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Review article

Effects of caffeine on anxiety and panic attacks in patients with panic disorder: A systematic review and meta-analysis

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ABSTRACT

Background: Caffeine has been purported to have anxiogenic and panicogenic properties, specifically salient in patients with panic disorder (PD). However, compilations of the magnitude of the effect of caffeine on anxiety and panic attacks are lacking and potential dose-response relationships have not been examined.
Objectives: In the present systematic review and meta-analysis, we aimed to examine the acute effects of placebo-controlled caffeine challenge on occurrence of panic attacks and subjective anxiety in patients with PD and healthy controls (HC), including dose-response relationships.
Methods: Systematic searches were performed in six databases. We included blinded placebo-controlled studies of acute caffeine challenge on panic attacks and/or subjective anxiety in adult patients with PD.
Results: Of the 1893 identified articles, ten met our inclusion criteria. The 9 studies investigating panic attacks included 237 patients, of which 51.1% had a panic attack following caffeine, but none after placebo. Six of these studies compared 128 patients with 115 healthy controls (HC), finding that patients (53.9%) were more vulnerable than HC (1.7%) for panic attacks following caffeine (log RR: 3.47; 95% CI 2.06–4.87). Six studies investigated subjective anxiety in 121 patients and 111 HC following caffeine, with an overall effect indicating increased sensitivity to the anxiogenic effects of caffeine in the patient group (Hedges' g = 1.02 [95% CI: 0.09–1.96]). The restricted range of caffeine employed [400–750 mg] and few studies (3) not using 480 mg prevented any meaningful analysis of a dose-response relationship.
Limitations: Of the ten studies included, only 2 reported anxiety data for the placebo condition, precluding a proper meta-analysis comparing anxiogenic effects of caffeine and placebo. The restricted dose range used prevented assessment of dose-response relationships.
Conclusions: The results confirm that caffeine at doses roughly equivalent to 5 cups of coffee induces panic attacks in a large proportion of PD patients and highly discriminates this population from healthy adults. Caffeine also increases anxiety in PD patients as well as among healthy adults at these doses although the exact relationship between caffeine-induced anxiety and panic attacks remains uncertain. The results suggest that caffeine targets important mechanisms related to the pathophysiology of PD.
Implications: Future studies should employ a wider range of caffeine doses and investigate contributions of biological and psychological mechanisms underlying the anxiogenic and panicogenic effects of caffeine. In the clinic, patients with PD should be informed about the panicogenic and anxiogenic effects of caffeine, with the caveat that little is known regarding smaller doses than 480 mg.
Registration.
PROSPERO (www.crd.york.ac.uk/prospero) registration number CRD42019120220.

1. Introduction

Panic disorder (PD) is a debilitating anxiety disorder affecting around 5% of the population [33]. The core symptom of PD is re-occurring panic attacks, sudden episodes of intense fear or discomfort along with a number of bodily symptoms, such as palpitations, shortness of breath, numbness, and dizziness [3]. Panic attacks can also occur in other anxiety disorders as well as in depressive disorders [32], and even

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occasionally in healthy individuals [33]. To achieve a PD diagnosis however, such attacks need to appear unexpectedly on a regular basis and must result in anticipatory fear of further episodes, alternatively a significant change in behavior [3].

Besides the vulnerability to experience spontaneous panic attacks, patients with PD show an increased sensitivity to several external triggers including anxiety-provoking situations in which earlier panic attacks may have occurred. Moreover, it was early noted that these patients react with increased anxiety and panic attacks to a variety of pharmacological agents. Pioneering work was reported in 1967 by Pitts and McClure [42] showing that lactate infusion caused anxiety attacks in susceptible patients. This was soon followed by a wide variety of chemical agents with varying targets, such as inhalation of carbon dioxide CO_2, yohimbine, meta-chlorophenylpiperazine (m-CPP) and norepinephrine, allowing researchers to study the topography of panic attacks as well as potential neurobiological underpinnings in a controlled manner [27,32].

One of the substances used in challenge paradigms for PD is the widely consumed psychostimulant caffeine [11,55], a methylxanthine common in foods and beverages such as coffee, tea, soft drinks, and chocolate, as well as in a number of over-the-counter drugs [19]. Contributing to its widespread use, caffeine has a number of positive effects, including improved mood, vigilance and alertness [37]. Moreover, epidemiological studies indicate that caffeine may be a protective factor against depressive states [26,31] and both animal [50] and clinical studies [25] suggest that caffeine may potentiate effects of antidepressant treatments. On the other hand, a link between caffeine consumption and worsened anxiety has been described, but findings regarding consumption patterns in patients with anxiety disorders as compared to healthy adults are mixed [7,47].

After oral intake, plasma caffeine concentration peaks after 15–120 min and readily crosses the blood-brain-barrier, resulting in a similar time-frame in the brain [20]. In healthy adults, caffeine has a half-life of 2.5–4.5 h. Pharmacologically, caffeine exerts its actions through antagonism of the adenosine receptor system [20]. The adenosine receptor system consists of the four receptors A1, A2A, A2B and A3 [16,22], of which A1 and A2A are the major targets of caffeine at normal physiological doses. Caffeine binds reversibly to both of these receptors with strong affinity. The A1 and A2A receptors are found in the brain as well as in peripheral tissue and are involved in a variety of functions related to homeostasis and neuromodulation, out of which several are implicated in panic disorder, including regulation of myocardic oxygen demand and coronary blood flow through vasodilation, and the systemic adaptation to hypoxia in the carotid bodies through mediation of respiratory stimulation [29].

