Department of Radiology, Virginia Commonwealth University (VCU), 203 East Cary Street, Suite 202, Richmond, VA 23219, USA

[3] Pauley Heart Center, Virginia Commonwealth University (VCU), Richmond, VA 23298, USA

[4] C. Kenneth and Dianne and Wright' Center for Clinical and Translational Research, Virginia Commonwealth University (VCU), Richmond, VA 23298, USA

[5] Catholic University of the Sacred Heart, Rome, Italy

[6] Department of Psychiatry, Virginia Commonwealth University (VCU), Richmond, VA 23298, USA

[7] Department of Pharmacology and Toxicology, Virginia Commonwealth University (VCU), Richmond, VA 23298, USA

[8] Department of Neurology, Virginia Commonwealth University (VCU), Richmond, VA 23298, USA

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has been shown in several case reports [12–14]. In a large sample of hospitalized patients ($n > 3000$), cannabis use was found to be an independent predictor of TTC [15]. These previous reports suggest that cannabis use could be one of the risk factors [1] for TTC. With the current trend of legalization of cannabis in the USA and the finding showing a trend that TTC could occur earlier in the cannabis users [15], it is important to understand brain effects of cannabis use that could lead to cardiac disease, especially life-threatening presentations like TTC. Here we review recent brain imaging studies exploring the evidence supporting the association between cannabis use and TTC, in a perspective of neurocardiology (i.e., brain-heart link) [16–18]. Brain-heart link is an emerging specialty that addresses the interaction between the brain and the heart, that is, the effects of brain function on the heart and the effects of cardiac injury on the brain.

Association Between Stress and Cannabis Use

Stress refers to an adaptive response of an organism to a real or perceived threat (i.e., stressful stimuli) in the environment which is aimed to re-establish homeostasis [19]. While the complete pathophysiology of TTC is still unknown, TTC has been linked to psychological or physical stress [1, 2], although, in rare cases, episodes of TTC may also follow unexpected pleasant events [20]. That is why TTC is also known as "stress" cardiomyopathy. A previous study [21] investigated the patients' narratives about long-term stress experienced before the onset of Takotsubo syndrome and revealed that the TTC patients lived under stressful circumstances long before the onset of TTC. This long-term stress wore down defenses against stress creating vulnerability, such that the smallest stressor could make them unable to cope, precipitating TTC [21]. Another study [22] reported that the onset of TTC was associated with exposure to multiple stressful life events during the 6 months preceding the onset of TTC but not with exposure to an acute, recent event. These findings support the role of stress, which could exert its influence in a long-term and cumulative way, in the pathophysiology of TTC.

A survey [23] of studies investigating the role of stress as a risk factor and motivation for cannabis use/misuse provides evidence that using cannabis to cope with stress or relieve tension is common and may be most prominent in heavier cannabis users [23], which is also supported by more recent studies [24, 25]. In addition, compared with other illicit drugs, cannabis may be most commonly used for stress reduction [23]. On the other hand, chronic drug use can affect stress systems, making stress related motivation to use more salient for chronic users and sensitizing individuals to the effects of subsequent life stressors [23]. Thus, at least for some individuals, there is a "vicious circle" between stress and cannabis use. Over time, this cycle could result in cannabis use disorder or stress-related disorders, including TTC. In addition, the effects of stress and cannabis use could be additive. Indeed, a recent research [26•] showed that adolescent mice treated with cannabis's psychoactive ingredient Δ9-tetrahydrocannabinol (THC) and exposed to stress, but not mice exposed to these two factors separately, exhibit impaired cued fear extinction in adulthood.

Exploring Brain-Heart Link

Central Autonomic Network

The central autonomic network (CAN) is an intricate system of brainstem, subcortical, and cortical structures that play key roles in the function of the autonomic nervous system [27]. The CAN regulates cardiovascular function [16–18, 28, 29] to maintain homeostasis by modulating the release of critical hormonal factors, chemical messengers, and neurotransmitters, in addition to mediating the activity of the sympathetic and parasympathetic autonomic nervous system, which regulates the function of different organs and tissues [29]. The CAN is composed of a complex network including, but not limited to, some key regions: amygdala, hypothalamus, insula, hippocampus, ventromedial prefrontal, and cingulate cortices [30–33]. These key regions of CAN largely overlap with the neuronal network underlying emotion processing [34, 35] and stress reactivity [30]. Through these common brain regions, CAN is able to integrate emotional stress (such as anxiety, fear, and sadness) in the autonomic response. By integrating the information from other CAN regions, the hypothalamus plays a central role in maintaining homeostasis, controlling involuntary functions such as breathing, blood pressure, heart rate, and inotropism [36].

