The Acute Effect of Hypericum Perforatum on Short-Term Memory in Healthy Adults

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This is a pre-print of an article published in Psychopharmacology. The final authenticated version is available online at: https://doi.org/10.1007/s00213-018-5088-0

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This work was supported by the I-CORE program of the Planning and Budgeting Committee and the Israel Science Foundation (1821/12). The authors declare that they have no conflict of interest.

Abstract

Rationale Over-the-counter drugs containing hypericum perforatum (*H. perforatum*), have been argued to improve memory and sustained attention. So far, these claims have not been supported in human studies. However, previous studies used rather high dosages, and little is known about the acute effect of small dosages.

Objective We evaluated whether an acute treatment with Remotiv 500 and Remotiv 250 (500 or 250 mg of H. perforatum quantified to either 1 or 0.5 mg of hypericin) improved memory, sustained attention, as well as mood and state anxiety in healthy adults.

Method A single dosage, randomized, double blind, placebo-controlled trial was conducted with 82 student participants (33 women). Each participant received placebo in one session and one of two dosages in the other session. Order of the sessions and dosage conditions were randomized between subjects. Participants completed a battery of tasks assessing short-term memory capacity and sustained attention.

Results A significant positive effect of Remotiv 250 on digit span (mean Cohen's d = 0.58; p = .01) was observed. By contrast, Remotiv 500 had a negative effect on digit span (mean d = -0.48, p = 0.04). A similar effect emerged when factoring across tests of short-term memory. Both dosages improved mood (d = 0.60, p = .03).

Conclusions The results indicate that acute treatment with small (250 mg) dosages of H. perforatum has a positive effect on the capacity of short-term verbal memory, and stress the importance of maintaining small dosages in nootropic applications.

Trial registration www.clinicaltrials.gov NCT02862236

Introduction

Considered a medicine since ancient Greece (Istikoglou et al. 2010), Hypericum perforatum (*H. perforatum*), also known as St John's Wort, is commonly used in treating mild to moderate depression (Linde et al. 2005; Rahimi et al. 2009). In the past twenty years, preclinical studies have additionally made the claim that administration of H. perforatum is capable of improving cognitive functions, particularly those associated with memory, in healthy and intact organisms. This was reported for chronic administration (e.g., Klusa et al. 2001; Hasanein and Shahidi 2011) as well as in a 3-4 day treatment (Khalifa 2001; Kumar et al. 2002; Widy-Tyszkiewicz et al. 2002) and even in acute administration (Khalifa 2001). It was further argued that chronic administration of H. perforatum reduces aging effects on memory (Trofimiuk et al. 2010; Griffith et al. 2010). Such claims are often easily taken up by pharmaceutical companies and currently there are many over-the-counter medications that feature H. perforatum as having the benefit of enhancing human memory (a search on Amazon.com conducted on February 2018 revealed 454 such products). Also, while not being a popular nootropic in healthy adults (Maher 2008), H. Performatum is commonly used by parents of children with ADHD as an organic alternative to methylphenidate (Cala et al. 2003).

However, up to now human studies of H. perforatum focusing on healthy adults and individuals with ADHD have shown no benefits on memory and sustained attention (Ellis et al. 2001; Timoshanko et al. 2001; Siepmann et al. 2002; Weber et al. 2008). In the current study we evaluate two potential explanations for the gap between preclinical and human studies of the nootropic effect of H. perforatum. On the one hand, it might be the case that H. perforatum does not enhance memory processes, particularly when

administrated in an acute fashion. On the other hand, as reviewed below, all previous studies of the effect of the compound on healthy adults have used high dosages (above 900 mg). Thus, the null findings in these studies may be due to overdosing. In addition, previous studies of healthy adults all employed small samples ($n < 15$) and may have been under-powered. We conducted the largest study of H. perforatum in healthy adults so far to examine whether it has a nootropic effect.

The mechanism argued to lead to the nootropic effect of H. perforatum in rodents is inhibition of synaptic uptake of several monoamines, including serotonin, dopamine, and noradrenaline (e.g., Khalifa 2001; Kumar et al. 2002). These monoamines are well known to have a regulatory role in animal and human memory functions (Quartermain et al. 1988). A single administration of H. perforatum was found to have an augmentative effect on dopaminergic transmission in humans as well, as indicated by an increase in growth hormone and decrease in prolactin levels (Franklin et al. 1999). Similar findings were also observed in an electroencephalography study (Schellenberg et al. 1998) and in a non-invasive brain stimulation study (Concerto et al. 2018).

Still, only two previous studies examined the cognitive effect of acute treatments with H. perforatum in healthy adults. In Ellis et al.'s (2001) study 12 healthy volunteers underwent three within-subject conditions of a single dose administration (Placebo, and H. perforatum 900 and 1800 mg). No significant differences between the 900 mg and placebo conditions were obtained for tasks assessing memory functions, while the highest dose (1800 mg) impaired performance in delayed picture recognition and numeric working memory. A study by Timoshanko et al. (2001) similarly examined 13 healthy volunteers who underwent four within-subject conditions (placebo, H. perforatum 900

and 1800 mg, and amitriptyline). Cognitive and psychomotor tests showed no effect of H. perforatum compared to placebo. Two additional studies evaluated the effect of a longer administration: Siepmann et al. (2002) examined 12 adults who received either H. perforatum (900 mg) or placebo daily for 14 days, and Weber et al. (2008) examined 54 children with ADHD for an 8-week period using similar dosages. Both studies reported no positive or negative cognitive effects.

Our study focused on a single administration in two sessions, one where participants received Remotiv (Zeller, Romanshorn, Switzerland) and another where they received placebo. We applied smaller dosages compared to previous studies: Remotiv 500, which contains 500 mg of H. perforatum quantified to approximately 1 mg of hypericin and Remotiv 250, which contains 250 mg of H. perforatum quantified to approximately 500 μg of hypericin. Though having two active ingredients (hypericin and hyperforin) H. perforatum is normally quantified based on the former because hyperforin is relatively unstable in the presence of oxygen and light as well as non-acidified aqueous solutions (Orth and Schmidt 2000). Following the extant preclinical literature (reviewed in Ben-Eliezer and Yechiam 2016), we focused on the effect of Remotiv on short-term memory and sustained attention.

