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Review Article

Caffeine, Mental Health, and Psychiatric Disorders

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Abstract. Caffeine intake is so common that its pharmacological effects on the mind are undervalued. Since it is so readily available, individuals can adjust their own dose, time of administration and dose intervals of caffeine, according to the perceived benefits and side effects of each dose. This review focuses on human studies of caffeine in subjects with and without psychiatric disorders. Besides the possibility of mild drug dependence, caffeine may bring benefits that contribute to its widespread use. These benefits seem to be related to adaptation of mental energy to the context by increasing alertness, attention, and cognitive function (more evident in longer or more difficult tasks or situations of low arousal) and by elevating mood. Accordingly, moderate caffeine intake ($<$ 6 cups/day) has been associated with less depressive symptoms, fewer cognitive failures, and lower risk of suicide. However, its putative therapeutic effects on depression and ADHD have been insufficiently studied. Conversely, in rare cases high doses of caffeine can induce psychotic and manic symptoms, and more commonly, anxiety. Patients with panic disorder and performance social anxiety disorder seem to be particularly sensitive to the anxiogenic effects of caffeine, whereas preliminary data suggests that it may be effective for some patients with obsessive compulsive disorder (OCD). The threshold for the anxiogenic effect of caffeine is influenced by a polymorphism of the A2A receptor. In summary, caffeine can be regarded as a pharmacological tool to increase energy and effortful behavior in daily activities. More populational (cross-sectional and prospective) and experimental studies are necessary to establish the role of caffeine intake in psychiatric disorders, especially its putative efficacy on depressive mood and cognitive/attentional disorders.

Keywords: Attention, anxiety, caffeine, cognition, depression, mood

INTRODUCTION

Caffeine is so widely consumed in the world that little attention is paid to the fact that about 80% of the population voluntarily and routinely manipulate their mind pharmacologically. Such widespread use suggests that caffeine has at least some reinforcing effect and that it is well tolerated in habitual doses. Also, being readily available at a low cost and with high social acceptance and incentive, at least compared to other available drugs, individuals can easily adjust their own dose, time of administration, and dose intervals of caffeine intake according to the perceived benefits and side effects of each dose.

Caffeine can be obtained from coffee, tea, energy drinks, soft drinks, chocolate, and over-the-counter medications. Although many other compounds are present, caffeine seems to be the most important mentally active substance in them [1,2]. For this reason, coffee consumption will be regarded as a proxy for caffeine intake in this review. Studies in which caffeine was acutely administered at much higher doses than routine use (i.e., over 300 mg), will receive lower emphasis, since regular caffeinated drinks have between 40 and 150 mg per serving, although the amount of coffee (and caffeine) per serving may be getting higher in some countries [3].

Even at somewhat larger doses, the effects of caffeine are ascribed to its antagonistic properties at A1

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and A2A adenosine receptors [4,5]. However, both A1 and A2A receptors interact with other neurotransmitters and proteins. Of particular relevance for this review, antagonism of A2A receptors increases neurotransmission through dopamine D2 receptors, and antagonism of A1 receptors interacts with D1 receptors and regulates the release of neurotransmitters such as dopamine, glutamate, and acetylcholine [4,5].

The objective of this article is to review the effects of caffeine on mood, cognition, and behavior of normal volunteers and in patients with different psychiatric disorders. This was not a systematic review and articles published in the last 10 years were emphasized. The role of adenosine in psychiatric disorders and the effects of specific adenosine antagonists will not be the focus of this review and can be found elsewhere [6, 7]. As a warning note, psychiatric disorders have not been validated as distinct or categorical disorders, i.e. they are often "comorbid", can be regarded as the extreme of dimensional features, and may share genetic and environmental risk factors [8]. This scenario arises from a diagnostic strategy based exclusively on symptoms, the lack of specific diagnostic markers, and a fragmented view of the mind that disregards the close interactions between personality, mood, behavior, and cognition. However, categorical concepts of such disorders as in ICD10 and DSM-IV are adopted in practice and in the scientific literature, so both dimensional and categorical approaches will be considered in this review.

GENERAL PSYCHOTROPIC EFFECTS OF CAFFEINE

Caffeine has "mental activating" properties, increasing alertness and energy and reducing sleepiness and fatigue (for reviews see [1,4,9]). These effects contribute to increased performance in some contexts, being particularly apparent in situations of low alertness, such as early morning, sleep deprivation, and when sustained performance is demanded.