Endocannabinoid System

The endocannabinoid system, composing of the cannabinoid receptors types 1 and 2 (CB1R and CB2R respectively) for THC, the endogenous ligands (*N*-arachidonoyl-ethanolamine or AEA and 2-arachidonylglycerol or 2-AG), and the enzymatic systems involved in their biosynthesis and degradation, has emerged as an important factor modulating emotional behaviors. The elements of the endocannabinoid system are prevalent throughout the neuronal circuits underlying stress-related disorders and CAN, including hypothalamus, hippocampus, prefrontal cortex, amygdala, and forebrain monoaminergic circuits. In other words, the neuronal circuits with prevalent endocannabinoid receptors largely overlap with the neuronal circuits underlying emotion processing, stress reactivity, and CAN. The natural endocannabinoid system

regulates anxiety and the response to stress by dampening excitatory signals that involve the neurotransmitter glutamate [37].

Resting State Networks

A growing literature suggests that brain networks identified during a resting state reflect co-activated regions during task-elicited cognitive activity [38] and are essentially the same networks in different states of activity vs. quiescence, including during sleep [39]. These networks have since been associated with certain mental processes [40]. Furthermore, in light of recent concerns about rigor and reproducibility in fMRI [41], ancillary resting-state data has been used to quasi "replicate" task-elicited co-activations in the same subject(s) [42]. Furthermore, of increasing interest is the degree to which separate brain networks (as identified by independent components analysis) interact with each other, as either a cause or marker of psychiatric illness. For example, alcohol use disorder is characterized by aberrant connectivity between salience and default mode networks [43]. To date, the most commonly studied interacting brain networks include default-mode, salience, central executive, dorsal attention, sensorimotor, visual, and auditory networks [38, 44].

Brain Model of TTC

Some key CAN regions (i.e., amygdala, insula, and anterior cingulate cortex) have been included in a previous brain model of TTC [33]. According this model, when exposed to anger/fear/sadness or environmental/psychological stressors, the relevant negative emotional information was first processed/evaluated by amygdala, insula, and anterior cingulate cortex [33]. For the individuals with risk of stress-related disorders, the evaluation could facilitate subsequent response in the subcortical autonomic network consisting of hypothalamus, nucleus tractus solitarius, rostral ventrolateral medulla, and parabrachial nucleus, which is signaled by the amygdala [33]. The response in the subcortical autonomic network could then result in subsequent physiological responses [33]. A direct catecholamine toxicity and microvascular spasm, due to the increased cardiac sympathetic outflow, might explain the wall motion abnormalities seen in patients suffering from TTC [1].

Brain Imaging Findings in Individuals with a Previous Episode of TTC

To date, several fMRI studies have been conducted in patients had previously experienced an episode of TTC, either during resting state [45–47, 48•] or when challenged by Valsalva maneuver [49] and low temperature [48•]. Klein et al. [46] found that resting state functional (non-directional) connectivity in left insula largely distinguishes TTC participants from healthy controls although the direction of the group comparison was not reported in this study. The other three studies found that relative to the healthy controls, the TTC participants had greater resting state functional connectivity in a posterior default mode network region (i.e., precuneus) and lower functional connectivity in an anterior default mode network region (i.e., ventromedial prefrontal cortex) [45]; lower resting state functional connectivity in parasympathetic- and sympathetic-associated subnetworks (including amygdala, hippocampus, insula, cingulate, parietal, temporal, and cerebellar regions) and default mode network and limbic regions (including the hippocampus, parahippocampal, and medial prefrontal regions) [47]; and greater resting state functional connectivity in the bilateral hippocampus [48•]. In response to autonomic challenges triggered by the Valsalva maneuver, TTC individuals showed greater activation in amygdala, insula, and hippocampus than healthy controls [49]. When stressed by local exposure to cold, the TTC participants differed significantly from both a prestress baseline interval and from the control group, showing increased connectivity in a network that included the left amygdala and the right insula [48•].