Method

Participants

The study was approved by the Helsinki committee of the Beer Yaakov-Ness Ziona Mental Health Center (Nes Ziona, Israel) as well as by the Technion Ethics Committee for Human Clinical Studies. Participants were recruited by ads posted on an institutional

mail-server and student listservs, calling for volunteers for a paid study about the effect of psychiatric medications on cognitive functions. Potential participants were contacted using a designated email and asked to fill out preliminary details allowing us to predict the compatibility of the participants to the experiment. This included affiliation as students, having ADHD, weight and height, and participants' availability to attend two sessions at the campus. This initial questionnaire was followed by a phone conversation with one of the investigators, a psychologist (D.B.E), who assessed participants' psychiatric background using a short semi-structured psychiatric assessment (the SCID-I/NP; First et al. 2002). The final exclusion decision based on the interview was made jointly by the psychologist (D.B.E) and another investigator, a senior psychiatrist (M.B.S).

Participants were included in the study if they were adult students of the Technion, between the age of 18 and 40, and with a weight between 50kg to 90kg (to increase the homogeneity of the drug effect). Additionally, we excluded pregnant or nursing women, non-fluent Hebrew speakers, those diagnosed with any DSM-V disorder (including ADHD, learning disabilities, and drug abuse),[1] and those with any motor or sensory difficulty that could hamper the ability to perform the experimental tasks. We also excluded participants who reported any ongoing medical conditions (e.g., photodynamic treatment or diagnosis, light sensitivity) or use of any medication (e.g., immune system inhibitors, HIV protease inhibitors) which may adversely interact with H. perforatum.

[1] Those with sexual dysfunctions and sleeping disorders were allowed to participate.

Participants who met these criteria were invited to the lab and completed the Beck Depression Inventory (BDI; Beck et al. 1961) and the State-Trait Anxiety Inventory (STAI; Spielberger et al. 1983), using validated Hebrew translations of these questionnaires (Horesh 1998; Teichman and Melnik 1984). Clinical cutoffs of the Hebrew versions were used: a score higher than 15 on the BDI (Beck et al. 1961; Teichman and Melnik 1984) and higher than 45 on the Trait scale of the STAI (Horesh 1998; Austin and Parker 2007). Given the large number of individuals who scored above the cutoff on the STAI (n = 15; 14.4%) it was decided to exclude these participants from the study so as to allow clear interpretation of its results.[2]

Participants received NIS 150 (about $42) for each session. Additionally, those who completed both sessions and performed well in a randomly selected task were paid an additional amount of NIS 20 or 40 for performing 1 or 2 SDs above average, respectively. The average was taken from a pilot group who performed the task battery once with no medication.

Study design and interventions

A single administration placebo-controlled study was conducted at a single site in two sessions, separated by at least two weeks. Participants were randomly assigned into a high (Remotiv 500) and low (Remotiv 250) dosage condition. Remotiv is a film coated tablet of Ze 117 containing either 500 mg (Remotiv 500) or 250 mg (Remotiv 250) of dry extract from H. perforatum (drug/extract ratio 4 - 7:1, extraction solvent: ethanol 57.9%

[2] One participant scored above cutoff on the BDI. Yet as his score was very close to the cutoff level it was decided to include him. As described below, all analyses were re-rerun controlling for BDI scores.

(V/V)). The extract contains 0.1 – 0.3% of total hypericins, quantified by specific high-performance liquid chromatography determination (see Pharmeuropa 2004), as well as low amounts of hyperforin (less than 1%). Participants were further randomly assigned into two order conditions: those who took placebo in the first session and Remotiv in the second session and those who had the reverse order.

The order of the sessions as well as the allocation of participants into the high and low dosage conditions were determined using a double-blind procedure. The capsules were prepared by a licensed pharmacist, authorized for drug preparation for clinical experiments. Each capsule had one of four possible colors (2 containing placebo and 2 containing Remotiv, either 250 or 500 mg). The same placebo color was always used for a given dosage condition.[3] The placebo pills included lactose gelatin. All capsules had the exact same shape, were wrapped uniformly, and corresponded to individual codes. The assignment of pill colors to experimental conditions was conducted by an independent psychologist who was not involved in the conduct of the trial, and was kept in sealed, opaque envelopes until the point of allocation. Randomization of participants into the four pill colors was executed by D.B.E for each individual participant using Microsoft Office 365 random number generator.

Outcome measures

The primary outcome measures were four tests of short-term memory and two additional tests assessing multiple cognitive capacities. All tests were programmed in Millisecond

[3] Additionally, colors were re-randomized after about half the subjects had been run to prevent an effect of color on the experimental results.

Inquisit® software (version 5). First, we administered two versions of a computerized Digit span test based on the WAIS-III (Wechsler 1981), in which participants are asked to recall digit sequences in forward or backward order. Digit sequences are presented beginning with a length of two digits, and two trials are presented at each increasing list length. Testing ceases when either an error occurs at two trials with the same list length or the maximal list length is reached (9 digits forward, 8 backward). The dependent measure was the longest list correctly reported before an error occurred at two trials with same list length (Wechsler 1981). Validation of psychometric properties for the computerized version of the task was conducted by Woods et al. (2011).

Next, we administered two tests that more directly evaluate working memory span: the Operation span task (Unsworth et al. 2005) and the Symmetry span task (Foster et al. 2014). The Operation span task focuses on phonological working memory. Participants are asked to memorize sequences of letters and to recall them in their presented order. Following each letter a calculation task is presented, inhibiting rehearsal of prior stimuli. The Symmetry span task similarly assesses spatial working memory by memorizing locations of lit boxes on a 3×3 grid. Following the presentation of each grid, a visual symmetry task is presented. Performance in both tasks is the total number of recalled letters/locations in sets without errors. Validation of the psychometric properties of the computerized versions of the Operation and Symmetry tasks is reviewed in Redick et al. (2012).