At higher doses, especially in sensitive individuals, caffeine can induce symptoms of a condition called "caffeinism" such as anxiety, restlessness, nervousness, dysphoria, insomnia, excitement, psychomotor agitation, and rambling flow of thought and speech [10,11], mimicking a clinical picture known as mixed mood state. On the other hand, caffeine withdrawal may cause headache, fatigue or drowsiness, anxiety, and depressive symptoms that peak 1–2 days after cessation of intake and may persist for a week [12,13]. Some individuals show clear caffeine dependence as evidenced by withdrawal symptoms, persistent desire or unsuccessful efforts to cut down or control use, and tolerance [14]. Abstinence is accompanied by increased cerebral blood velocity and increased EEG theta and decreased beta 2 power [15]. Thus, caffeine has mild to moderate reinforcing effects and has a "therapeutic window" of psychostimulant properties that may bring about some benefit. In contrast to other drugs with dependence potential, caffeine is clearly devoid of important negative consequences on health, performance, and social adjustment [16,17]. Specifically for mental health, in the general population caffeine intake was moderately associated with risk for a wide range of psychiatric and substance use disorders, but not as a causal factor [17]. Familial factors, likely in part genetic, seem to predispose to both caffeine intake and the risk for psychiatric disorders.

Of note, positive effects of caffeine are highlighted when the study design favors the reversal of short term withdrawal, which has not been consistently controlled for in many studies [18]. Some studies with low doses of caffeine (50–100 mg) suggest that most effects are due to withdrawal reversion in regular users [19,20]. However, other studies in volunteers without caffeine withdrawal, either by long term abstinence or ongoing caffeine use, showed significant effects of caffeine on performance, alertness, and mood [21–23]. Moreover, a recent study [24] found that in light, nondependent caffeine users (mean 116 mg/week) caffeine produced increased energy, vigour, and arousal and less fatigue at 150 mg, but not 50 mg. Anxiety increased with 450 mg but not with 150 mg or 50 mg. Caffeine also failed to produce reinforcing effects of "liking" and "wanting more" at any dose, contrary to *d*-amphetamine.

The effects of caffeine have mostly been studied using a single large dose, which contrasts with repeated use of smaller doses over a longer time period. However, Brice and Smith [25,26] found that the improved mood and enhanced performance after a single dose of 200 mg were also present with four doses of 65 mg given at hourly intervals.

SPECIFIC EFFECTS OF CAFFEINE

Mood and mood disorders

Healthy and pathological mood involve internalized symptoms such as sadness, anhedonia, apathy, and

anxiety as well as externalized manifestations such as overactivity, euphoria, irritability, and high pleasure-oriented behavior. Overall, caffeine has been shown both to induce mood changes, particularly at higher doses, and to protect from mood symptoms at moderate doses.

Caffeine has been classically regarded as an inducer of anxiety at higher doses, typically over 300 mg [10, 24,27,28], but the consumption of caffeine is poorly correlated with anxiety or anxiety traits [17,29,30]. Besides dosage, the anxiogenic effect of caffeine is influenced by individual factors, such as preference for caffeine, presence of some anxiety disorders, and genetic background.

Regarding preference, individuals who prefer caffeine pills over placebo tend to report stimulant and "positive" mood effects of caffeine, whereas those that choose placebo tend to ascribe aversive effects after caffeine (increased anxiety and dysphoria) [31]. Similarly, caffeine only had significant reinforcing, mood, and psychomotor performance effects in caffeine consumers, although caffeine increased self-rated alertness of both caffeine consumers and non-consumers [32]. Haskell et al. [33] found that caffeine tended to benefit consumers' mood more, while improving performance more in non-consumers. Doses of 50–100 mg of caffeine are usually sufficient to induce mood effects and in some individuals the effect of 20–30 mg is still clearly noticeable [34].