Although sparse, these previous fMRI studies collectively indicate that TTC individuals have an altered CAN network and default mode network. These results, found both during resting state and when being challenged, tend to support the hypothesis that a dysregulation of autonomic control at the central level plays a significant role in the pathology of TTC [48•]. When challenged, the amygdala showed hyperactivity [48•, 49], consistent with its crucial role in the brain model about TTC proposed by Nagai et al. [33]. Relatively more resting state fMRI studies have been conducted, possibly because resting state fMRI is relatively easy to implement (no task performance in the scanner, particularly useful and feasible for TTC patients).

Brain Imaging Findings in Stress

Resting State Studies In a study conducted by Soares et al. [50], resting state networks were compared between healthy participants exposed to prolonged stress (long period of preparation for the medical residence selection examination) and gender- and age-matched controls who did not expose to stress (under normal academic activities). This study found that the stressed participants had greater resting state functional connectivity in the default mode network, dorsal attention, ventral attention, sensorimotor, and primary visual networks than controls. In addition, the deactivation of these resting state networks was found to be lower in the stressed participants than controls. The same research group [51] also examined the change of the resting state networks by comparing the same individuals before and after recovery from the exposure

to prolonged psychological stress and comparing these stressed participants and controls who did not expose to stress (under normal academic activities). This study shows that after recovery from the exposure to prolonged stress, the stressed individuals displayed a partial recovery in the default mode network, ventral attention network, and sensorimotor network (lower functional connectivity than immediately after stress but greater functional connectivity than controls). While these studies suggest that the stress is associated with greater activation in the default mode network, others [52, 53] also demonstrated that the stress may be associated with increased functional connectivity between the salience network and default mode network. Spripada et al. [52] investigated posttraumatic stress disorder (PTSD) and found that during resting state, the PTSD participants had lower functional connectivity within the default mode network, greater functional connectivity within the salience network, and greater functional connectivity between the default mode network and the salience network. Another study [53] compared resting state functional connectivity in healthy participants before and after a mild social stressor and found that the default mode network exhibited increased resting-state functional connectivity following the stressor to the key nodes of the salience network, i.e., the dorsal anterior cingulate cortex and the anterior insula, as well as sensorimotor regions and higher-order visual areas.

Task-Based Studies Admon et al. [54] examined the emotional experience and brain responses of healthy soldiers before and after their subsequent exposure to stressful combat events. This study found that increase in combat stress symptoms was significantly correlated to the amygdala's reactivity before stress and also the hippocampal change in activation over time. van Winden et al. [55] investigated the influence of severe stress in soldiers before and after deployment to a combat zone. The authors of this study reported that within the stressed individuals, amygdala and insula reactivity to biologically salient stimuli increased after combat stress. In addition, perceived threat was positively associated with the functional connectivity between the amygdala and insula and the functional connectivity between the amygdala and dorsal anterior cingulate cortex.

Brain Imaging Findings in Cannabis Use

Resting State Studies Focusing on the default mode network and salience network, Pujol et al. [56] found that relative to healthy non-drug-using controls, cannabis users showed greater functional connectivity in the posterior default mode network (i.e., posterior cingulate cortex or PCC). The greater functional connectivity in this PCC area was associated with greater amount of cannabis used and partially persisted after 1 month of abstinence. Another resting state study [57] found that the cannabis users had lower functional connectivity in the PCC, the cerebellum, medial prefrontal cortex, parahippocampus, and anterior insula. In cannabis-dependent individuals, PCC-right anterior insula connectivity strength correlated with duration of cannabis use.

Task-Based Studies Spechler et al. [58] used an fMRI emotional face processing task to compare a group of young cannabis user and non-drug-using controls. As demonstrated in Fig. 1, this study showed that cannabis users had greater reactivity in the bilateral amygdalae to angry faces than neutral faces, an effect that was not observed in the non-drug-using controls. Employing a combination of fMRI and positron emission tomography (PET), Bhattacharyya et al. [59] investigated whether the effects of THC, the main psychoactive ingredient of cannabis, on anxiety and on amygdala response while processing fearful stimuli were related to local availability of its main central molecular target, CB1 receptors in males. Relative to the placebo condition, THC induced increased anxiety and increased right amygdala activation while processing fear. Both these effects (increased anxiety and increased right amygdala activation) were positively correlated with CB1R availability in the right amygdala. Ma et al. [60•] used dynamic causal modeling to measure effective (directional) connectivity and found that when exposed to angry/fearful facial expressions, cannabis users showed greater changes in the left amygdala to hypothalamus effective connectivity (positively associated with Perceived Stress score), the right amygdala to bilateral fusiform gyri effective connectivities (positively associated with Perceived Stress score), and the left ventrolateral prefrontal cortex to bilateral fusiform gyri effective connectivities (negatively associated with Perceived Stress score); see Fig. 2 for the schematic diagram summarizing above effective connectivity results.