In the central nervous system, the A1 receptors are widely distributed with high levels in the cortex, thalamus, hippocampus and striatum. The A2A receptors on the other hand are most abundant in the olfactory bulb and in the striatum, but are also found in the hippocampus, thalamus, cerebellum and neocortex [45]. As neuromodulators, the adenosine A1 and A2A receptors regulate the activity of other neurotransmitters such as glutamate, gamma-aminobutyric acid (GABA), acetylcholine, serotonin, and dopamine [21], which have been implicated in anxiety [17,23,24,30]. Moreover, A1 and A2A receptors functionally interact with each other and with other receptors, such as forming heterodimers with dopamine D1 and D2 receptors respectively in the striatum and carotid bodies [6,18]. The A1 and A2A receptors are involved in physiological mechanisms such as vasoconstriction and microglial function [21] as well as in a variety of psychological functions including the regulation of sleep, arousal, memory and anxiety [45,56]. Specifically, genetic knock-out studies of A1 and A2A receptors in the amygdala, striatum, hippocampus and the forebrain of mice have revealed the involvement of these receptors in fear conditioning and anxiety-related behavior [48,56,57].

Using acute caffeine challenge paradigms, panic attacks and increased anxiety have been induced in patients with PD and healthy comparison subjects starting in the 1980s [10,11,52]. Although one systematic review on the effects of caffeine on anxiety and panic attacks in patients with PD has been published a decade ago [55], meta-analytic compilations of the magnitude of the anxiogenic and panicogenic effects of caffeine in PD as compared to healthy adults are still lacking.

Thus, the aim of this systematic review and meta-analysis was to examine the acute effects of placebo-controlled caffeine challenge on subjective anxiety and occurrence of panic attacks in patients with panic disorder and healthy individuals. The following questions were addressed:

1. What is the acute effect of caffeine on subjective anxiety in adult patients with panic disorder and healthy adults, and do these effects differ and show dose-response relationships?
2. What is the acute effect of caffeine on occurrence of panic attacks in adult patients with panic disorder and healthy adults, and do these effects differ and show dose-response relationships?

2. Methods

2.1. Protocol and registration

The systematic review protocol for this study was registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42019120220; www.crd.york.ac.uk/prospero) on 16 January 2019 and was latest updated on 30 October 2019. Two deviations from the registered protocol should be noted. First, in the protocol we included the additional outcome of mood, which is not investigated in the current study. Second, only studies investigating patients with panic disorder were included here, hence no studies only assessing effects in healthy individuals were included in the present review. Importantly, these decisions were not influenced by any results, but rather due to time constraints and a need to focus this systematic review.

2.2. Eligibility criteria

Eligible for our review were randomized placebo-controlled trials (RCTs) and controlled clinical trials (CCTs) investigating panic disorder patients with a clinician-verified diagnosis of panic disorder, based on DSM-III, DSM-IV, DSM-5, ICD-9, or ICD-10 criteria. We included studies with or without a psychiatrically healthy control group in addition to the patients, and all participants were required to be adults (18 years or older). The study intervention of eligible studies was acute placebo-controlled caffeine challenge(s) consisting of administration of oral (e.g. pill or beverage) or intravenous caffeine. All studies were required to include a placebo-arm as a comparator and for studies administering the intervention as a beverage, the flavors of the intervention and comparator solutions needed to be identical or as similar as possible, e.g. adding caffeine to decaffeinated coffee. All interventions were required to be administered in a blinded manner, but we did not require double-blind administration or randomized order of administration in within-subject designs. As outcomes, the studies were obliged to report anxiety (reported as continuous self-rating or clinician-administered scales) and/or occurrence of panic attacks (i.e. proportion of each sample experiencing self-reported or a clinician-reported panic attack), within a time frame spanning from immediately after the intervention up to 24 h after the intervention. Settings were restricted to laboratory or clinical. Only original articles written in the English language were included. No date limits for publications were imposed.

2.3. Information sources

Systematic searches were performed in the databases PubMed, PsycINFO, Cinahl, Scopus, Web of Science and Cochrane Library up to October 142,019. Complementary manual searches were performed in

the reference lists of all articles that were included from the systematic search.

2.4. Search

The search strategy was structured according to the Participant, Intervention, Comparator and Outcome (PICO) framework and was developed in cooperation with a research librarian. As search terms we used a mix of Medical Subject Headings (MeSH) terms and free text words related to caffeine and panic disorder, such as "caffeine" OR "Coffeinum*" OR "Durvitan" OR "Dexitac" OR "Percutaféine" OR "Caffedrine" OR "Vivarin" OR "No Doz" OR "Percoffedrinol N" OR "1,3,7-Trimethylxanthine" AND "anxiety disorders" OR "anxiety*" OR "panic disorder" OR "panic*". The literature search was limited to published original articles written in English language. No date limits were used.

2.5. Study selection

Study selection was performed by the two study authors independently in a non-blinded manner using the systematic review software Covidence (Veritas Health Innovation, Melbourne, Australia; www.covidence.org). Duplicate studies were identified by the data management software Covidence and complemented by manual screening. In a first step, title and abstract were screened, and in the second step, full-texts were checked for eligibility. Any disagreement was resolved through discussion.

2.6. Data collection process

Data was extracted manually by one of the study authors (LK), using a data extraction sheet. The sheet was developed by the two study authors together and refined continuously through the extraction process. The other study author checked the extracted data. Disagreement was resolved through discussion. The following information was sought: number of participants, participant characteristics (gender, age, daily caffeine use), recruitment methods, diagnosis (panic disorder with/without agoraphobia, healthy control) diagnostic protocol, previous and current psychotropic medication under study period, minimum period of abstinence from psychotropic medication, previous and current psychotherapeutic treatment under study period, average/minimum number of panic attacks per week before study start, duration of caffeine abstinence before study start, duration of fasting before study start, route of administration for the intervention, characteristics of the intervention substance, caffeine dose, time to measure of effect, type of rating scales for the anxiety and panic attack outcomes respectively, level of anxiety and occurrence of panic attacks at baseline and after intervention (and/or changes in anxiety, panic attack pre-post intervention), time of day for intervention, additional tasks during test day and additional interventions (e.g. breakfast).

Three authors of studies with incomplete reporting were contacted via e-mail in an effort to complement or clarify missing outcome data. We received answers from two of the authors, however no additional data was retrieved through this procedure.