The presence of specific anxiety disorders influences the perceived effects of caffeine. Earlier studies have found higher sensitivity to anxiogenic effects of high dose caffeine (typically higher than 400 mg) in patients with panic disorder [35,36], generalized anxiety disorder [37], and to a lesser extent in depressed patients [38]. More recent studies extended these findings to patients with performance social anxiety disorder, but not generalized social anxiety disorder [39], and to first degree relatives of patients with panic disorder [40]. Also, patients with panic disorder who develop caffeine-induced panic attacks have significantly higher non-specific general psychopathology [41]. In contrast, a recent randomized controlled trial showed that caffeine led to clinical response in 7 out of 12 patients with treatment-resistant obsessive compulsive disorder (OCD) and a 55% reduction of symptom score in these responders, which was comparable to d-amphetamine [42]. It should be noted that OCD, although classified as an anxiety disorder, is more related to control of thought and behavior than to fear and worry, as other anxiety disorders.

The genetic basis for the anxiogenic effects of caffeine has been investigated. Individuals with the 1976T/T genotypes for A2A adenosine receptors reported greater increases in anxiety after caffeine administration than the other genotypic groups [43,44]. This genotype (also referred to as 1083 C>T) was associated with less caffeine intake [45] as well as with blood-injury phobia [46] and panic disorder in western population [47,48], but not in Asians [49,50].

Thus, vulnerability to marked anxiogenic effects of caffeine seems to be restricted to some individuals with at least a predisposition for specific anxiety disorders, and is influenced by genetic and ethnic factors and higher levels of psychopathology.

Conversely, caffeine intake at low doses can also reduce anxiety and elevate mood in humans [33,51–54]. Caffeine cessation over a couple of days may increase anxiety and depression scores in about 10% of volunteers with a moderate daily intake (mean 235 mg per day), and lead to headache in about 50% of volunteers [55]. Also, in one of the few population studies on regular caffeine intake, Smith [56] has shown that consumption of caffeine, even at low doses, was associated with a reduced risk of depression (OR = 0.32, CI 0.2–0.5; OR = 0.18, CI 0.1–0.3 and OR = 0.12, CI 0.1–0.2 for 1–140 mg/day, 141–260 mg/day and > 260 mg/day, respectively, compared to those with no caffeine intake). This study was conducted in a non-working population, which may have higher baseline levels of depression, probably making it easier to identify this effect compared to a working population.

Regarding suicide, uses of coffee and tea were associated with a lower risk at higher intake (relative risk per cup of coffee per day = 0.87, 95% confidence interval = 0.77 to 0.98) [16]. Also, a significant inverse association was reported between moderate coffee drinking (2–6 cups/day) and the risk of suicide [57]. However, another study suggests that caffeine has a J-shaped relationship with suicide [58]: a similar trend was found for lower suicide rates at low and moderate doses but suicide was significantly increased in those who take 8 or more cups of coffee/day. This pattern is mimicked by the dose – response trend to improved performance in those who take around 400 mg caffeine per day regularly.

Adenosine has been hypothesized to mediate the rapid onset antidepressant effects of sleep deprivation [59]. If this were the case, caffeine may be deleterious to depressed patients undergoing such treatment. However, caffeine (150 mg three times overnight) failed to affect mood improvement in the next day of sleep

deprivation [60]. The only observed effect was lack of decreased energy during sleep deprivation, suggesting that adenosine is not involved in the therapeutic antidepressant effects of caffeine, and that caffeine intake may make it easier for patients to undergo the procedure of depriving from sleep.

A few case reports have also suggested that caffeine can induce mania [61] and that excessive caffeine intake may hamper the recovery of patients with bipolar disorder or manic-type mood episodes [62–64]. These observations are in line with both its psychostimulant and antidepressant effects. Of relevance for mania, caffeine can increase elation in healthy volunteers at 250 mg and irritability at higher doses (500 mg) [65]. Moreover, high coffee intake was associated with suicidal behavior in patients with bipolar disorder, although causality cannot be established with the transversal design of this study [66] and the lack of genetic control, as performed by Kendler et al. [17]. Expert opinions and guidelines for the treatment of bipolar disorder recommend discontinuation of caffeine intake as one of the first steps in the treatment of mania [67,68], although no systematic study is cited. These are important observations, but given the widespread use of caffeine by the general population and patients with psychiatric disorders, these few case reports suggest that problematic use of caffeine is quite an exception rather than the rule. Based on the data reviewed here and clinical experience, the most conservative approach is that high caffeine intake should be avoided in patients with bipolar disorder, especially during manic or mixed episodes, but complete abstinence may also be detrimental. In most patients, low to moderate intake of caffeine is probably not harmful and may play a role against depressive symptoms. However, this topic needs further study.