Summary of the Reviewed Brain Imaging Studies

As reviewed above, there exist brain imaging studies showing similar findings across TTC, stress, and cannabis use. These similar findings are centered on a key CAN region, the amygdala, i.e., amygdala hyperactivity/hyperconnectivity when exposed to challenge, stress, or negative stimuli. This similarity supports a pathophysiological association among cannabis use, stress, and TTC.

While processing fear, amygdala hyperactivation/hyperconnectivity can be observed both following acute administration of THC [59] and in chronic cannabis users [58, 60•]. It is still unclear whether amygdala hyperactivation/hyperconnectivity was a consequence of chronic cannabis use or actually preceded cannabis use. If it is a consequence of cannabis use, it is possibly related to the interaction between exogenous cannabinoids and the endocannabinoid system. It has been shown that exogenous cannabinoids inhibit GABAergic neurotransmission in the amygdala [61], and this

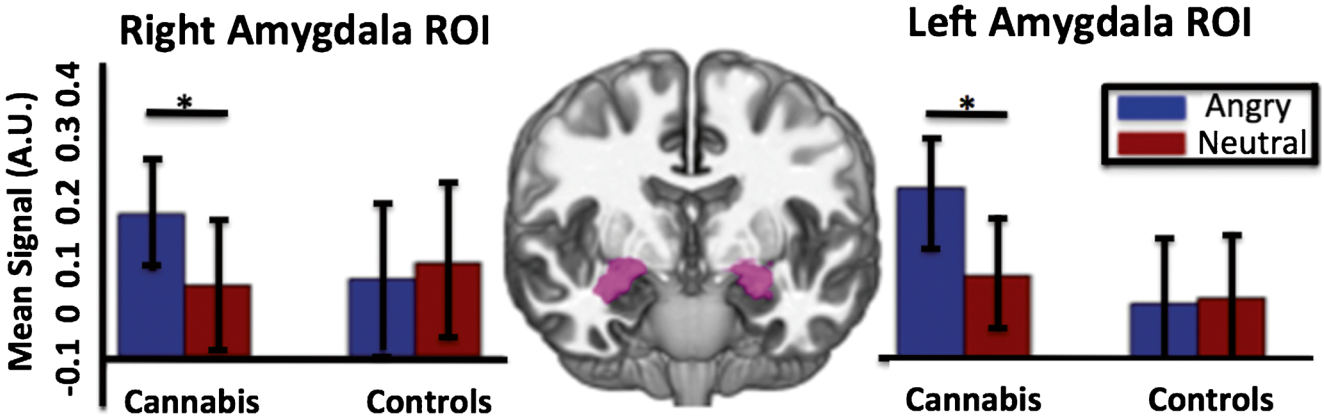

Fig. 1 Cannabis users showed greater reactivity (mean signal) in the bilateral amygdalae to angry faces than neutral faces, an effect that was not observed in the non-drug-using controls. Asterisks indicate post hoc *t* test differences significant at $p < .05$, corrected. Error bars represent the standard error of the mean. ROI region of interest. (Adapted from: Spechler PA, et al. Dev Cogn Neurosci. 2015;16:63–70. doi:https://doi.org/10.1016/j.dcn.2015.08.007, with permission from Elsevier) [58]

effect is enhanced when the animal was placed in a threatening environment and was given THC [62].

Amygdala-centered circuits may be one of the factors underlying cannabis as a risk factor for TTC. According to a model proposed in [63], the basolateral amygdala AEA/CB1R couple "gates" Hypothalamic–pituitary–adrenal (HPA) axis activation: when basolateral amygdala AEA concentrations are high, CB1R signaling inhibits the activation of HPA axis; on the other hand, HPA axis activation could be initialized when AEA concentrations in the basolateral amygdala are low [64]. As commented by Spechler at al. [58], exogenous cannabinoids may compromise the inhibitory mechanism within the amygdala and lower the threshold for HPA axis activation, especially when affected by threat. Indeed, it has been shown [60•] that when exposed to angry/fearful facial expressions, the cannabis users showed greater changes in the amygdala to hypothalamus effective connectivity, and the greater change of this effective connectivity was associated with greater Perceived Stress score.