2.7. Risk of bias in individual studies

To assess the risk of bias in our study sample, we used the modified Cochrane Risk of Bias Tool covering the following parameters: sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective outcome reporting. For each domain in the tool we described the procedures undertaken for each of the studies included in our review. Each study was rated on each of the six domains as "high risk", "low risk", or "unclear" if insufficient information was available. The rating procedure was carried out by the two study authors independently and any disagreement was resolved through discussion.

2.8. Summary measures

The meta-analyses for effects of acute caffeine on anxiety levels were performed using a random-effects model on standardized mean differences (SMD). SMD with 95% confidence intervals were computed from available data (e.g. means and SD) as Hedges' g.

For occurrence of panic attacks, risk ratios (RR) with 95% confidence intervals were computed using a random-effects Mantel Haenszel calculation. Because panic attacks were never reported following placebo administration and only in one study in healthy individuals following caffeine administration, continuity correction (adding 0.5 to each cell) was applied to calculate and plot effects for individual studies. It should be noted that the overall RR estimate was calculated without continuity correction.

All statistical analyses were conducted in R version 4.0.0 [44] with the packages metafor [54], meta [4], and dmetar [28].

2.9. Planned method of analysis

The questions comparing caffeine effects between patients with PD and healthy adults included only studies with both patients and healthy adults because comparisons of groups from potentially different settings may introduce systematic bias. We tested for statistical heterogeneity between studies using the Q and I^2-statistics.

2.10. Risk of bias across studies.

Funnel plots were used to assess publication bias and small-study bias.

2.11. Additional analyses

Since correlation coefficients between baseline and post caffeine anxiety measures were not presented in any of the studies, we used 0.5 as an estimate for the correlation coefficient and performed sensitivity analyses using r = [0.1, 0.3, 0.7, 0.9] as coefficients. We planned to assess dose-response relationships using meta-regression, however, the restricted range of doses in the collected studies precluded such analyses.

3. Results

3.1. Study selection

A total of 10 studies were included in the review. The systematic database search resulted in 2647 hits out of which 754 duplicate records were identified and removed automatically by the data management program and 1893 passed to the title and abstract screening. Out of these, 1875 were excluded and 18 were screened in full-text for eligibility. After exclusion of studies that did not fulfill our eligibility criteria, ten studies remained for inclusion. Reasons for exclusion included wrong comparator (lack of a placebo-arm in one or more of the participant groups; 3 studies), data not available for the outcome measures of our interest (2 studies), study not presenting original data (1 study), wrong intervention (participants told they were given caffeine and the expected effects of caffeine, regardless if they were given caffeine or placebo; 1 study), and wrong outcomes (1 study) (Table S1). One study [11] included patients with the diagnosis agoraphobia with panic attacks as diagnosed with DSM-III. Since this diagnosis is considered as panic disorder in later versions of DSM [2,3], we included this study in our review. See flow diagram Fig. 1 for a summary of the study selection process.

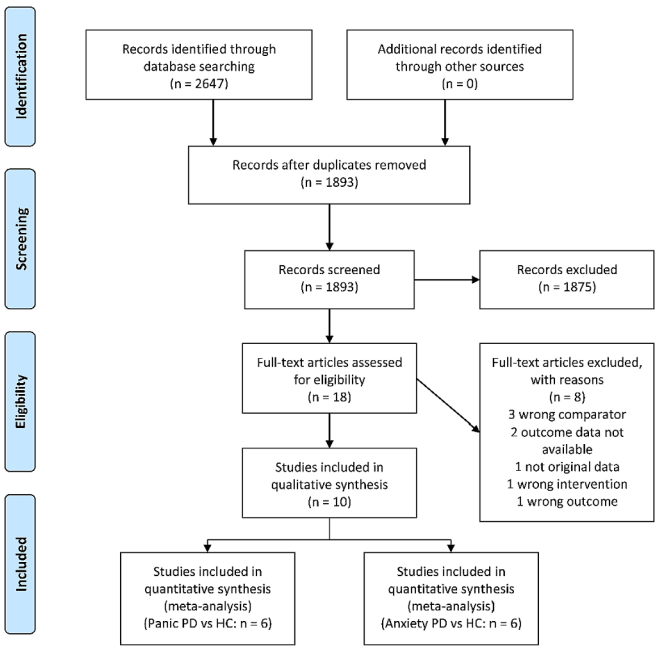

Fig. 1. PRISMA Flow diagram. Flowchart of the systematic review and meta-analysis according to the PRISMA.

3.2. Study characteristics

See Table 1 and Table S2 for study characteristics.

3.2.1. Methods

Out of the ten studies selected for review, all had a within-subjects design administering both caffeine and placebo to all subjects. Eight employed a randomized order of caffeine/placebo, whereas two had a fixed order with caffeine always being administered last. Patients were blinded to administered drug in all studies.

3.2.2. Participants

In total, the 10 studies included in the review involved 244 patients with PD, recruited from outpatient clinics in nine of the studies and way of recruitment not reported in one [53], and 122 healthy controls. Three of the studies did not involve a control group.

3.2.3. Intervention

All caffeine and placebo interventions were administered orally in capsules (2 studies), as instant coffee (5 studies), or other liquids (3 studies). Seven of the studies used fixed caffeine doses of 480 mg and one fixed 400 mg, whereas two based the caffeine dose on the body weight, 10 mg/kg and 7 mg/kg, which equals 750 mg and 525 mg caffeine respectively in a participant with a body weight of 75 kg. Participants rested after caffeine administration and no additional tasks or interventions besides outcome measurements were used in the selected studies.

3.2.4. Outcomes

Nine studies included anxiety as an outcome measure, employing continuous self-rating and item-based self- and clinician-rating scales, whereas eight investigated the ratio of the sample experiencing panic attacks. Time to measure effects ranged from 30 min up to 240 min after intake of caffeine or placebo. Three of the studies measured anxiety outcomes at multiple time points.

3.3. Risk of bias within studies

See Fig. 2 and Fig. S3.

Table 1
Study characteristics.