Additionally, we included a Go/No-go Task (Votruba and Langenecker 2013) for examining effects on sustained attention and inhibition. In this task participants are asked to respond to a signal (the target) and to inhibit their response to a different signal. In the

first half of the task, the target is less frequent (at about 18% of total stimuli), and in the second half, it is more frequent (82% of stimuli). The task was performed in two conditions, one with stimulus-presentation times (SPTs) of 2 seconds (similar to the Test of Variables of Attention; Greenberg and Kindschi 1996), and a faster version with a SPT of 667 ms (following Niculescu et al. 2010). As the findings were similar in the two versions, we report results averaged across SPTs.

Finally, we included the Groton Maze task (Pieterzak et al. 2008), a measure of short and long-term spatial memory, and spatial learning. The task involves finding a path in a grid by checking whether adjacent boxes are the next step in the path or not. When revealing a correct box, it is lit in green; otherwise in red. The same maze is repeated four times enabling examination of learning over time.

As secondary outcome measures, changes in the participants' state anxiety and mood were assessed using the State scale of the State-Trait Anxiety Inventory (STAI; Spielberger et al. 1983; Teichman and Melnik 1984) and the Positive and Negative Affect Schedule (PANAS, the 10 items international short version; Watson et al. 1988; Karim et al. 2011). The STAI and PANAS were administered before the dispensation of the drug/placebo and once again following completion of the experimental tasks. Additionally, following task completion we administered the State Anxiety scale of the Depression Anxiety and Stress Scale (DASS; Lovibond & Lovibond, 1995), which focuses on physiological symptoms of anxiety. At the end of the task battery participants were asked to estimate their performance level on a 0 to 100 scale compared to the score of their peers, to evaluate their confidence.

Procedure

The experiment consisted of two identical sessions of about three hours each. The sessions were conducted from February 2017 to February 2018, with an average of 34.1 days between sessions for a given participant. The experiment always started between 8:15 AM to 8:30 AM, and took place in a standard computer lab, with up to 16 seats, equipped with identical screens, PCs, and operating systems. Participants were instructed to avoid consumption of any psychoactive substance 72 hours prior (except for tobacco and coffee for which they were asked to maintain their day to day habits). On arrival participants were identified using a national identity card or a student card including a photo, then signed an informed consent form following a verbal explanation by one of the researchers. Next, a licensed physician verified their health and obtained vital signs. This included cardiovascular measures of beats per minutes (BMP) and blood pressure. The physician in charge was blind to the participants' treatment assignment. Participants were then asked to fill out several psychological questionnaires measuring trait anxiety and depression as noted above. Following that they were administered with a capsule containing drug or placebo (based on randomization) which was taken with a glass of water. They received a sandwich (in keeping with the manufacturer recommendation of digesting the pill with food) and had a sixty-minute break. During the break they were instructed to stay on the premises and not to engage in physically arousing activities. Following the break they were given general instructions on task performance (see Supplementary section) and underwent the main task battery. Performance of the battery took 80 minutes on average. Participants then underwent another examination by the physician, at which time they were asked to report any adverse influence on their health

and wellbeing. One participant in the Remotiv 500 session complained about parched throat, and there were no additional side effects. After finishing the second day of the experiment, participants were paid and thanked.

Analysis

A repeated measures analysis of variance (ANOVA) was conducted, with drug condition (Remotiv vs. placebo) as a within subject factor and dosage condition (Remotiv 250 vs. 500) and order of sessions (placebo first vs. drug first) as between subject factors. Additionally, in the analysis of the two Digit span tests, task version (forward vs. backward) was used as an additional within subject factor. To examine potential moderating factors we conducted regressions for each dosage condition, with the difference between the Remotiv and placebo conditions as the dependent variable, and with depression and trait anxiety (on the BDI and STAI Trait scale) and changes in mood and state anxiety (on the PANAS and STAI State scale), as predictors.

Results

Study population and experimental allocation

As indicated in Fig. 1, a total of 189 students were screened (via questionnaire and phone interview) and 104 of them were randomized into the study conditions. The final analyzed dataset included 82 participants (49 men and 33 women; mean age 24.9) after excluding those above the clinical cutoff on the STAI (15 participants), and those who did not attend the second session of the experiments (7 participants). Three participants who initially completed the placebo condition and 4 who initially completed the drug

condition did not attend the second session, hence there was no selection bias in this respect.

Before conducting the main analysis we examined if there were any prior differences between order and dosage conditions. This was done using Bonferroni-corrected logistic regressions for gender, native language, and marital status; and ANOVAs for age and baseline levels in BDI, STAI, and PANAS (with order and dosage condition as between subject factors). Importantly, the results revealed no significant differences between order conditions in any of the examined variables (p's > 0.3). The results also did not show a significant difference between the two dosage conditions in all measures except for the BDI, in which individuals allocated to the higher dosage condition (Remotiv 500) had higher scores ($F(1,78) = 10.63$, $p = .01$). To ensure that our interpretations of the findings were not affected by this difference, we conducted separate tests for each dosage condition where there was a main effect of drug across dosages. Additionally, to examine the effect of depression on the variance between dosage conditions, we examined whether this variable moderated any differences observed between dosage conditions using bootstrapping analysis (Preacher and Hayes 2004). Finally, we also re-ran all analyses covarying for BDI scores.