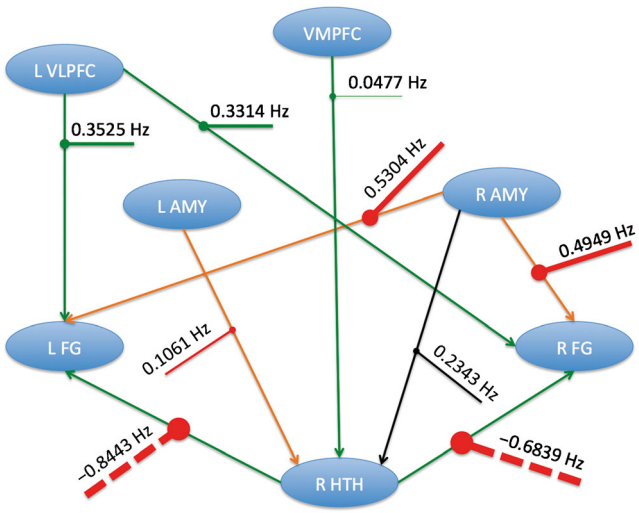

Fig. 2 When exposed to angry/fearful facial expressions, cannabis users showed greater changes in the left (L) amygdala (AMY) to hypothalamus (HTH) effective connectivity (positively associated with Perceived Stress score), the right amygdala to bilateral fusiform gyri (FG) effective connectivities (positively associated with Perceived Stress score), and the left ventrolateral prefrontal cortex to bilateral fusiform gyri effective connectivities (negatively associated with Perceived Stress score). (Adapted from: Ma L, et al. Biol Psychiatry Cogn Neurosci Neuroimaging. 2019 Jun 5. pii: S2451–9022(19)30141–7. doi: https://doi.org/10.1016/j.bpsc.2019.05.013. [Epub ahead of print], with permission from Elsevier) [60•]

Another relatively important finding is the hyperactivation/hyperconnectivity in the posterior default mode network (i.e., PCC/precuneus). The findings on the posterior default mode network could reflect the neuropsychopharmacological effects of cannabinoids, consistent with very high density of CB1 receptors in the PCC [65]. Specifically, as commented by Wall et al. [66], the acute effect of THC is to disrupt PCC function [66–68]. Chronic use may lead to downregulation of CB1 receptors in the PCC/precuneus, as evidenced by a PET study showing that CB1R distributions were downregulated in daily cannabis smokers in the PCC/precuneus, and that this downregulation was reversible after 4 weeks of abstinence [69]. The longer-term impairment of PCC function may then lead to hyperactivation/hyperconnectivity of the PCC in chronic cannabis users. Prashad et al. [70] have shown that cannabis users exhibited heightened salience to external self-relevant stimuli that were modulated after repetitive transcranial magnetic stimulation (rTMS) which targeted the PCC and precuneus.

Conclusive Remarks

Authors' Opinion

Based on the literature reviewed above, we propose the following (Fig. 3): (1) Both chronic stress and cannabis use are

