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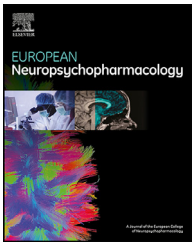

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# Role of adenosine A2A receptors in hot and cold cognition: Effects of single-dose istradefylline in healthy volunteers

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**Abstract**
The role of the adenosine neurochemical system in human cognition is under-studied, despite such receptors being distributed throughout the brain. The aim of this study was to shed light on the role of the adenosine A2A receptors in human cognition using single-dose istradefylline. Twenty healthy male participants, aged 19–49, received 20 mg istradefylline and placebo, in a randomized, double-blind, placebo-controlled cross-over design. Cognition was assessed using computerized cognitive tests, covering both cold (non-emotional) and hot (emotion-laden) domains. Cardiovascular data were recorded serially. Cognitive effects of istradefylline were explored using repeated measures analysis of variance and paired t-tests as appropriate. On the EMOTICOM battery, there was a significant effect of istradefylline versus placebo on the Social Information Preference task ($t = 2.50$, $p = 0.02$, $d$=-0.59), indicating that subjects on istradefylline interpreted social situations more positively. No other significant effects were

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observed on other cognitive tasks, nor in terms of cardiovascular measures (pulse and blood pressure). De-briefing indicated that blinding was successful, both for participants and the research team. Further exploration of the role of adenosine A2A receptors in emotional processing may be valuable, given that abnormalities in related cognitive functions are implicated in neuropsychiatric disorders. The role of adenosine systems in human cognition requires further clarification, including with different doses of istradefylline and over different schedules of administration.



## 1. Introduction

It is widely established that distinct cognitive functions are under the modulatory influence of various neurochemical systems (Kehagia et al., 2010; Ott and Nieder, 2019; Robbins and Roberts, 2007). The role of particular receptors and neuromodulators in cognition is highly relevant to understanding the neurobiology of neuropsychiatric disorders. Using single-dose pharmacological agents to 'probe' the role of particular systems in human cognition has shed considerable light on the roles of the neurotransmitters noradrenaline, dopamine, and serotonin (e.g. Chamberlain and Sakakian, 2006; Mehta et al., 2001, 1999). In contrast, the role of the adenosine neuromodulatory system in human cognition is relatively understudied. For example, a PubMed search using the terms "adenosine AND cognition AND humans" yielded 630 results whereas a search for "serotonin AND cognition AND humans" yielded 5294 results.

Adenosine is a key neuromodulator that is widespread throughout the brain (Fink et al., 1992). It acts through multiple mechanisms and has indirect effects on neurotransmitter pathways, such as dopaminergic, glutamatergic and noradrenergic systems (Ioannidis et al., 2014). Adenosine is a synaptic modulator, and adenosine receptors broadly act to enhance/sharpen the salience of incoming information (Cunha, 2016). The two main receptor types, A1 and A2, act to inhibit and stimulate adenylyl cyclase respectively, and they affect transmitter release, nerve activity, and transmitter system interactions (for detailed review see Fredholm et al., 2005). Adenosine A2A receptors are abundant in the basal ganglia and synapses throughout the entirety of the brain, and are mainly located in synapses, notably those that form parts of the glutamatergic, GABAergic, cholinergic, dopaminergic, serotonergic, and noradrenergic pathways (Cunha, 2016). These receptors have been found to enhance glutamate release and the function of glutamate receptors, as well as tuning other neuromodulation systems (Cunha, 2016).

Perhaps the most widely studied pharmacological agent acting on the adenosine system – and certainly the most widely used in everyday life – is caffeine, whose cognitive effects are substantially mediated via non-specific antagonism of multiple adenosine receptors (Ioannidis et al., 2014; McLellan et al., 2016). Caffeine is widely used throughout the world for its alerting properties (Ioannidis et al., 2014) but its effects on cognition are mixed and further research is needed. For example, there is consensus that caffeine improves reaction time and vigilance (Encycl. Diet. Suppl., 2010; McLellan et al., 2016), while its effects on memory and executive function are less consistent (McLellan et al., 2016). The effects of caffeine on cognition may differ depending on the nature of dosing. At non-toxic doses, preclinical data indicate that regular caffeine consumption may antagonize adenosine A1 receptors whereas regular caffeine consumption may antagonize adenosine A2A receptors (Cunha and Agostinho, 2010). There is also evidence, from a double-blind controlled trial in previously caffeine-naïve human volunteers, that acute caffeine can impact memory consolidation according to an Inverted-U function (Borota et al., 2014). Thus, acute moderate caffeine may enhance memory consolidation whereas higher acute caffeine may impair this function.