Memory tests

Table 2 and Fig. 2 present the effect of H. perforatum on the four memory tests. A visual scan of the findings suggests a curvilinear pattern, with a more positive effect for the smaller dosage than for the larger dosage. For the two Digit span tests, the results showed a significant drug by dosage interaction effect, $F(1,78) = 11.15$, $p = .001$; and no main effect of drug, $F(1,78) = 0.02$, $p = .89$. Examining the two dosage groups separately

showed a significant positive effect for Remotiv 250, $F(1,40) = 7.19$, $p = .01$; and a significant negative (impairing) effect for Remotiv 500, $F(1,39) = 4.38$, $p = 0.04$. Importantly, the task version (forward vs. backward) did not interact with the effect of the drug, $F(1,78) = 1.84$, $p = .18$, or with the drug by dosage effect, $F(1,78) = 0.25$, $p = .62$. The effect size (Cohen's *d*) for the improvement with Remotiv 250 equaled 0.46 for the forward version and 0.70 for the backward version, denoting a medium to large effect. Effect sizes for the respective impairment with Remotiv 500 were -0.65, and -0.31.

For the Operation span task, although the trend was similar, the results indicated no significant main effect of drug, $F(1,78) = 2.24$, $p = .14$, or interaction of drug by dosage, $F(1,78) = 1.21$, $p = .28$. For the Symmetry span task, there was a significant impairing effect of the drug, $F(1,78) = 6.07$, $p = .02$, and no interaction with dosage, $F(1,78) = 0.21$, $p = .65$. [4]

These results were replicated when covarying for BDI depression, with the exception of the negative effect on symmetry span (see details in the Supplementary section). We also created a composite score for the four tests using factor analysis (see Turner and Engle 1989). Analysis of the composite score replicated the curvilinear drug by dosage interaction, $F(1, 78) = 8.12$, $p = .006$ (see Supplementary section).

Additional neuropsychological tests

Results for the remaining tests are presented in Table 2. For Go/No-Go omission and commission errors, there was no main effect of drug, $F(1,78) = 0.87$, $p = .35$; $F(1,78) =$

[4] In all of these analyses there was no significant main effect of dosage (p's > 0.30), confirming the absence of a difference between the two dosage groups independently of the administration of the drug.

1.44, $p = .23$. Also, for both omission and commission errors there was no drug by dosage interaction, $F(1,78) = 0.80$, $p = 0.37$; $F(1,78) = 0.11$, $p = .74$. Similar results emerged for the Groton Maze task: $F(1,78) = 1.06$, $p = .31$; $F(1,78) = 1.27$, $p = .26$; respectively. These findings were replicated when controlling for group differences in BDI depression (see Supplementary section).

We also examined participants' evaluation of their performance relative to their peers (See Table 2). The results indicated that although participants felt slightly more confident in the Remotiv 250 condition compared to the placebo condition, there was no significant difference between the placebo and drug conditions, $F(1,78) = 0.95$, $p = .33$, and no interaction with dosage, $F(1,78) = 0.77$, $p = .38$.

State anxiety and mood

Changes in state anxiety on the STAI are presented in Table 2 and Fig. 3. A statistical analysis indicated no main effect of drug, $F(1,78) = 0.58$, $p = .45$; and a significant drug by dosage interaction effect, $F(1,78) = 4.54$, $p = .04$. Nevertheless, the (alleviating) effect on state anxiety was not significant for Remotiv 500, $F(1,38) = 3.21$, $p = .08$, $d = 0.61$, as well as for Remotiv 250, $F(1,40) = 1.30$, $p = .26$. Similarly, on the DASS (see Table 2) there was no significant main effect of drug or a drug by dosage interaction: $F(1, 78) = 0.13$, $p =. 72$; $F(1, 78) = 1.44$, $p = 0.29$, respectively.

Changes in positive and negative feelings on the PANAS are presented in Table 2 and Fig. 3. This analysis showed a significant main effect of drug, $F(1,78) = 5.10$, $p = .03$, $d = 0.60$; and no drug by dosage interaction, $F(1,78) = 0.11$, $p =.74$. Thus, it appears that both dosages improved the participants' mood.

Moderation

We examined whether participants' self-reported trait anxiety and depression as well as changes in their state anxiety and mood, moderated the observed positive effect of Remotiv 250 and negative effect of Remotiv 500 on digit span and symmetry span. The results, presented in Table 3, indicated no moderator effects within the low or high dosage conditions. These null findings were replicated when conducting separate regressions for each predictor. We also examined whether depression (on the BDI) moderated the drug by dosage interaction. This analysis was carried out using Process Model 1 (Preacher and Hayes 2004), with 5,000 Bootstrap samples and bias correction. The results showed no significant moderating effect on drug minus placebo scores in digit span, $t(78) = 0.68$, $p = 0.50$, or symmetry span, $t(78) = 0.36$, $p = 0.71$. Thus, the difference between dosage conditions was not affected by individuals' self-reported depression.

Discussion

The current findings show for the first time a positive effect of a low dosage of H. perforatum (Remotiv 250) on short-term memory, particularly in the Digit span tests. By contrast, a larger dosage (Remotiv 500) had a negative effect on digit span as well as spatial working memory performance. Although the current findings should be interpreted with caution, as this is the first study that examined the effect of low doses of H. perforatum on human performance, they suggest that enhanced memory functions with H. perforatum, previously recorded with rodents (Klusa et al. 2001; Kumar et al. 2002; Widy-Tyszkiewicz et al. 2002; Hasanein and Shahidi 2011), emerges in humans

following acute administration of Remotiv. The negative effect recorded for the larger dose (Remotiv 500) is consistent with previous findings in tasks involving memory of digits and spatial patterns (e.g., Ellis et al. 2001). Therefore, the current findings suggest that previous studies of healthy adults using H. perforatum may have employed overly large doses which masked the substance's positive effects on memory performance.

Also, both Remotiv 250 and Remotiv 500 had a significant effect on participants' mood, leading to an increase in reported positive feelings and a decrease in negative feelings compared to placebo. These findings seem interesting because the effect of H. Perforatum on mood is often argued to take a few weeks to develop (Rodríguez-Landa and Contreras 2003). These positive effects on mood and anxiety did not, however, moderate the effects of the compound on performance.