Study	Participants	Caffeine Intervention	Anxiety[1]	Panic attacks[2]
Charney [11]	**PD** *n* = 21 PD/APA (DSM-III), age: 38 (10.8), 71% w **HC** *n* = 17, age: 37.9 (12.1) (YY.Y), 71% women (w)	Caffeine citrate (10 mg/kg body weight) dissolved in ginger ale (0.18 l). Fixed order, caffeine last.	**C**: VAS (30 min): PD > HC **C > P**: VAS (30, 60, 90, 120, 180 min): PD > HC VAS (240 min): PD=HC	PD: 15/21 (71%) HC: 0/17 (0%)
Klein [34]	**PD** n = 7 PD(A) (DSM-III), age: 42 (9.6), 71% w	Caffeine capsule (480 mg). Fixed order, caffeine last.	**C > P**: ZAS, NIMH (90, 150 min): PD	PD: 5/17 (71%)
Masdrakis [59]	**HC** *n* = 19, PD(A) (DSM-IV), age: 35 (6.9), 79% w	Instant coffee (400 mg). Random order.	–	PD: 9/19 (47%)
Nardi [39]	**PD** *n* = 29 PD (DSM-IV), age: 34.2 (12.3), 59% w **HC** *n* = 28, age: 35.2 (8.8), 71% w	Instant coffee (480 mg) and two tablets low-calorie sucralose sweetener. Random order.	**C**: SUDS (30 min): PD > HC **C > P**: Not reported	PD: 17/29 (59%) HC: 2/28 (7%)
Nardi [40]	**PD** *n* = 83, PDA (DSM-IV), age range: 18-55, 71% w	Instant coffee (480 mg). Random order.	–	PD: 38/83 (46%)
Nardi [41]	**PD** *n* = 25, PD (DSM-IV), age: 33.9 (3), 68% w **HC** *n* = 22, age: 31.7 (12.7), 73% w	Instant coffee (480 mg) and two tablets low-calorie sucralose sweetener. Random order.	**C**: SUDS (30 min): PD=HC **C > P**: Not reported	PD: 13/25 (52%) HC: 0/22 (0%)
Nardi [38]	**PD** n = 28 PDA (DSM-IV), age: 37.4 (8.6), 68% w **HC** *n* = 26, age: 35.5 (12.1), 50% w	Instant coffee (480 mg) and two tablets low-calorie sucralose sweetener. Random order.	**C**: SUDS (30 min): PD > HC **C > P**: Not reported	PD: 17/28 (61%) HC: 0/26 (0%)
Newman [60]	**PD** n = 7, PD (DSM-III-R), age: 36 (6.2), 71% w **HC** *n* = 7, age: 32.1 (5), 57% w	Caffeine-containing liquid (7 mg/kg body weight). Random order.	**C, C > P**: ZAS, VAS (90 min): PD > HC	–
Tancer et al. [51]	**PD**[3] n = 11, PD (DSM-III), age: 32.7 (6.6), 73% w **HC** *n* = 11, age: 31.6 (9.8), 73% w	Caffeine capsule (480 mg). Random order.	**C, C > P**: STAI (90 min): PD=HC **C, C > P**: ZAS (150 min): PD > HC	PD: 3/11 (27%) HC: 0/11 (0%)
Uhde [53]	**PD** *n* = 14, PD (DSM-III), age:	Caffeine base (480 mg). Random order.	**C > P**: STAI, ZAS (90	PD: 4/14 (29%)

(*continued on next page*)

Table 1 (*continued*)

Study	Participants	Caffeine Intervention	Anxiety[1]	Panic attacks[2]
	32.5 (5.9), 50% w **HC** n = 11, age: 32.8 (9.4), 36% w		min): PD > HC	HC: 0/ 11 (0%)

A: agoraphobia; APA: agoraphobia with panic attacks; DSM: Diagnostic and statistical manual of mental disorders; HC: healthy controls; PD: panic disorder; STAI: Spielberger State-Trait Anxiety Inventory-State; SUDS: Subjective units of distress; VAS: Visual analog scale; ZAS: Zung Anxiety Scale; [1]Reported changes in anxiety levels post caffeine (C) and as compared to placebo (P); [2]Caffeine reported here. No panic attacks occurred after placebo; [3]One patient only received caffeine.

3.4. Results of individual studies

See Table 1 and Figs. 3 and 4 for an overview of the results of individual studies.

3.5. Synthesis of results

3.5.1. Subjective anxiety

Only 2 studies reported data for the placebo condition [11,51]. Hence, we focused on caffeine trials in the meta-analysis. That is, we did not include effects of placebo on anxiety, other than that the study design used kept the participant blinded to the intervention administered. Two studies did not randomize the order of drug administration and always gave caffeine as the last drug, after placebo [11] or after placebo and m-CPP delivered in a randomized order [34].

Anxiety levels following caffeine administration were reported in 6 studies including 121 patients with PD and 111 HC. In a pooled random effects analysis of these studies, caffeine increased anxiety levels in both patients with PD (Hedges' g = 1.94 [95% CI: 1.19–2.69]; Fig. S1) and HC (Hedges' g = 0.91 [95% CI: 0.46–1.36]; Fig. S2) with an overall greater increase in patients (Hedges' g = 1.02 [95% CI: 0.09–1.96]; Fig. 3). There was considerable heterogeneity between studies (Q = 15.0, p = 0.01; I^2 = 66.8%; [95% CI: 20.7%–86.1%]). Results of the meta-analysis were in line with the 2 studies examining subjective anxiety after caffeine, but excluded from the formal meta-analysis because they did not report data possible to pool [53] or did not include HC [34], as they also found increased anxiety following caffeine, and greater anxiety increase in patients than controls.

Only 3 studies presented data on changes in anxiety levels for both caffeine and placebo, precluding a proper meta-analysis of the effects of caffeine compared to placebo. However, all of the 5 studies that reported statistical comparisons between caffeine and placebo noted greater increase in anxiety from caffeine than placebo, and all of the 4 of these including HC reported larger effects in patients with PD than HC. The remaining 3 studies that included measures of subjective anxiety reported that placebo did not alter anxiety levels, but they did not include any comparison between caffeine and placebo.