Adenosine receptors are pertinent to understanding various conditions (Pasquini et al., 2022) including Alzheimer's Disease, Parkinson's Disease, and psychiatric conditions such as depression and ADHD (França et al., 2020) [ADHD being a disorder of childhood onset with symptoms persisting into adulthood in 30–60% of cases (e.g. Kessler et al., 2005)]. Focusing on ADHD as an example, there is evidence that caffeine can ameliorate ADHD symptoms, albeit not as effectively as first-line treatments such as psychostimulant medication (Garfinkel et al., 1975; Ioannidis et al., 2014). Psychostimulants are currently the most effective treatment for ADHD (Kollins, 2008) and primarily affect dopaminergic transmission (Challman and Lipsky, 2000). Recent research demonstrates that dopamine transmission is also influenced by adenosine receptors (Ferré et al., 2011). Furthermore, caffeine has been shown to modulate impulsive behaviour in a rodent model of ADHD (Leffa et al., 2019), whilst a separate rodent model of ADHD indicated that antagonism of multiple adenosine receptor types could enhance spatial working memory and social recognition, whereas antagonism of a specific adenosine receptor, the adenosine A2A receptor, was required for improvement of social recognition (Takahashi et al., 2008). In spontaneously hypertensive rats (an animal model of ADHD), caffeine consumption plus physical exercise has been found to enhance neuroplasticity and ameliorate deficits in olfactory discrimination and short term recognition memory (França et al., 2020). In 6-hydroxy-dopamine (6-OHDA)-lesioned rats, 14-days of caffeine treatment improved attentional deficits (Caballero et al., 2011). For an in-depth review of caffeine's effect on animal ADHD models see (Vázquez et al., 2022).

Moreover, studies indicate that adenosine A2A receptors influence mental tracking (Geiger et al., 2016) and social cognition (Moscoso-Castro et al., 2016), whilst in animal

studies, these receptors have been implicated in aspects of working memory (Giménez-Llort et al., 2007), reversal learning (Wei et al., 2011), habit formation (Yu et al., 2009), decision-making (Leffa et al., 2018), goal-directed behaviour (Li et al., 2018), cognitive flexibility (Zhou et al., 2019), and fear memory (Simoes et al. 2016).

Istradefylline is a selective adenosine A2A receptor antagonist, developed as an adjunctive treatment in Parkinson's disease (PD) (Hauser et al., 2008). For discussion of its development and eventual use in this clinical context, see Chen and Cunha, 2020. It has potent selective affinity for these receptors (Saki et al., 2013). Some cognitive enhancing effects of istradefylline have been identified in participants with Parkinson's Disease (Uchida et al., 2014). There is also evidence of effects in different animal models, showing primarily that istradefylline may prevent or ameliorate deterioration in memory and learning rather than necessarily enhancing these domains in control animals (Kadowaki Horita et al., 2013); Dall'Igna et al., 2007; Yu et al., 2008; Shen et al., 2008; Canas et al., 2009; Cognato et al., 2010; Kaster et al., 2015; Laurent et al., 2016).

Therefore, the aim of the current study was to use istradefylline as a pharmacological probe to explore the role of adenosine A2A receptors in human cognition. This was a randomized, double-blind, cross-over design in healthy volunteers. In light of the above research, we hypothesized that istradefylline would have beneficial effects on classic executive functions but also on social cognition.