Comparison to other drugs

In order to contextualize the current findings it is useful to consider the effect of other more conventional antidepressant drugs on short-term memory of healthy adults, especially tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). An early extensive review of the effect of acute and subacute administration of antidepressants on cognitive functions in healthy adults (Amado-Boccara et al. 1995) indicates that TCAs generally had a negative effect on sustained attention; with some (notably, amitriptyline) also having a negative effect on short-term memory. The same review also reported no effect of SSRIs (e.g., cericlamine, fluvoxamine) on sustained attention and short-term memory. Siepmann et al. (2002) examined the effect of sub-acute treatment with low doses of amitriptyline, and reported no positive or negative

effects on short-term memory. Similar null findings were reported for low doses of the SSRI escitalopram (Rose et al. 2005). Also, sub-acute treatment of Bupropion, an atypical antidepressant (which like H. Perforatum targets several different biological targets) was found to have no effect on short-term memory in healthy adults (Amado-Boccara et al. 1995; Carvalho et al. 2006; Chevassus et al. 2012), while acute treatment with hydrocortisol had a negative influence (Terfher et al. 2011).

Thus, it seems that the cognitive effect of H. perforatum is unique among other commonly prescribed antidepressant drugs, and more similar to the effect of stimulants (such as methylphenidate; cf., Agay et al. 2010). Nevertheless, some stimulant medications seem to exert a more robust effect on cognitive performance. For example, in a recent meta-analysis (Ilieva et al. 2015) methylphenidate was found to positively affect short-term memory of healthy adults as well as long-term episodic memory and sustained attention. Similar findings were observed for the atypical stimulant modafinil (Repantis et al. 2010b). The current study did not find any effect of H. perforatum on sustained attention (and inhibitory control) in the go/no-go task, and its effect on long-term memory was not examined.

The current findings thus raise interesting possibilities for application of H. perforatum for stimulating memory performance. One possible target population in this respect is elderly individuals. Interestingly, a recent review of the effect of common anti-dementia drugs (commonly used by elderly individuals) in healthy adults shows no evidence for increased memory performance, for either acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) or memantine (an NMDA receptor agonist)

(Repantis et al. 2010a). To date, however, no clinical study has investigated the effect of H. Perforatum on cognitive performance and dementia in the elderly.

Potential mechanisms driving the acute effect

What are the potential mechanisms that may lead to the observed improvement in short-term memory performance? Remotiv is relatively rich in hypericin and poor in hyperforin. Therefore, it may seem reasonable to assume that hypericin modulates its cognitive effect. It appears however, that hypericin mostly acutely affects the serotonergic system, and does not increase dopamine or noradrenalin neurotransmission (Franklin et al. 1999, 2000). While it is clear that the serotonergic system affects memory performance, most of the relevant human studies have shown that modulation of brain serotonin affects long-term memory and not short-term memory. For example, decreasing serotonergic neurotransmission using tryptophan depletion has been shown to impair long- term memory performance (Park et al. 1994; Riedel et al. 1999; Schmitt et al. 2000) but not short-term memory (Riedel et al. 1999). Similarly, acute administration of citalopram, a selective serotonergic re-uptake inhibitor, was found to enhance delayed but not immediate recall (Harmer et al. 2002), suggesting that it only affects the consolidation of long-term memories. Also, as noted above studies of SSRIs which similarly inhibit the re-uptake of serotonin obtained null findings for effects on short-term memory (e.g., Amado-Boccara et al. 1995; Rose et al. 2006). Thus, it seems unlikely that the effect of H. perforatum on short-term memory is solely modulated by the serotonergic system.

A second potential neurochemical leading to the acute effects is hyperforin.

Franklin et al. (2000) examined the acute effect of hyperforin and found that it affected dopamine mediated neuroendocrine responses and to a lesser extent also serotonin mediated responses in the rat brain (see also Rommelspacher et al. 2001). In primates dopamine enhances neuronal processes associated with short-term memory (Brozoski et al. 1979; Sawaguchi et al. 1988). However, in humans acute administration of the D_2 dopamine agonist bromocriptine was found to specifically improve performance in spatial but not in non-spatial short-term memory tasks (Luciana and Collins 1997; Mehta et al. 2001; Bartholomeusz et al. 2003), while D_2 dopamine antagonist sulpiride, as well as the mixed dopamine antagonist haloperidol, were found to have an opposite effect (Luciana and Collins 1997; Mehta et al. 2004). Nevertheless, most non-spatial tasks used in these studies involved visually presented objects with different patterns similar to the symmetry-span task in which we also have found no positive effect (e.g., Luciana and Collins 1997; Bartholomeusz et al. 2003; Mehta et al. 2001). Thus, it might be that mild dopaminergic neurostimulation improves short-term memory in verbal tasks as well.

Our finding of a dose-dependent effect is also consistent with the commonly assumed inverted U-shaped relation between dopaminergic neurotransmission and memory performance (Cools and D'Esposito 2011; see also Wood et al. 2013). Still, the inverted U-shape effect in the current study might also be driven by other unique factors. One possibility is that the single administration of Remotiv 500 has led to euphoria which distracted participants from the task, owing to its serotonin-mediated effects on mood (Siepmann et al. 2002). Alternatively, Remotiv 500 might require a longer neural adjustment process, and in this case its negative effect should tone down or even reverse with repeated administration. Additionally, we cannot rule out that the non-monotonic

effect might be driven by different permeability of the examined dosages. Although the penetrability of the blood-brain barrier itself is normally not dose dependent, dosage related effects could be indirectly induced through gut microbiota (Vissiennnon et al. 2012).

Conclusions

In summary, a low dosage of H. perforatum seems to have not only a positive effect on mood, but also a positive effect on short-term verbal memory. For the higher dosage we replicate the previously found null or negative effects on verbal and spatial short-term memory. Thus, somewhat surprisingly, our findings suggest that in terms of one's cognitive performance a healthy person could benefit from a mild dosage of H. perforatum. However, the dosage supplied by many of the over-the-counter compounds is often difficult to determine, being unstandardized for hypericin and hyperforin level, and might very well exceed the minimal dosage that was found to produce a positive cognitive effect.

Figure legends

Fig. 1 Flow chart of the participant selection process.