3.5.1.1. Sensitivity analyses. Because the correlation coefficient (r) between baseline and post caffeine anxiety levels, which was needed to calculate the variance of the SMD effect measure, was unknown, we assumed r = 0.5. Sensitivity analyses using a range of correlation coefficients [r = 0.1–0.9] yielded similar increased anxiety in patients following caffeine (Table S3). Two studies reported outcome data for multiple time points. Charney et al. [11] reported change from baseline anxiety levels at 6 time points (30–240 min) post caffeine. We chose the first of these time points, because 30 min was the most frequently reported time point. Sensitivity analyses using the other most common time point, 90 min, revealed similar results (Table S3). Tancer et al. [51] reported post caffeine anxiety at two time points using different measures, 90 min (Spielberger State-Trait Anxiety Inventory State version) and 150 min (Zung Anxiety Scale). We chose to use data from 90 min because this was the most common time point of these. Sensitivity analyses substituting the 90 min with the 150 min outcome showed that results remained similar. It should be noted that Tancer et al. reported that anxiety increased more in patients than in HC only for the 150 min outcome (Table S3).

3.5.2. Panic attacks

Occurrence of panic attacks following caffeine and placebo were reported in 9 studies including 237 patients with PD and 6 studies including 115 HC. A fixed effects meta-analysis using Mantel-Haenzel continuity correction of the 6 studies including both patients (n =

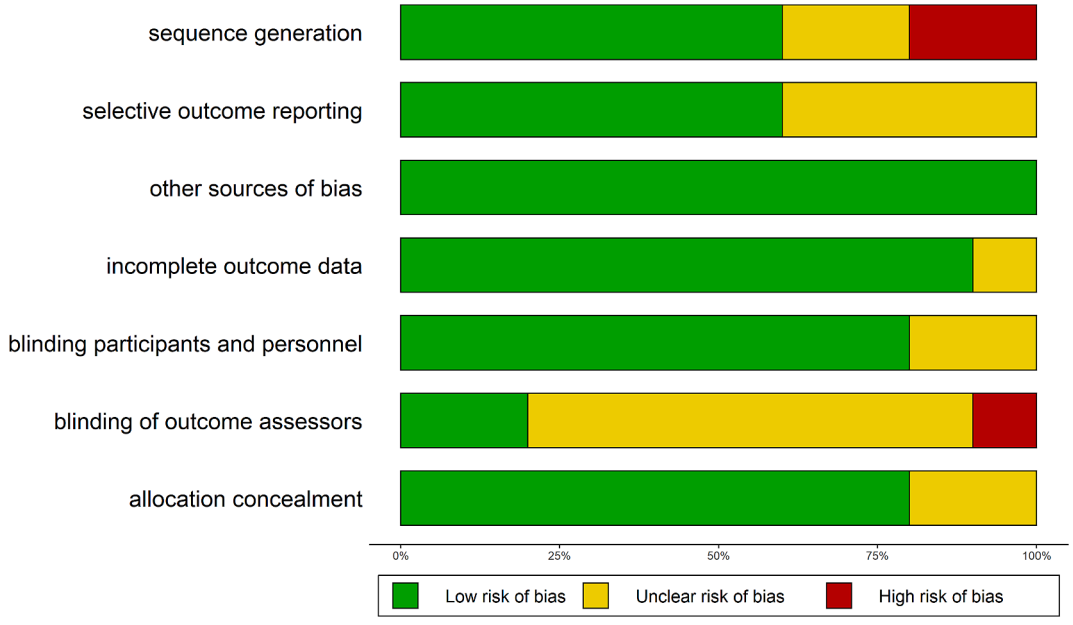

Fig. 2. Risk of bias. Assessments of risk of bias in included studies. Green indicates low risk, yellow unclear risk, and red high risk of bias. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

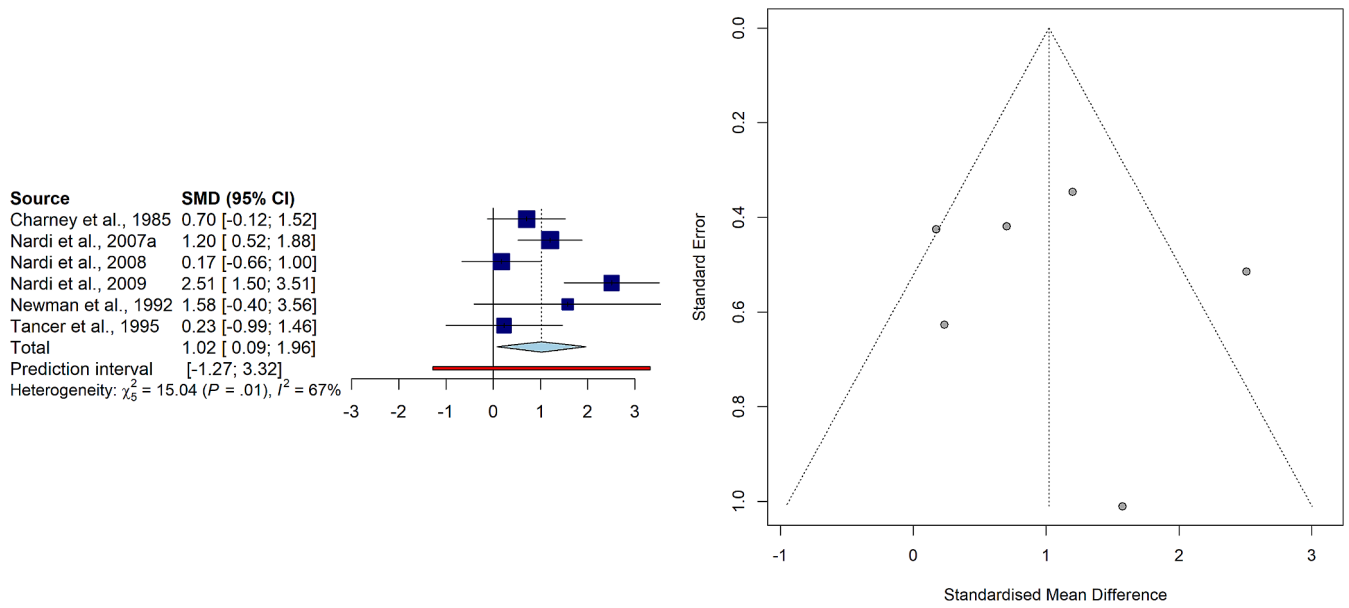

Fig. 3. Meta-analysis and funnel plot of the effects of caffeine on anxiety levels in patients with panic disorder as compared to healthy adults.