## 2. Experimental procedures

### 2.1. Subjects and screening procedures

Twenty healthy male volunteers were recruited using advertisements in a local newspaper. After a complete description of the study had been provided, and the risks and benefits discussed, participants provided written informed consent. All potential recruits were screened for significant history of psychiatric or medical illnesses using a structured clinical interview supplemented with the Mini International Neuropsychiatric Inventory (MINI) (Sheehan et al., 1998), administered by a trained researcher. Participants provided a urine sample prior to participation in order to exclude recent use of illicit substances (One Step 10 in 1 Drug Testing Kit, Home Health UK). Intelligence Quotient (IQ) was assessed using the National Adult Reading Test (NART) (Nelson, 1982), and current depressive mood with the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery SA, 1979). Past week total caffeine intake was quantified using a detailed instrument developed for this study: the Ioannidis Caffeine Questionnaire (ICQ; see Supplement). Trait impulsivity was assessed using the Barratt Impulsiveness Scale (BIS-11) (Patton et al., 1995; Stanford et al., 2009). We included these measures to examine whether they moderated any observed cognitive effects of istradefylline.

The study was approved by Local Research Ethics Committee (Cambridge, REC reference number: 207,190), and was exempted from clinical trials status by the Medicines and Healthcare Products Regulatory Agency (MHRA).

### 2.2. Inclusion/Exclusion criteria

Healthy male participants were recruited, aged 19–49. Exclusion criteria included: taking medication in the past two weeks likely to impact cognition, history of Parkinson's Disease, history of clinically significant hepatic/cardiac/renal disease (and other major physical health disorders), current depression (as determined by MINI and the Montgomery-Asperg Depression Rating Scale), known substance dependence (including nicotine), recent illicit drug use (determined by self-report and urine illicit drug screen), history or presence of major mental disorders (including bipolar disorder, psychosis, attention-deficit hyperactivity disorder, obsessive-compulsive disorder, or personality disorder), any known contraindication to istradefylline, history of major head injury, baseline cardiovascular parameters outside normal range, insufficient proficiency with English to understand the procedures, involvement in research in the preceding three months that could impact the neurocognitive assessment (such as participation in studies using the same or similar cognitive tasks), age outside the 18–49 bracket and IQ $<$ 80 based on the NART.

### 2.3. Study design

Participants meeting the inclusion criteria attended for two study visits: on one occasion they received a single oral dose of istradefylline (20 mg), and on the other occasion an oral placebo of identical appearance and weight. Medication was over-encapsulated by the supplying pharmacy to ensure visual blinding. The order of drug dosing was randomized and counter-balanced across participants. This was a randomized, within-subject, cross-over, double-blind design. Based on the established pharmacokinetic profile of istradefylline (Hauser et al., 2003), cognitive assessments were undertaken from 1.25 to 2.75 h after capsule administration. Prior to cognitive assessments, volunteers spent time in a quiet, waiting room, relaxing. Blood pressure and pulse data were collected three times per visit: at baseline, before starting cognitive assessments and after completion of the cognitive tests. At the end of each study visit, we conducted a debriefing to ask participants if they had noticed any effects of the capsule (including 'side effects'); and they were asked to indicate one of three options: believed they had been on active drug, believe they had been on placebo, or completely unsure. We asked the equivalent question to the member of the research team running the sessions, in order to evaluate study team blinding.

### 2.4. Neuropsychological assessment

Neuropsychological batteries consisted of tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB, v6.0.23, www.camcog.com) for "cold cognition" and EMOTICOM (v1, Bland et al., 2016) for "hot cognition". Cognitive testing was performed using a touch-screen computer in a quiet room, supervised by a trained test administrator. Cognitive tasks included in this study are described in Table 1.

### 2.5. Statistical analyses

Analyses were conducted using SPSS v26.0. Effects of drug versus placebo on blood pressure and pulse rate were evaluated using repeated-measures analysis of variance (RM-ANOVA), including effects of time and treatment condition. Effects of istradefylline on cognition versus placebo were quantified using paired t-tests.