Fig. 2 Performance on the memory tests following acute administration of Remotiv 250, Remotiv 500, or placebo. The two simple span tests (Digit span forwards/backward) are presented in the top panels, and the two complex span tests (Operation and Symmetry span) are presented in the bottom panels. Error terms denote within-subject corrected standard errors (following Cousineau 2005).

Fig. 3 Changes in state anxiety and positive and negative feelings following administration of Remotiv 250, Remotiv 500, or placebo. Tests were completed upon arrival to the lab and following the experimental tasks (about 2.5 hours after drug consumption). Error terms denote within-subject corrected standard errors (following Cousineau 2005).

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Table 1: Demographics and mean baseline characteristics of participants in the two dosage conditions (Remotiv 250, Remotiv 500) and two order conditions. Standard errors appear in parentheses.

Dosage condition	Remotiv 250		Remotiv 500	
Order condition	Placebo first	Drug first	Placebo first	Drug first
Initial n size (randomized)	26	25	27	25
Final n size (analyzed)	23	19	21	19
Female (%)	39.1%	36.8%	42.9%	42.1%
Hebrew mother language (%)	78.3%	68.4%	85.7%	84.2%
Married or civil partnership (%)	13.0%	15.8%	23.8%	10.5%
Age	23.9 (0.76)	24.7 (0.76)	25.8 (0.55)	25.4 (0.81)
Depression (BDI) *	2.02 (0.44)	1.60 (0.45)	3.29 (0.74)	4.58 (0.90)
Trait anxiety (STAI)	30.44 (1.03)	31.87 (1.50)	33.88 (1.39)	35.34 (1.64)
State anxiety (STAI)+	28.61 (1.76)	26.63 (0.95)	28.26 (1.22)	30.55 (1.60)
Positive feelings (PANAS)+	12.65 (0.38)	12.32 (0.59)	12.88 (0.42)	12.97 (0.74)
Negative feelings (PANAS)+	6.41 (0.32)	5.63 (0.26)	6.52 (0.30)	6.71 (0.32)

BDI = Beck Depression Inventory, STAI = State-Trait Anxiety Inventory, PANAS = Positive and Negative Affect Schedule, * = Significant difference between dosage conditions ($p < .05$), + = Baseline measure in this test.

Table 2: Mean scores on the cognitive tests and self-report questionnaires in the two dosage conditions (Remotiv 250, Remotiv 500) and two order conditions. Standard errors appear in parentheses.

	Remotiv 250		Remotiv 500	
	Placebo	Drug	Placebo	Drug
Cognitive tests:				
Digit span forward	6.98 (0.23)	7.24 (0.19)	6.93 (0.21)	6.49 (0.21)
Digit span backward	5.98 (0.24)	6.45 (0.22)	6.24 (0.23)	6.02 (0.22)
Operation span	45.31 (2.39)	49.48 (2.50)	45.61 (2.19)	46.02 (2.37)
Symmetry span	26.0 (1.24)	24.71 (1.33)	25.80 (1.48)	23.66 (1.44)
Go/no-go omission (%)	3.92% (1.06)	2.19% (0.42)	1.69% (0.43)	1.78% (0.48)
Go/no-go commission (%)	25.99% (2.38)	27.79% (2.76)	28.01% (2.41)	26.64% (2.20)
Groton maze (% errors)	20.51% (4.97)	15.04% (2.09)	13.72% (1.61)	13.91% (2.19)
Questionnaires:				
State anxiety (STAI)$^{+}$	-1.50 (0.85)	-0.54 (0.52)	-0.09 (0.88)	-1.97 (0.71)
State anxiety (DASS)	0.76 (0.14)	0.88 (0.14)	0.93 (0.12)	0.65 (0.12)
Positive feelings (PANAS)$^{+}$	-0.31 (0.27)	0.00 (0.27)	-0.29 (0.28)	0.05 (0.28)
Negative feelings (PANAS)$^{+}$	-0.86 (0.13)	-0.56 (0.13)	-0.68 (017)	-0.63 (0.17)
Self-rated performance	69.93 (2.53)	72.74 (2.34)	72.07 (2.59)	72.59 (2.47)

STAI = State-Trait Anxiety Inventory, DASS = Depression Anxiety and Stress Scale, PANAS = Positive and Negative Affect Schedule, + = These tests were conducted prior to drug administration and at the end of the task battery. The scores denote the difference between these measures.

Table 3: Results of regression analyses examining potential moderators. The dependent variable was the effect of Remotiv on performance in tests where a significant main effect of drug or a drug by dosage effect was observed in each dosage condition (Remotiv 250 and Remtiv 500). For conciseness, scores in the forward and backward Digit span tests were averaged. Columns denote unstandardized coefficients and their standard errors (in parentheses). None of the predictors were significant (at $p < .05$). Variance inflation factors (VIF) ranged between 1.03 and 2.00, indicating acceptable multicollinearity.

Remotiv 250

Variables	Digit span
Trait anxiety (STAI)	-0.02 (0.03)
State anxiety (STAI)	0.02 (0.03)
Depression (BDI)	0.02 (0.08)
Mood (PANAS)	-0.01 (0.03)
Model r^2	0.03

Remotiv 500

Variables	Digit span	Symmetry span
Trait anxiety (STAI)	-0.004 (0.04)	0.26 (0.25)
State anxiety (STAI)	0.01 (0.03)	0.05 (0.20)
Depression (BDI)	0.06 (0.07)	-0.68 (0.46)
Mood (PANAS)	0.01 (0.05)	-0.09 (0.33)
Model r^2	0.03	0.06

STAI = State-Trait Anxiety Inventory, BDI = Beck Depression Inventory, PANAS = Positive and Negative Affect Schedule