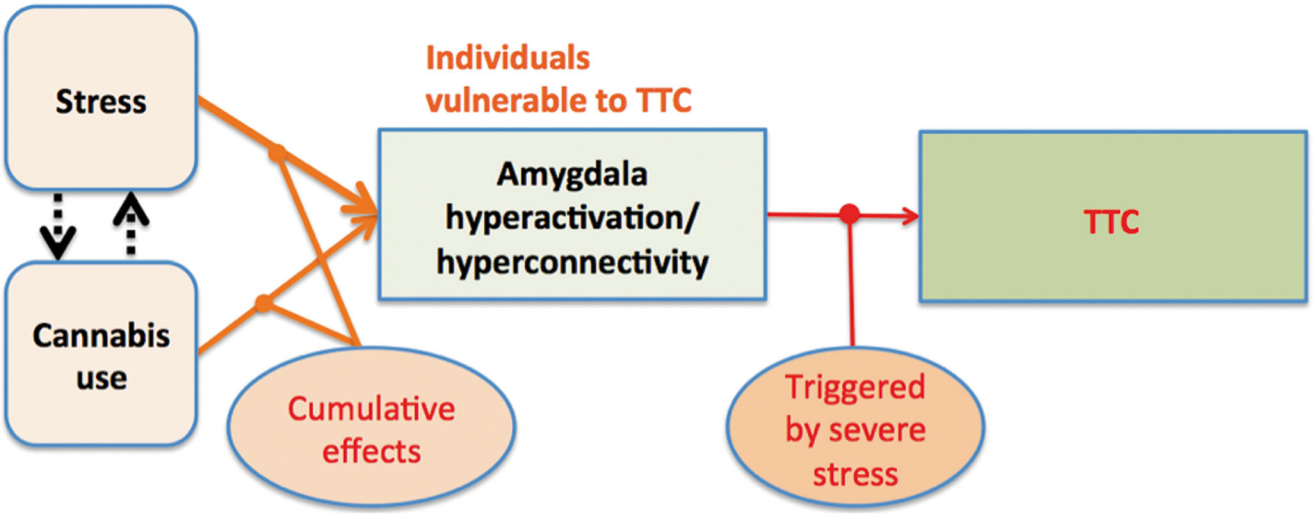

Fig. 3 Diagram depicting author's opinion regarding the interplay between stress, cannabis use, and TTC. Chronic stress and cannabis are interlinked, both playing as risk factors to TTC. The cumulative effects of chronic stress and or/cannabis use can result in hyperactivation/hyperconnectivity in amygdala. With-long term cumulative effects of the risk factors, TTC could occur when suddenly triggered by severe stressor(s)

risk factors for TTC; (2) there is close association between stress and cannabis use that, at least for some individuals, represents a "vicious circle"; (3) the effects of stress and cannabis use are similar, additive, and cumulate over time; (4) the cumulative effects of stress and or/cannabis use can result in hyperactivation/hyperconnectivity in amygdala; (5) with-long term cumulative effects of the risk factors, TTC could occur when suddenly triggered by severe stressor(s).

Limitations

Several limitations of the present opinion deserve mention. (1) The number of brain imaging studies investigating TTC is quite small ($n = 5$), as well as the number of TTC participants in these studies, suggesting that the findings are still preliminary warranting further investigation. (2) TTC often occurs in females and we could not draw any conclusion on gender effects. (3) Although both hyperactivation/hyperconnectivity and hypoactivation/hypoconnectivity were reported in the majority of the TTC brain imaging studies, there exists an exception [47], in which only hypoconnectivities were reported. (4) Given the rare cases of TTC in cannabis users, we did not conduct exhaustive review about stress and cannabis use. It should be expected that there exist findings which are not consistent with those found in TTC, in parallel with the fact that only a very small portion of persons who are exposed to stress and/or cannabis develop to TTC. (5) The dosage of chronic cannabis assumption leading to potential alteration of central autonomic network is still unknown. (6) Users of cannabis may concomitantly use other illicit drugs which may have some effect on central autonomic network. (7) Transient microvascular or epicardial coronary artery spasm in the absence of atherosclerotic coronary artery disease has been described in cannabis users with potential clinical overlap with TTC.

Future Directions

Based on our opinion and the limitations summarized above and described in Fig. 3, we propose several future directions of research in order to further advance our understanding of cannabis use as a risk factor for TTC. (1) The hypothesis that the hyperactivation/hyperconnectivity in amygdala is the key underlying neuronal factor could be tested by directly comparing individual with episode of TTC, cannabis users, and healthy controls. (2) A previous study [60•] suggests that against amygdala-centered risk circuits, there may be prefrontal cortex related circuits reflecting a protective mechanism in cannabis users. Investigating these potential protective circuits may shed light on potential treatment mechanisms. (3) Based on the fact that TTC more frequently occurs in females, it would be interesting to test if more hyperactivation/hyperconnectivity in amygdala can be observed in the female cannabis users than the male cannabis users. (4) It is still unclear if the proposed hyperactivation/hyperconnectivity in amygdala

preexists or is due to cannabis use. Therefore, longitudinal studies are needed to test if more hyperactivation/hyperconnectivity in amygdala can be observed after some duration of continued cannabis use or if treatments which reduce cannabis use alter amygdala hyperactivation/hyperconnectivity. (5) There is increasing interest in characterizing brain network at larger scale [71, 72]. Functional connectivity is easy to compute, but there is lack of information about direction of connectivity; effective connectivity provides information of connectivity but requires additional computation time. Therefore, we propose to combine functional connectivity and effective connectivity: starting from a large brain network, use functional connectivity analysis to provide preliminary information about the nodes involved in the altered functional connectivities. After that, conduct effective connectivity analysis within a smaller brain network with the nodes found by the functional connectivity analysis.

Compliance with Ethical Standards

Conflict of Interest Liangsuo Ma, Marco Giuseppe Del Buono, and F. Gerard Moeller declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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