The sample size was determined *a priori* based on a power calculation, which indicated that $N = 20$ would yield $>$80% power to detect a significant effect of drug of effect size $d = 0.7$ or larger, at alpha $= 0.05$ two-tailed, based on paired t-tests. This was the minimum effect size deemed to be of significant interest. Based on the

**Table 1** Descriptions of cognitive tasks included in this study.

| Task | Task Description |
|---|---|
| CANTAB Spatial Working Memory (SWM) | A measure of working memory. Participants are asked to search a number of coloured squares in order to find a yellow token (Chamberlain et al., 2005). On each stage of the task, a number of 'closed' boxes are presented on the screen; and a token has been hidden by the computer behind one of these boxes. The participant opens a given box by clicking it on the screen, and the aim is to identify the token without returning to previously searched boxes. After identifying each token, the computer then hides a new token behind one of the other boxes on that task stage. Overall the aim is to identify all tokens whilst avoiding returning to boxes where tokens were previously found, thereby measuring spatial working memory. The number of boxes can be gradually increased to 12 in order to increase the difficulty level of the task. Outcome measures include strategy and errors (revisiting boxes already found to be empty). |
| CANTAB Rapid Visual Processing (RVP) | A measure of sustained attention in which participants are required to detect a target sequence of digits (Soar et al., 2012). On the screen, participants view a single box that shows a stream of single digits (e.g. "1", then "6", then "8"…) and the aim is to look out for a target sequence (e.g. "2", "4", then "6"). Target sequences are shown in advance, so participants know what to look out for. Whenever the participant believes they have seen a target sequence, they press a button to indicate this. Outcome measures include speed of response, probability of false alarms and sensitivity. False alarms refers to pressing the button when a target sequence did not actually occur. Sensitivity refers to how successful the participant was at identifying the target sequences. |
| CANTAB Intra-Extra Dimensional Set Shift (IED) | Measures set-shifting by testing rule acquisition and reversal. On this task, individuals observe two pictures (i.e. stimuli) on each trial, and must choose the picture they believe to be 'correct' according to a rule the computer has determined. After making a selection, the computer provides feedback 'correct' or 'incorrect'. Thus through trial and error, participants can learn the underlying rule about which picture is correct. Over the course of the task, the nature of the underlying rule is changed by the computer, in order to test different aspects of attention and flexible responding (García-Villamisar and Dattilo, 2015). Total errors adjusted is the number of errors made overall on the task, accounting for stages not attempted (the task can prematurely end if a participant becomes stuck and does not learn a rule). ED errors is the number of errors made on the hard stage of the task. The ED stage requires individuals to shift attention between stimulus dimensions and as such is particularly challenging and relates to the ability to show flexible responding. |
| EMOTICOM Reinforcement Learning (RL) | An assessment of learning through reward and punishment. On each trial, the aim is to select the circle that is more likely to lead to a reward (e.g. gain of a virtual 50p), and less likely to lead to punishment (e.g. loss of a virtual 50p) (Bland et al., 2016). This task examines the ability of participants to learn the optimal choice of coin whilst receiving degraded feedback – i.e. the 'optimal' coin does not always give the optimal outcome. |
| EMOTICOM Cambridge Gambling Tast (CGT) | Assesses decision making and risk-taking behaviour. During the task participants are shown a roulette wheel divided into two colours, with the proportions of each colour changing on every trial. Participants are required to choose the colour they wish to bet on and the size of the bet (Bland et al., 2016; Dam et al., 2019). This task is adapted from the classic Cambridge Gamble Task (CGT) which seeks to fractionate different aspects of decision-making. |
| EMOTICOM Social Information Preference ("Theory of Mind; SIP) | A task designed to assess information preference by hiding nine pieces of information in a socially ambiguous situation. Participants view a scene comprising three faces (feelings), three facts, and three thoughts about the scene hidden from view. They can reveal a subset of this information in an attempt to learn about the scene. They then choose from a range of possible outcomes for the trail based on this information: positive, neutral, or a negative outcome. Thus the individual attempts to interpret social scenes based on partial information, which entails use of theory of mind (i.e. being cognizant of, and able to interpret, others' mental states) (Dam et al., 2019; Skandali et al., 2018). |
| Delay Discounting task (DD) | Participants are offered choices between monetary awards available immediately and larger rewards available following a delay (Ainslie, 1975). Such DD tasks present two choices: a more immediate theoretical smaller reward or a larger theoretical delayed reward. For example, a participant may need to choose between £10 now, or £30 in three days. As such the task, overall, measures preference for more immediate reward over delayed rewards. |

a priori power calculation, there was no correction for multiplicity, and significance was defined as $p<0.05$.

## 3. Results

The characteristics of the study sample are summarized in Table 2. No adverse events were reported during the study.