Fig 1

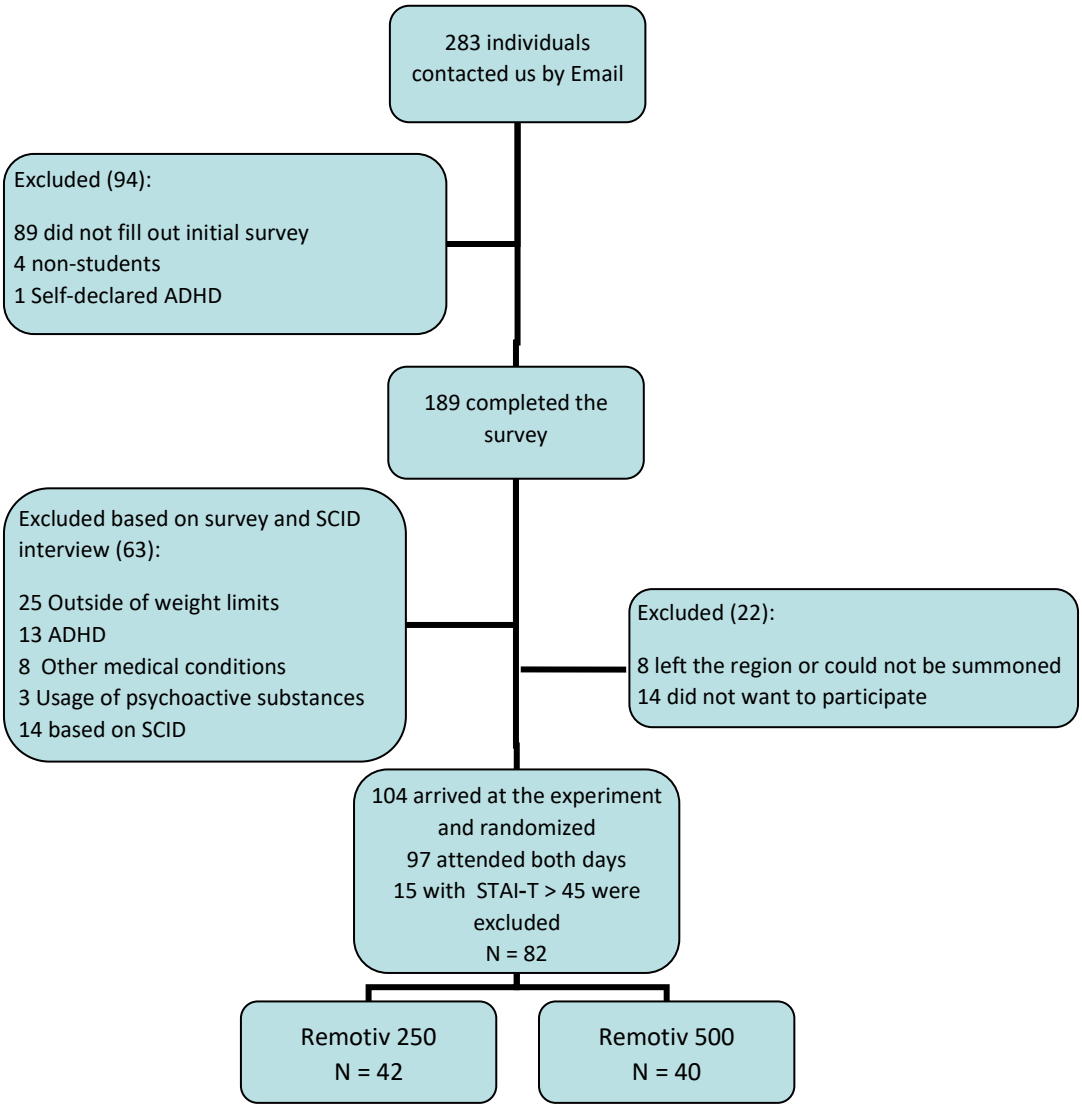

283 individuals contacted us by Email
Excluded (94):
89 did not fill out initial survey
4 non-students
1 Self-declared ADHD
189 completed the survey
Excluded based on survey and SCID interview (63):
25 Outside of weight limits
13 ADHD
8 Other medical conditions
3 Usage of psychoactive substances
14 based on SCID
Excluded (22):
8 left the region or could not be summoned
14 did not want to participate
104 arrived at the experiment and randomized
97 attended both days
15 with STAI-T > 45 were excluded
N = 82
Remotiv 250
N = 42
Remotiv 500
N = 40