In summary, for mood and anxiety disorders, caffeine may have beneficial effects for depressive or low energy states, and may be detrimental for some hypersensitive patients with panic and/or performance anxiety disorder, as well as for patients with bipolar disorder. However, total abstinence is unlikely to lead to significant improvement in patients with low to moderate caffeine intake, and may be detrimental to others with predominant depressive symptomatology.

Psychosis and schizophrenia

Case reports also support the idea that caffeine may induce psychotic symptoms in some individuals without previous psychotic disorders [69–71]. However, this may result from an exacerbation of underlying paranoid traits. Also, reduction of caffeine intake has been associated with symptom improvement in some cases of patients with psychotic disorders [71–73], and in a hospital setting with patients suffering from chronic schizophrenia [74]. However, other studies did not find significant differences when caffeine intake was restricted in patients with schizophrenia [75, 76]. Lucas et al. [77] tested patients with chronic schizophrenia with 10 mg/kg, which led to increased psychosis, thought disorder, unusual thought content, and euphoria-activation. In these patients, anxiety was not increased by caffeine, which may be particular to patients with schizophrenia, but may also be related to concurrent treatment with antipsychotics.

Despite this suspected induction or exacerbation of psychotic symptoms, some reports have shown that caffeine intake may be higher in patients with schizophrenia, or at least in a subgroup of them [75,78]. This high intake is at least partially associated with the excessive cigarette smoking often observed in these patients [79, 80]. The role of these drugs in schizophrenia remains to be elucidated. One hypothesis is that nicotine may be used as self-medication since it corrects sensory gating deficits found in schizophrenia [81]. However, the xanthines, theophylline and caffeine, were found to induce such alterations in normal volunteers [82, 83]. Other possibilities to be further studied are that caffeine may improve negative and cognitive symptoms and motor side effects of antipsychotics, which may contribute to high intake of caffeine by some patients with schizophrenia. Interestingly, subchronic treatment with caffeine attenuates cognitive deficits induced by an NMDA receptor antagonist used to model schizophrenia in rodents [84], and chronic treatment with caffeine renders rats less susceptible to motor effects of a typical antipsychotic [85].

Attention, impulsivity, cognitive performance, and attention deficit and hyperactivity disorder

ADHD is a heterogeneous syndrome characterized by inattention, impulsivity, hyperactivity, motivational/effort deficit, executive dysfunction, and impaired performance that arises during childhood and usually persists, sometimes at lower levels, during adulthood [86]. This disorder involves structural and functional pathological changes in frontal-subcortical-cerebellar circuits and monoaminergic alterations [87]. The main pharmacological strategy is the use of the psychostimulants, such as methylphenidate and am-

phetamine derivatives [86]. Thus, in contrast to potentially problematic use of caffeine in subjects with psychotic, bipolar, and anxiety disorders, caffeine may have a therapeutic role in ADHD. Since the symptoms of ADHD are normally distributed in the population [88], this section discusses the effects of caffeine on these cognitive and behavioral functions in both normal volunteers and patients with ADHD.

Caffeine is often used as a strategy to increase the ability to sustain attention, particularly in situations of low arousal or fatigue. The effects of caffeine on attention and performance have been studied using several paradigms and protocols.

Caffeine has been repeatedly shown to attenuate performance impairments due to decreases in arousal induced by sleep loss, fatigue, working at night, or by sedative drugs [89–93]. Furthermore, caffeine can remove the impaired performance and negative mood associated with the common cold [94] and attenuate memory impairment induced by scopolamine in humans [95]. In general, effects of small doses of caffeine are detected in low alertness paradigms, whereas more global and positive effects can be observed with doses of 200–300 mg (1,53,96). Consistent positive effects of caffeine have been shown in reaction times and vigilance performance [34,51,97]. Haskell et al. [33] showed that caffeine enhanced self-reported alertness and performance in attention and working memory tasks in both nonconsumers and consumers after overnight abstinence. Additionally, Christopher et al. [23] reported that caffeine increased self-rated alertness and decreased reaction times on visual, cognitive, and verbal reasoning tasks in regular caffeine users who were not in withdrawal. Also light, non-dependent caffeine users increase vigilance parameters with 150 mg of caffeine [24]. Addicot and Laurienti [98] showed that caffeine had a greater effect on mood and choice reaction time in the abstained state than in the normal caffeinated state, but caffeine improved selective attention and memory in both states. Smith [54] found that caffeinated gum containing 40 mg led to better performance, particularly in tasks requiring sustained attention. These studies suggest that despite the development of tolerance and withdrawal reactions to some extent, caffeine can produce these effects in regular users without abstinence and in non-regular users.