Results of neuropsychological test batteries are presented in Tables 3 and 4. No significant effects of istrade-

**Table 2** Demographic data and results of self-administered psychological tests.

| | Mean (SD) | Range |
|---|---|---|
| Age (years) | 30.2 (7.9) | 19–49 |
| Caffeine Consumption (mg per week) | 1670 (1246) | 0–4122 |
| NART | 121.0 (4.5) | 111–126 |
| BIS-11 total score | 59.2 (9.3) | 42–77 |
| Motor | 22.7 (4.2) | 13–29 |
| Non-Planning | 21.1 (4.5) | 11–30 |
| Attentional | 15.5 (3.9) | 8–23 |
| SOC | 116.6 (6.5) | 104–128 |
| SDS | 17.9 (7.2) | 5–29 |
| NEO-FFI-3 total score | 137.2 (16.9) | 115–171 |
| Neuroticism | 16.4 (7.7) | 2–30 |
| Extraversion | 28.5 (6.8) | 15–43 |
| Openness to experience | 30.9 (5.9) | 20–42 |
| Agreeableness | 29.6 (7.0) | 13–41 |
| Conscientiousness | 31.7 (6.9) | 21–46 |

Abbreviations. SD: standard deviation, NART: National Adult Reading Test, BIS-11: Barratt Impulsiveness Scale 11 (BIS-11), MADRS: Montgomery-Asberg Depression Rating Scale.

**Table 3** Neuropsychiatric data of CANTAB.

| Batteries | Measures | Drug Conditions (SD)(20 participants each) | | Statistic (t value) | p value | Cohen's *d* |
|---|---|---|---|---|---|---|
| | | Istradefylline | Placebo | | | |
| IED | Adjusted total error | 11.3 (7.9) | 12.2 (11.7) | 0.42 | 0.68 | 0.09 |
| | Extra dimensional error | 2.7 (3.0) | 3.5 (5.2) | 0.81 | 0.43 | 0.18 |
| RVP | Median latency | 358.1 (59.3) | 344.3 (39.5) | 1.73 | 0.10 | −0.39 |
| | Probability of hit | 0.80 (0.14) | 0.77 (0.17) | 1.02 | 0.32 | −0.23 |
| | Probability of false alarm ($*10^2$) | 0.30 (0.38) | 0.34 (0.49) | 0.24 | 0.81 | 0.05 |
| SWM | Between-search errors | 54.9 (46.3) | 44.3 (44.4) | 1.44 | 0.17 | −0.32 |
| | Double errors | 2.0 (2.7) | 2.8 (5.2) | 0.57 | 0.57 | −0.13 |
| | Total errors | 56.0 (47.3) | 45.2 (44.7) | 1.37 | 0.19 | −0.31 |
| | Within errors | 3.9 (8.0) | 2.8 (3.6) | 0.50 | 0.62 | −0.11 |

Abbreviations. SD: standard deviation, IED: Intra-Extra Dimensional Set Shift, RVP: Rapid Visual Processing, SWM: Spatial Working Memory.

fylline versus placebo were found for the CANTAB tasks (paired t-tests, all $p>0.10$). On the EMOTICOM tasks, there was a significant effect of istradefylline versus placebo on the Social Information Preference task ($t=-2.50$, df=19, $p = 0.02$, $d=-0.59$). This was due to participants on active treatment more positively interpreting social situations than under placebo conditions. No significant effects were detected on the other EMOTICOM tasks (all $p>0.10$).

Drug-related changes on the Social Information Preference task (affective bias) did not correlate significantly with baseline caffeine intake ($r = 0.095$, $p = 0.708$), nor with baseline impulsivity on the BIS (total scores, $r = 0.105$, $p = 0.679$).

In terms of cardiovascular parameters (Figure 1; in supplementary file), RM-ANOVA indicated no significant effects of time or of treatment, nor were there significant treatment x time interactions (all $p > 0.10$).

In relation to study blinding, participants and researchers were unable to accurately identify the active medication sessions beyond chance levels (Table 5), indicating that the double-blind was successful.