Fig 2

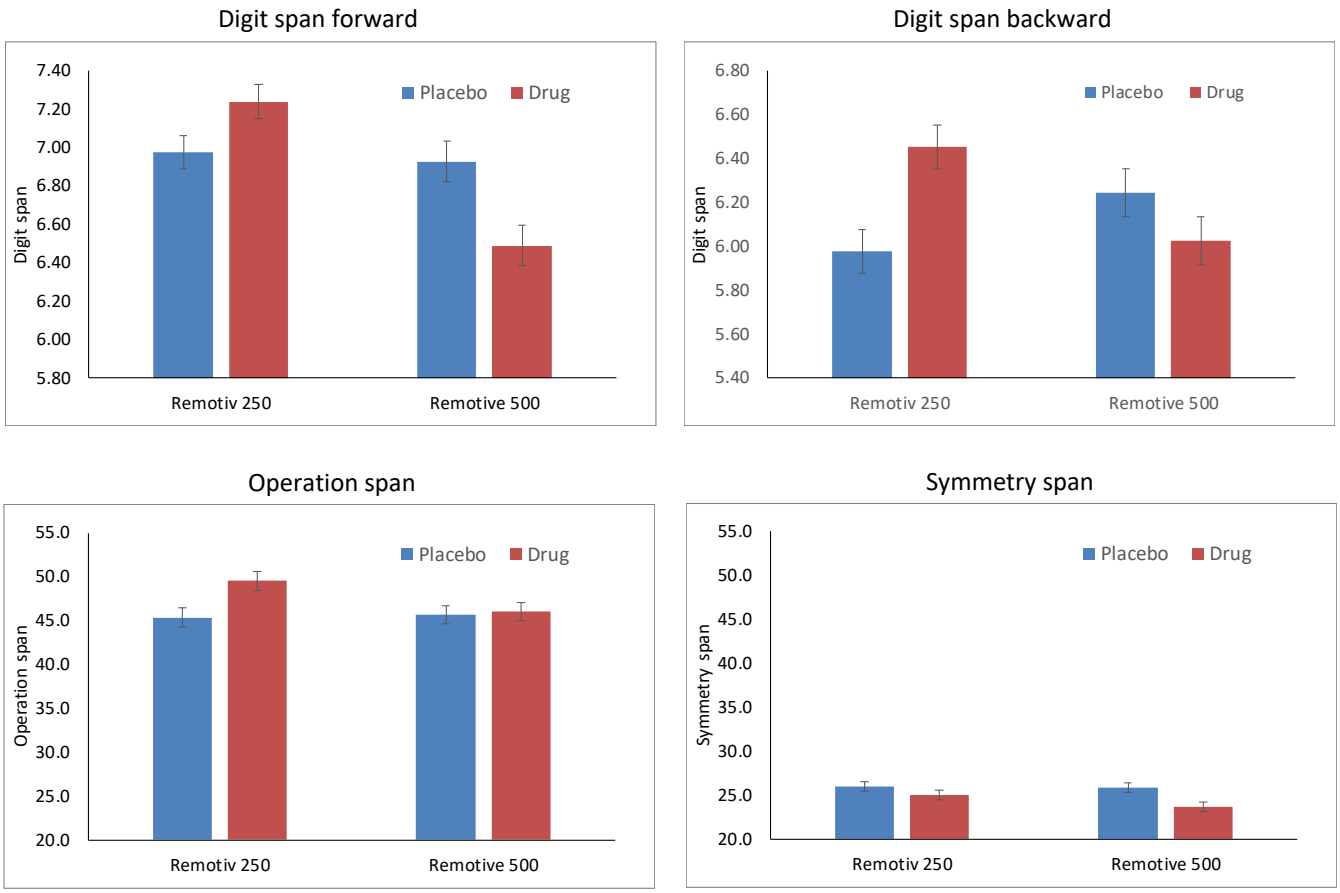
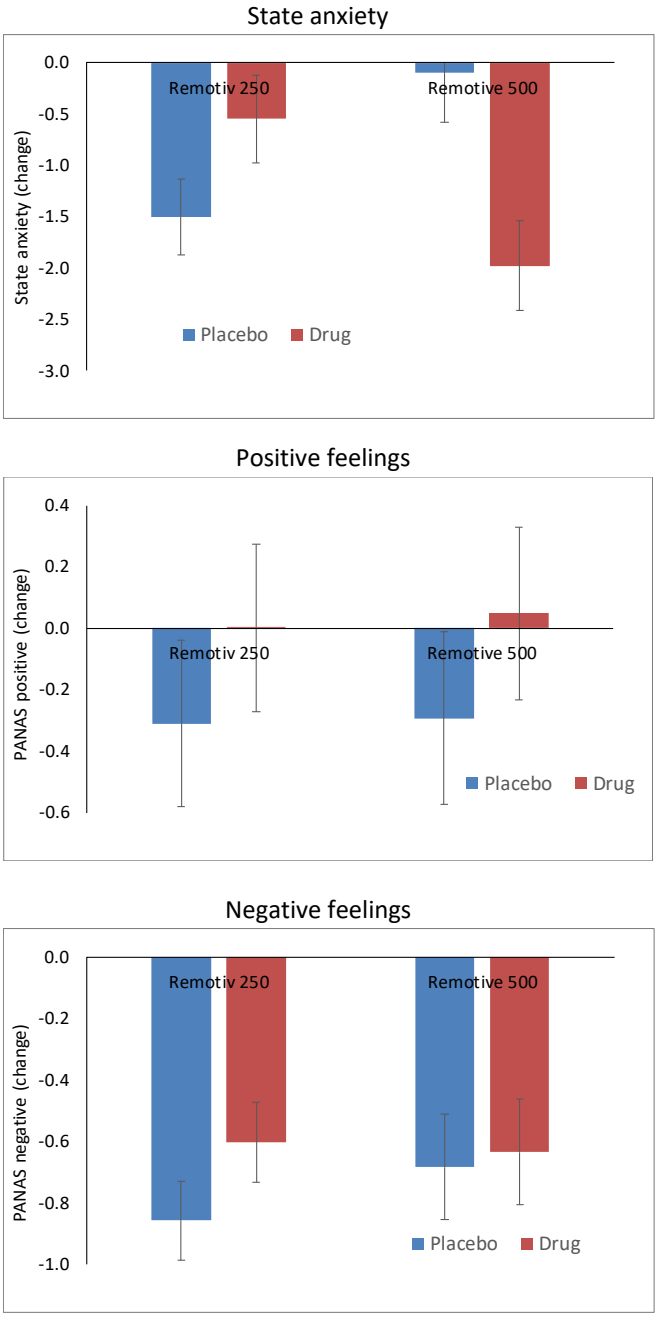

Digit span forward
Digit span
7.40
7.20
7.00
6.80
6.60
6.40
6.20
6.00
5.80
Placebo
Drug
Remotiv 250
Remotive 500
Digit span backward
Digit span
6.80
6.60
6.40
6.20
6.00
5.80
5.60
5.40
Placebo
Drug
Remotiv 250
Remotive 500
Operation span
Operation span
55.0
50.0
45.0
40.0
35.0
30.0
25.0
20.0
Placebo
Drug
Remotiv 250
Remotive 500
Symmetry span
Symmetry span
55.0
50.0
45.0
40.0
35.0
30.0
25.0
20.0
Placebo
Drug
Remotiv 250
Remotive 500

Fig 3


State anxiety
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
State anxiety (change)
Remotiv 250
Remotive 500
Placebo
Drug
Positive feelings
0.4
0.2
0.0
-0.2
-0.4
-0.6
PANAS positive (change)
Remotiv 250
Remotive 500
Placebo
Drug
Negative feelings
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
PANAS negative (change)
Remotiv 250
Remotive 500
Placebo
Drug