Caffeine can also influence stimulus processing. Streufert et al. [99] have shown that caffeine increases the speed of processing new stimuli, which was later confirmed [53]. Lorist and Snel [100] have also shown better target detection and response preparation by caffeine, whereas Ruijter et al. [101] have demonstrated that the quantity of information processed is greater after caffeine. Recently, caffeine was shown to improve alerting and executive control function in a dose-response manner, peaking at 200 mg [102]. More rapid encoding of new information was also found with 40 mg caffeinated gum in volunteers with mean daily consumption of 138 mg [54]. However, caffeine failed to reduce resistance to distraction [103].

Three important cross-sectional populational studies evaluated the association between cognitive functioning and caffeine intake in real-life situations [56,104, 105]. Jarvis [104] found a dose-response trend to improved performance in simple reaction time, choice reaction time, incidental verbal memory, and visuospatial reasoning with higher levels of coffee consumption ($P < 0.001$ in each task). Best performance was associated with about 400 mg caffeine per day. For tea consumption the associations were similar but weaker. Interestingly, these results were more apparent in older that in younger people. Smith [105] studied full time workers who had a median daily caffeine intake between 120 and 159 mg. Caffeine consumption was significantly associated with fewer cognitive failures (e.g., forgetting where things are, failures of concentration or doing the wrong thing). Those who had higher caffeine consumption ($>$ than the median) had about half the risk of self-reporting frequent/very frequent cognitive failures and accidents at work compared to those with low caffeine intake. A similar study was conducted in a nonworking sample and again all caffeine groups showed around 50% less risk of cognitive failures compared to those who abstain from caffeine (lowest quartile of caffeine intake) [105]. Also, the findings extended to much lower risk of depression, as mentioned above. These beneficial effects of caffeine did not seem to be associated with negative health consequences and may be related or add to the putative neuroprotective action of caffeine [106] (and companion articles of this issue). Thus, caffeine consumption is associated with better cognitive functioning and reduced risk of depression, and these effects do not seem to undergo significant tolerance. However, since these are cross-sectional studies, two main interpretations are possible: i) caffeine produces benefits in cognitive functioning and mood, or ii) those who naturally take more caffeine have better functioning, i.e., higher caffeine intake is a behavioral marker of personality traits associated with better cognitive performance or healthier mood.

Regarding personality traits, high consumers of caffeine are more sensation-seekers and impulsive accord-

ing to two studies [30,107], whereas impulsive individuals, particularly men, were found to have higher caffeine intake [108]. Two other studies failed to find correlations of caffeine intake with personality measures [109,110]. Importantly, these results go against the interpretation that caffeine is a behavioral marker of traits associated with better performance or more elevated mood, since impulsivity would increase the chance of making cognitive mistakes, and it is not particularly associated with better mood. Also, harm avoidance and self-directedness, which are associated with mood, performance and adjustment (i.e., high harm avoidance and low self-directedness are consistently found in subjects with mood disorders [111, 112]), were not different among low, moderate, and high caffeine consumers [30]. Thus, the interpretation that caffeine produces better functioning is the most likely based on current data. Another possibility is that higher caffeine intake may be a self-medication strategy in some impulsive individuals. Indeed, caffeine facilitates the performance of impulsive individuals and impairs the performance of non-impulsive individuals taking complex cognitive tests in the morning, but not in the evening [113,114].