## 4. Discussion

We sought to use istradefylline to probe the role of adenosine A2A receptors in human cognition. We found a significant effect of istradefylline on affective bias on the Social Information Preference (SIP) task, which measures the difference in the proportion of selected positive and negative scenario outcomes. This result indicated that participants interpreted social situations more positively in the istradefylline condition compared to placebo. There were no significant effects on the other cognitive tasks that were examined although there was a non-significant trend effect of istradefylline on risk adjustment loss on the Cambridge Gamble Task (CGT). Some caution is needed however, as this study did not correct for multiple comparisons due to the limited sample size. In animal models, adenosine 2A receptors have been found to play a role in reward-based decision-making and effort choice (Leffa et al., 2019; Font et al., 2008).

The SIP task assesses a participant's preference for selecting different types of information (facial expression,

**Table 4** Neuropsychiatric data of delay discounting and EMOTICOM.

| Batteries | Measures | Drug Conditions (SD)(20 participants each) | | Statistic(t value) | p value | Cohen's *d* |
|---|---|---|---|---|---|---|
| | | Istradefylline | Placebo | | | |
| DD | Log of overall k* | −2.33 (0.81) | −2.22 (0.83) | 1.14 | 0.27 | 0.07 |
| | Log of small k | −2.16 (0.91) | −2.08 (0.88) | 0.76 | 0.46 | 0.06 |
| | Log of medium k | −2.29 (0.83) | −2.29 (0.89) | 0.01 | 1.00 | −0.0005 |
| | Log of large k | −2.46 (0.75) | −2.35 (0.82) | 1.08 | 0.30 | 0.09 |
| RL | Learning rate in win condition | 0.12 (0.29) | 0.23 (0.34) | 1.24 | 0.23 | 0.26 |
| | Temperature in win condition | 0.91 (1.68) | 0.47 (0.82) | 1.30 | 0.21 | −0.29 |
| | Learning rate in loss condition | 0.39 (0.36) | 0.28 (0.30) | 1.00 | 0.33 | −0.21 |
| | Temperature in loss condition | 0.87 (0.80) | 0.78 (1.26) | 0.27 | 0.79 | −0.05 |
| CGT | Risk adjustment loss | 2.5 (0.7) | 2.2 (1.0) | 1.99 | 0.06 | −0.46 |
| | Risk adjustment win | 2.1 (0.8) | 1.8 (0.9) | 0.94 | 0.36 | −0.22 |
| SIP | Faces | 5.7 (5.6) | 8.2 (7.1) | 1.38 | 0.19 | 0.33 |
| | Thoughts | 39.9 (7.4) | 39.7 (8.4) | 0.08 | 0.94 | −0.02 |
| | Facts | 26.4 (5.3) | 24.1 (4.8) | 1.52 | 0.15 | −0.36 |
| | Affective bias | 3.7 (4.0) | 1.5 (3.9) | 2.50 | 0.02 | −0.59 |

Abbreviation. DD: delay discounting, RL: Reinforcement Learning Task, CGT: Cambridge Gambling Task, SIP: Social Information Preference ("Theory of Mind").
* $k$ = coefficient of delay discounting.

**Table 5** Blinding results from debriefing sessions pertaining to active treatment visits. Top row shows the N and percentage of participants correctly guessing the were on active treatment, incorrectly guessing they were on active treatment, and indicating they were completely unsure. The bottom row indicates the equivalent responses for what the Researcher running each visit thought about the participant (i.e. study team blinding).

| | Correct | Incorrect | Unsure |
|---|---|---|---|
| Study participants | 20% (4/20) | 35% (7/20) | 45% (9/20) |
| Researcher | 5% (1/20) | 5% (1/20) | 90% (18/20) |