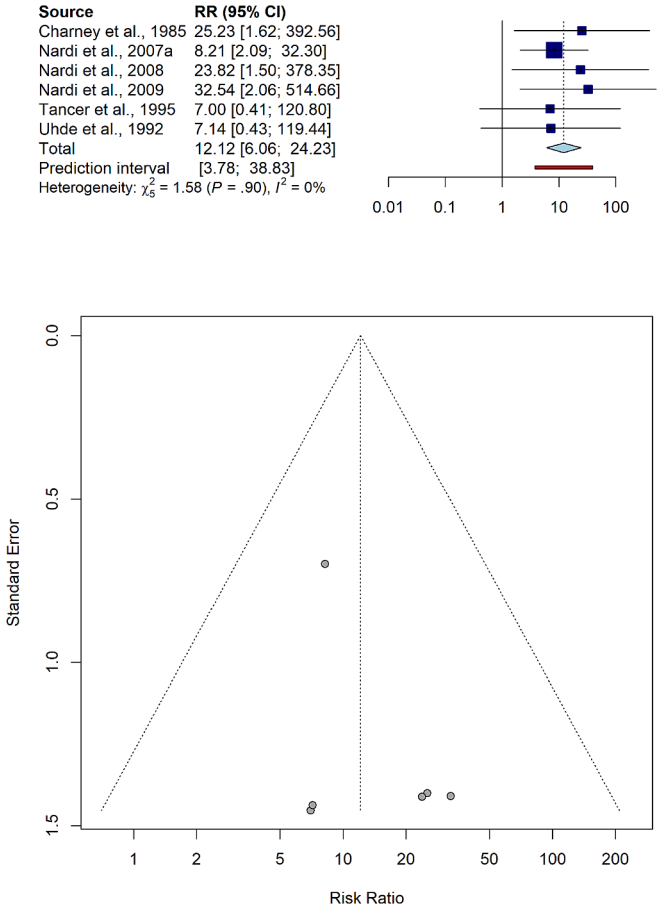

Fig. 4. Meta-analysis and funnel plot of the effects of caffeine on panic attacks in patients with panic disorder as compared to healthy adults.

128) and HC (n = 115) revealed an increased risk of a panic attack following caffeine in patients compared to HC (log RR: 3.47; 95% CI 2.06–4.87), Q(5) = 8.45 p = 0.133. In total 69 patients (53.9%) and 2 HC (1.7%) experienced a panic attack following caffeine (Fig. 2). Similarly, in the 3 studies not examining HC and thus not included in the meta-analytic effect size compilation, 52 of 109 patients (47.7%) had a panic attack (Table 1). Overall in the 9 identified studies, 121 (51.1%) patients and 2 (1.7%) HC experienced a panic attack after caffeine administration. None of the studies reported any panic attack following placebo.

Due to the distribution of caffeine doses used in the included studies, no dose-response relationships could be calculated.

3.6. Risk of bias across studies

Funnel plots indicated that one study [38] provided an unusually large effect, i.e. a potential bias, for the effect of caffeine on anxiety levels (Fig. 3). No indication of small-study bias was found for effect of caffeine on panic attacks in the funnel plot (Fig. 4).

3.7. Attrition

The reported attrition rate was low, with only two studies reporting attrition of a total of 4 individuals (Klein: 3; Tancer: 1), all from the caffeine condition [34,51].

4. Discussion

In this systematic review and meta-analysis, we show that caffeine roughly equivalent to 5 cups of coffee induces anxiety in both patients with panic disorder and healthy individuals, with patients being more vulnerable to caffeine-induced anxiety and at higher risk of experiencing a panic attack. The small number of studies using caffeine doses other than 480 mg precluded analyses of dose-response relations. Overall, these findings are consistent with anxiogenic and panicogenic effects of caffeine in patients with PD and extend those of an earlier systematic review [55] by quantifying effect sizes, showing anxiogenic effects of caffeine also in healthy individuals, and by providing a more detailed compilation of randomized blinded caffeine-challenge studies.

4.1. Summary of evidence

The present review and meta-analysis shows that caffeine challenges in doses of 400–750 mg to a high extent discriminates PD from healthy controls regarding the induction of panic attacks. Caffeine-induced panic attacks were experienced as similar to spontaneous panic

attacks, including symptoms such as fear of dying, shortness of breath, palpitations, and dizziness etc. Roughly half of patients and less than 2% of healthy controls experienced a panic attack following caffeine administration, and none after placebo. The restricted range of caffeine doses used in caffeine challenge studies in PD hitherto, with a majority of studies using 480 mg (roughly equivalent to 5 cups of coffee), makes it difficult to draw any conclusions regarding whether caffeine in high enough doses induces panic attacks even in healthy adults, or whether this effect is truly specific for subjects with certain baseline characteristics such as panic disorder.

The results also indicate that caffeine has a robust effect on subjective anxiety in PD patients as well as healthy controls, with both groups experiencing more anxiety following caffeine. The fairly large heterogeneity of effect sizes in the included studies should be noted, and individual studies reported both higher anxiety levels in the PD group and equal levels in both groups. Hence, the compiled effect measure may not be as representative of the true population effect as in the case of panicogenic effects of caffeine, where all studies pointed in the same direction of increased risk of panic attacks in patients. Nonetheless, we could not identify any defining features of studies finding higher levels of anxiety in PD groups compared to studies reporting equal levels. One suggested factor might be differences in adenosine receptor genotype distributions between studies, e.g. ADORA2A polymorphisms shown to affect sensitivity of caffeine-induced anxiety in healthy individuals [1,13]. However, we can only speculate, as ADORA2A polymorphisms were not investigated in any of the included studies, nor have they, to the best of our knowledge, been included in any study of caffeine challenge in patients with PD. Genetic predisposition to anxiogenic and panicogenic effects of caffeine is further highlighted by a study showing similar vulnerability in patients and their first-degree relatives, and that for all healthy first-degree relatives experiencing a panic attack after caffeine challenge, their family member with PD also did [41].