Few studies with a small number of patients and using far from ideal protocols have tested the efficacy of caffeine in children with minimal brain dysfunction, a diagnosis that nowadays corresponds to ADHD [115–120]. In comparison to methylphenidate and d-amphetamine, caffeine was in general less effective. However, some ADHD patients responded well or particularly well to caffeine [119,120], and addition of caffeine to methylphenidate was also beneficial [117]. Unfortunately, clinical trials with larger and broader samples (e.g. adults), wide dosage range, or flexible dose protocols are yet to be conducted. Interestingly, caffeine improves cognitive performance in an animal model of ADHD [121] and promotes effort-related behavior in animals treated with dopamine antagonists [122]. Therefore, based on observational and experimental studies, caffeine is a candidate treatment for ADHD. If proven effective, caffeine has the advantage of being easily available without the level of abuse potential of methylphenidate and amphetamine derivatives.

MECHANISMS OF ACTION OF CAFFEINE WITH REFERENCE TO PSYCHIATRIC DISORDERS

The primary action of caffeine is to block adenosine A1 and A2A receptors. However, as adenosine is a neuromodulator and affects several other neurotransmitters, some indirect actions of caffeine are of particular relevance to understand its effects on subjects with the psychiatric disorders discussed in this paper.

One pivotal interaction of caffeine is with the dopaminergic system (reviewed in [5,123]). There are multiple and functionally different antagonistic interactions between adenosine A2A and dopamine D2 receptors, both post- and presynaptically, in such a manner that activation of A2A receptors reduces D2 receptor recognition, coupling, and signaling. This interaction results in reduced reward functions mediated via the indirect pathway, and lower glutamate drive to the prefrontal and motor areas of the cerebral cortex. There are also relevant antagonistic A1–D1 receptor interactions at the receptor and second messenger levels in the basal ganglia and prefrontal cortex.

Reduced activity of dopaminergic system is thought to play a central role in depression [124] and ADHD [86,87]. In contrast, higher dopamine activity leads to increased salience perception, which probably contributes to bipolar mania [125] and may be the final common pathway for psychosis [126]. Accordingly, antidepressants and psychostimulants such as methylphenidate increase dopaminergic activity [86,**?**], whereas D2 receptor antagonists exert antimanic and antipsychotic effects [126]. Thus, increased dopaminergic activity induced by caffeine can have positive effects on mood, cognition, effort-related behavior, and executive functions, but this effect may, on the other hand, promote mania (or mood instability) and psychosis.

Other putatively important effects of caffeine for mood and attention are the increase in noradrenaline, acetylcholine, and serotonin turnover, and noradrenergic and cholinergic firing (reviewed in [4]), but such interactions need further studies.

CONCLUDING REMARKS

Caffeine acts on two receptors with contrasting actions, which exert neuromodulating and homeostatic effects. Thus, there may be optimal levels of adenosinergic activity that can be influenced or manipulated by the A1 and A2A receptor antagonism of caffeine, depending on the context. The similarity of symptoms present with high dose caffeine and caffeine withdrawal reinforce this notion of an optimum activity level, which may be reached by adaptation of the adenosinergic system in different situations. Clinically, a sim-

ilar phenomena under "opposite" circumstances occurs comparing two psychiatric conditions: i) mixed mood episodes (mood instability, dysphoria, poor concentration, distractibility, insomnia, irritability, agitation), which is compatible with excessive monoaminergic tone since improvement is achieved with atypical antipsychotics by D2 receptor blockade, and ii) ADHD (hyperactivity, distractibility, agitation, inattention, dysphoria, impulsivity, sleep problems), which may reflect deficient monoaminergic tone since psychostimulants are effective to treat this condition.

Since caffeine is so easily available, most individuals tend to naturally select doses that do not produce unfavorable subjective and somatic effects, or performance impairment. In other words, individuals have intrinsic thresholds that may limit or prevent the repeated intake of more than optimal doses of caffeine, which may limit the emergence of anxiety, paranoid symptoms, or mood instability. On the other hand, the reinforcing effects of caffeine and emergence of withdrawal symptoms induce repeated intake.

Besides the possible induction of mild drug dependence, caffeine may bring some kind of benefit that contributes to its widespread use. These benefits seem to be related to adaptation of mental energy to the context by increasing alertness, attention, and cognitive function (more evident in longer or more difficult tasks or situations of low arousal), and by elevating mood. Thus, caffeine can be regarded as a pharmacological tool to increase effortful behavior in daily activities. More populational (cross-sectional and prospective) and experimental studies are necessary to establish the role of caffeine intake in psychiatric disorders, especially its putative efficacy on depressive mood and cognitive/attentional disorders.

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