'theory of mind' related, and fact-related), to interpret ambiguous or incomplete scenarios, and is from a battery of tasks designed to assess hot cognition (EMOTICOM). Hot cognition refers to the cognitive processing of emotionally salient information (Roiser and Sahakian, 2013) and disruptions in these processes have been implicated in neuropsychiatric disorders, including ADHD (Dam et al., 2019), as well as psychosis (Berry et al., 2015). Interestingly, a previous study indicated that paranoia was associated with a negative interpretation of ambiguous social information (Savulich et al., 2015). Given that istradefylline was associated with more positive interpretation of social situations on the SIP task in the current study, it would be potentially interesting to explore effects of adenosine receptor manipulation in clinical populations characterised by abnormalities of social information processing. In a resting state neuroimaging study, habitual coffee drinkers displayed decreased functional connectivity in a network encompassing subcortical and posterior brain regions associated with somatosensory, motor, and emotional processing, as compared to non-coffee drinkers (Magalhaes et al., 2021). As such, it is possible istradefylline may have exerted its effects on affective bias via such brain networks, given that caffeine modulates adenosine receptors. This prediction could be tested in future work. Relatedly, there is evidence from a rodent study that caffeine can impact hippocampus function including aspects of neuroplasticity (Paiva et al., 2022). There is also evidence that A2A receptor modulators can impact aspects of mood in animals, including in animal models of depression (Kaster et al., 2015; Padilla et al., 2018). There is some evidence linking A2A receptor gene variants to depression as well as sleep and attentional problems from a cross-sectional population-based study (Oliviera et al., 2019).

Contrary to our expectations, given pre-clinical findings, and the distribution of adenosine A2A receptors throughout the brain, we did not detect any other effects across a variety of hot and cold cognitive domains. However, it should be noted that this study was designed to detect only drug effects of large size or greater, and so it would have been underpowered to detect subtler cognitive effects. Nonetheless, the current data suggest acute doses of 20 mg istradefylline did not have any untoward (e.g. sedative) deficits using cognitive tests with established sensitivities to such effects, nor were any cardiovascular effects noted, which is reassuring in terms of the use of this medication as an add-on treatment for Parkinson's Disease in some jurisdictions, at least at this dose level. The general lack of cognitive effects observed in the current study is however arguably accordance with animal models, which suggest cognitive effects are mainly detected using istradefylline in models of existing cognitive impairment or disease, rather than in healthy control animals (Kadowaki Horita et al., 2013); Dall'Igna et al., 2007; Yu et al., 2008; Shen et al.,

2008; Canas et al., 2009; Cognato et al., 2010; Kaster et al., 2015; Laurent et al., 2016).

Though we believe this to be the first study to comprehensively assess cognitive effects of istradefylline in humans using a range of tests, several limitations should be considered. This was a single-dose study; as such, we do not yet know if istradefylline given in higher doses and/or with repeated dosing could impact cognition. Our sample size, while adequate to detect large effects, was underpowered to detect subtler effects. It should be noted that this sample had an above average IQ. Future work could examine whether these findings generalize to a wider population. Though subjects had higher than population average IQs, we feel it unlikely that ceiling effects contributed to the negative findings reported herein. For example, on the CANTAB SWM, there were an average of 51 errors across placebo and drug conditions, while on the CANTAB RVP, the probability of identifying the correct target sequences was well beneath 100% across placebo and drug conditions, suggesting there would be ample scope for improvement in task performance through a cognitive enhancing manipulation. While we cannot rule out the possibility that differences in participants' caffeine intake could have affected the study results, we feel this is unlikely: the study used a cross-over design with each participant acting as their own control to minimize inter-individual differences. We did not correct for multiple comparisons because this was an exploratory study with a sample size inappropriate for statistical correction due to power. This may provide a potential alternative explanation for the significant result on the SIP. Our participants were moderate consumers of caffeine (on average), and this could have influenced effects of istradefylline. For example, if some participants had not taken caffeine on their testing days, then for these individuals, istradefylline could have ameliorated cognitive effects of not taking their usual caffeine. Lastly, our study did not measure polymorphisms of adenosine A2A receptors, which could influence effects of medication. Prior work has found these polymorphisms can influence caffeine intake and mood (Huin et al., 2019).

In conclusion, we found initial novel evidence of a role for adenosine A2A receptors in emotional processing on the Social Information Preference test, biasing towards positive. The study findings suggest that future research might explore the impact of istradefylline on this and other aspects of emotional processing, as well as brain mechanisms underpinning any behavioural effects observed, using neuroimaging. The data also suggest it may be valuable to study effects of istradefylline in clinical conditions associated with emotional processing abnormalities.

## Contributors

SRC designed the study and led it. RH contributed to the data collection and statistical analyses. All authors contributed to the writing of the manuscript and approved it for publication.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Supplementary materials

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