Moreover, there was a lack of reported data on anxiety levels following placebo, precluding meta-analytic compilations and definitive conclusions of caffeine vs placebo effects. However, available evidence makes it likely that caffeine induces higher anxiety levels than placebo when summarizing the available information from those studies that did report anxiety levels after placebo and those that compared anxiety levels following caffeine and placebo statistically. Also, included studies generally reported no increase in anxiety following placebo, without reporting any quantitative support. In summary, the anxiogenic effect of caffeine and the increased sensitivity of patients to this effect is less certain than the panicogenic effect.

4.2. Clinical implications

Despite a number of caffeine challenge studies having been conducted, as summarized here, many questions remain unanswered. One of the main questions remaining is if there exists a dose-response relationship between caffeine and anxiety/panic attacks. This is an important consideration when discussing clinical implications of the results, because the large doses of caffeine (5 cups of coffee) employed in the challenge studies do not reflect the normal dose of a caffeine serving in everyday life (about 100 mg in a brewed cup of coffee). In healthy individuals, moderate doses of caffeine (100–300 mg) have positive effects on mood, vigilance and learning, whereas higher doses (>400 mg) may induce anxiety [37]. Certainly, patients with PD are more sensitive to anxiogenic and panicogenic effects of caffeine compared to healthy individuals, but it is still unknown how they respond to small-to-moderate doses when it comes to anxiety and cognitive function. Adenosine receptor 2A gene (ADORA2A) variants have been linked to both increased risk of developing PD and stronger anxiogenic effects of normal serving sizes of caffeine (100–150 mg) [1,13], but this may be restricted to individuals with low habitual caffeine use [46]. Thus, healthy individuals can through caffeine consumption develop tolerance to the anxiogenic effects of caffeine, but it is uncertain if this also applies to patients with PD. No apparent difference in habitual caffeine consumption was noted between patients and healthy controls in studies included in the present review (Table S2), and findings from previous observational studies are mixed [7,47], suggesting that patients may not develop tolerance to the anxiogenic effects. On the contrary, there are case reports of patients with excessive anxiety showing improvement when abstaining caffeine [9]. Based on these findings, there are recommendations stating that patients with panic disorder should abstain from caffeine, but we would rather argue that recommendations should be individually-tailored rather than focus on a group of patients with probable heterogeneous etiology, manifestation, and response to caffeine, in line with more personalized treatment strategies. We thus recommend that assessments of caffeine consumption and its effect on the individual patient should be implemented in standard care. There are positive effects of caffeine consumption and not all patients with PD or other anxiety disorders need to quit caffeine due to anxiogenic effects, but clinicians and patients should be aware of the potential anxiogenic effects of caffeine. Furthermore, clinicians should consider that patients experiencing a panic attack following caffeine use may have an underlying panic disorder, as healthy individuals rarely suffer from caffeine-induced panic attacks, at least not for doses up to roughly 750 mg used in the reviewed studies.

Caffeine challenge, in line with other challenge protocols, is an important tool for researchers as it can provide experimental control over expression of panic attacks and anxiety levels. From this perspective, the full potential of this test has yet to be realized. Of note, all caffeine challenge studies in PD to date have assessed anxiety levels and panic attacks during rest. In other words, there is a lack of studies combining caffeine challenge with other symptom provocation or emotional processing tasks (e.g., to investigate interactions between caffeine and emotional arousal). Although the present findings show that resting protocols evoke increased anxiety levels and panic attacks in about half of patients with PD, adding emotional processing tasks could further our knowledge of emotional processing during increased anxiety levels and perhaps better reflect naturalistic settings where patients are faced with emotional demands after habitual caffeine consumption. This would also help in formulating clinical recommendations. Another clinically important consideration is the interaction between caffeine and treatment. Caffeine challenge studies, as those summarized here, were all conducted during abstinence from psychotropic treatment, preventing investigation of how clinical treatments interact with and potentially counteract the anxiogenic effects. Applying caffeine challenge tests in conjunction with pharmacological or psychological treatment could further help delineate treatment mechanisms. Furthermore, there have been no studies relating caffeine-induced anxiety and panic attacks to changes in brain activity and connectivity in patients or in healthy individuals. Such information could be used to disentangle the central and peripheral contributions of caffeine to anxiety and panic attacks and inform on the mechanisms underlying the anxiogenic and panicogenic effects of caffeine.

Interestingly, about half of the patients with PD experienced a panic attack during caffeine challenge. This may indicate that these patients are characterized by different pathways involved in panic attacks and full-blown PD compared to those that did not have a panic attack. Indeed, accumulating evidence has implicated baseline homeostatic and respiratory deviations in those patients who respond with panic to the caffeine challenge [36,40]. This is consistent with the increasing recognition of heterogeneity of both etiology and symptomatology of PD and other anxiety and psychiatric diagnoses, and of importance to both basic understanding of the disorder and to develop new and more personally tailored treatments. To this end, challenge studies such as the ones reviewed here may give valuable information into this heterogeneity and the underlying processes involved in panic attacks. Since a full account of the mechanisms and processes underlying anxiety and panic attacks is outside the scope of the current review, we will only in brief mention some potential mechanisms involving caffeine.

4.3. Anxiogenic mechanisms of caffeine

The anxiogenic and panicogenic mechanisms of caffeine are still largely unknown, but as mentioned in the introduction, caffeine non-selectively blocks adenosine receptors [20], of which inhibitory A1 and mainly excitatory A2A receptors are of most interest. Of interest in this context is the involvement of these receptors in chemosensation and respiratory regulation, heart rate regulation, and threat detection and emotional processing.

Regarding chemosensation, adenosine receptors may mediate caffeine-induced panic either through an increased respiratory drive in chemosensing brain regions such as the brainstem, or through other direct or indirect alterations of homeostasis. For example, caffeine generally causes vasoconstriction through A2A receptor binding in the endothelium [21], and it has been proposed that some individuals may be particularly sensitive to this effect [40]. Evidence from respiratory challenge studies points toward shared underlying mechanisms behind caffeine-induced panic and respiratory vulnerabilities. Thus, the respiratory subtype of PD, which is characterized by respiratory symptoms such as breathlessness, sensations of choking and hyperventilation during panic attacks, have been found to be associated with an increased sensitivity to caffeine [58]. Moreover, patients responding with panic to caffeine in provocation studies also panic when exposed to a 35% CO_2 challenge [40] and display baseline deviations in respiratory symptoms such as breath-holding duration and sensitivity to hyperventilation [35,40]. This suggests that caffeine shares a common pathway with CO_2 in the induction of panic.

Adenosine A1 and A2A receptors are also involved in the regulation of myocardial oxygen function and coronary blood flow. Antagonism of these receptors results in an increase in heart rate, another common symptom in panic attacks. However, heart rate does not seem to differ between PD patients and controls in caffeine challenge studies [11,39,41], which implies that caffeine acts through other mechanisms to induce anxiety and panic attacks. It may also suggest the involvement of cognitive mediation in panic attacks [14].

Psychological perspectives can contribute to the understanding of the panicogenic and anxiogenic effects of caffeine. According to the cognitive account of panic attacks, vulnerable individuals misinterpret bodily symptoms, such as increased heart rate, to signal impending disaster (e.g. an impending heart attack) [15]. Hence, increased heart rate from peripheral adenosine receptor antagonism may thus contribute to panic attacks in vulnerable individuals. In other words, the positive arousal effects induced by smaller doses of caffeine (up to about 300 mg) [37] may lead to increased anxiety and panic attacks, especially in larger doses inducing more arousal or in sensitive individuals. The behavioral manifestations of caffeine in patients may also, in part, be learned responses [8]. The sensations initially produced by caffeine are in this framework associated with anxiety and panic through interoceptive conditioning. In accordance interoceptive exposure has been reported to be an effective component of evidence-based psychological treatments targeting PD [43]. From this perspective PD may be viewed as unique among the anxiety disorders as the stimuli triggering anxiety and fear are interoceptive. Thus, psychological treatments targeting PD may be likened to psychological treatments both for other anxiety disorders, with the goal of reducing anxiety, and for somatic conditions, with the goal to reduce anxiety to somatic symptoms rather than reduce the actual somatic symptoms. Moreover, peripheral receptor antagonism, triggering bodily sensations, may also interact with blockage of receptors in the brain, for example in the amygdala and other brain regions such as the PAG, where receptor antagonism may lower the threshold for threat detection, making vulnerable individuals even more vulnerable to catastrophic misinterpretation of normal bodily symptoms. Supporting this proposal, the only study to date to examine effects of caffeine on emotional processing in the brain using functional magnetic resonance imaging (fMRI) found increased threat-related activity in the PAG [49], a brain region implicated in panic attacks and PD [27,32]. It should also be mentioned that panic attacks sometimes appear without any experience of fear [5,12], pointing to the need for more studies disentangling the changes in homeostatic mechanisms causing bodily symptoms from psychological factors such as catastrophic misinterpretation and anxiety sensitivity in the induction of panic attacks.

In conclusion, we propose that the anxiogenic and panicogenic effects of caffeine in PD are best understood as involving one or many innate homeostatic vulnerabilities which can in themselves be modulated at several levels and which interact with psychological and environmental variables.

4.4. Limitations

Our study has several limitations that should be noted. First, the results are based on a relatively small number of studies and should thus be interpreted with caution, and ideally be replicated in larger caffeine challenge studies. Nonetheless, increased anxiety levels and heightened risk of caffeine-induced panic attacks in patients with panic disorder was robustly found across studies. Further, the estimates of caffeine's effect on anxiety levels was conducted using an imputed regression coefficient, potentially affecting the results. However, sensitivity analyses revealed that the effect size was robust for a wide range of possible regression coefficients, indicating that the imputation might not have had a large impact. A number of studies included in this review used potentially inexact dosing of caffeine as they relied on commercially available instant coffee. Despite this, effect sizes were large and relatively homogenous, indicating that the interventions may not have varied between studies to any significant degree or that the doses used were at least large enough to produce the effects, but nevertheless future studies should ideally use verified doses of caffeine to more reliably establish the exact doses at which these effects appear. It should be noted that the present data cannot discern if the effects of caffeine are reproducible within individuals, that is, if the individuals would experience the same outcome if the challenge was repeated. This is an important prerequisite if we want to draw firm conclusions regarding the underlying neurobiology and psychology of caffeine-induced panic and anxiety.

4.5. Conclusions

In conclusion, caffeine in doses of roughly 5 cups of coffee is panicogenic in patients with panic disorder, and anxiogenic in both healthy adults and patients, with patients being more vulnerable. We propose that caffeine-induced changes in homeostatic and brain-mediated psychological processes are at the core of caffeine-induced anxiety and panic attacks. Future studies should further elucidate these and other mechanisms underlying the effects of caffeine, preferably through examination of the pathways from genetic risk polymorphisms via risk phenotypes to the presentation of PD. The relative role of the main targets of caffeine, adenosine A1 and A2A receptors, should be elucidated, as well as their interaction with other receptors in different brain regions. In order to draw more precise mechanistic conclusions, a framework simultaneously involving physiological as well as neurobiological and psychological variables should ideally be applied. Moreover, the caffeine challenge paradigm should be investigated using a wider range of doses to elucidate dose-response effects and whether caffeine is a dimensional or categorical trigger of panic attacks across healthy and panic disorder populations.

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Declaration of Competing Interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.genhosppsych.2021.11.005.

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