

Supplementation of gamma-aminobutyric acid (GABA) affects temporal, but not spatial visual attention



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ABSTRACT

In a randomized, double-blind, and placebo-controlled experiment, the acute effects of gamma-aminobutyric acid (GABA) supplementation on temporal and spatial attention in young healthy adults were investigated. A hybrid two-target rapid serial visual presentation task was used to measure temporal attention and integration. Additionally, a visual search task was used to measure the speed and accuracy of spatial attention. While temporal attention depends primarily on the distribution of limited attentional resources across time, spatial attention represents the engagement and disengagement by relevant and irrelevant stimuli across the visual field. Although spatial attention was unaffected by GABA supplementation altogether, we found evidence supporting improved performance in the temporal attention task. The attentional blink was numerically, albeit not significantly, attenuated at Lag 3, and significantly fewer order errors were committed at Lag 1, compared to the placebo condition. No effect was found on temporal integration rates. Although there is controversy about whether oral GABA can cross the blood-brain barrier, our results offer preliminary evidence that GABA intake might help to distribute limited attentional resources more efficiently, and can specifically improve the identification and ordering of visual events that occur in close temporal succession.

1. Introduction

One of the most prominent research questions in cognitive neuroscience today is how the human brain is able to process the fast flow of information from the quick, ever-changing visual environment around us. It must be able to select and extract meaningful information that is comparatively rare from oft-substantial levels of irrelevant background noise. The success of this filtering mechanism depends on complex perceptual and attentional operations, which collectively guide the efficient processing of objects and events. Indeed, any shortcomings or lapses can cost us dearly, as can be witnessed in traffic incidents. Optimizing perception and attention could therefore bring tangible benefits. One way of doing so is by altering the balance of neurotransmitters in the brain. A prime candidate is the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), which is one of the most extensively studied brain chemicals.

Empirical evidence from a large variety of research fields points towards a link between GABA levels in the brain and visual attention (e.g., Petersen, Robinson, & Morris, 1987). For example, animal studies have shown that GABA producing neurons play a key role in the regulation of attentional resources (McGarrity, Mason, Fone, Pezze, & Bast,

2017; Paine, Slipp, & Carlezon, 2011). In line with this, blockade of cortical GABA receptors by antagonists is associated with impaired visuospatial attention as measured by a 5-choice serial reaction time task, which is analogous to tasks that assess sustained attention in humans (Paine et al., 2011). At the same time, if supra-normal GABA levels in the brain increase functional inhibition beyond an optimal level, impaired attentional processing has also been observed (Pezze, McGarrity, Mason, Fone, & Bast, 2014). Further evidence from animal studies suggests that the inhibitory neurotransmitter is directly involved in visual attention by mediating stimulus selectivity in the primary visual cortex of the cat brain (Katzner, Busse, & Carandini, 2011).

In humans, Sandberg et al. (2014) found a negative correlation between GABA levels in the occipital cortex and self-reported cognitive failures – the deficiency to attend to relevant stimuli and to suppress irrelevant information – in daily life. Possibly, GABA strengthens inhibitory processes in the visual cortex improving the ability to disengage from irrelevant stimuli and suppress elaborate object processing, thereby promoting a more balanced distribution of attentional resources (Sandberg et al., 2014).

Furthermore, GABAergic system alterations have been found to affect visual integration processes through lorazepam administration,

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which is a benzodiazepine that enhances the neurotransmitter's effects (Giersch, 2001). Experiments have also shown that identifying gaps between line segments is easier after lorazepam intake compared to a placebo intake, indicating that GABA modulates and improves the processing of discontinuities in line segments (Giersch, 2001; Giersch, Boucart, Danion, Vidailhet, & Legrand, 1995).

Finally, there is also indirect evidence from transcutaneous vagus nerve stimulation that GABA levels modulate the efficiency of response selection (Steenbergen et al., 2015a). Transcutaneous vagus nerve stimulation is a non-invasive experimental technique that triggers the release of the neurotransmitter in the brain (Van Leusden, Sellaro, & Colzato, 2015), and which has been mainly used to treat patients with epilepsy, who suffer from an abnormal reduction in GABA-ergic function (Treiman, 2001). Transcutaneous vagus nerve stimulation has been linked with increased GABA-ergic cortical activity (Capone et al., 2015), and increased free GABA levels in the cerebrospinal fluid (Ben-Menachem et al., 1995). Increased GABA-A receptor density has also been observed after long-term exposure (Marrosu et al., 2003). However, it is also known to affect a wide range of other physiological mechanisms. Steenbergen et al. (2015a) had their participants perform a stop-change action cascading task, in which the speed of changed responses was measured. Stimulation resulted in faster responses than a sham condition, suggesting that response selection was facilitated by increased GABA levels, although it must be noted these were not measured in the study so that the link between performance and GABA levels remains only circumstantially supported.

In view of these various effects of GABA, it would be desirable to be able to modulate GABA levels in the brain more easily, for instance to attain cognitively beneficial levels. As it happens, in the past few years, GABA has become more widely available as a food supplement to the general population (Boonstra et al., 2015), holding the promise that simply ingesting GABA could result in attaining cognitive benefits. However, the evidence to date for cognitive effects of GABA ingestion are limited. Indeed, it has long been thought that the blood-brain barrier would prevent the uptake of GABA, rendering its consumption ineffective (Van Gelder & Elliott, 1958). Nevertheless, Steenbergen, Sellaro, Stock, Beste, and Colzato (2015b) administered an oral dose of 800 mg GABA to participants, who performed a stop-change paradigm, as in the previously cited study by Steenbergen et al. (2015a), and observed enhanced action selection, replicating and extending their previous study.

In view of these results, it is conceivable that oral ingestion of a comparable dose of GABA could also enhance attentional processing, but there is no evidence for that to date. Therefore, the specific effect of GABA supplementation on attentional deployment was investigated in the present study. To measure both temporal and spatial aspects of attention, two different tasks were implemented: A rapid serial visual presentation (RSVP) task, and a visual search (VS) task. The overarching hypothesis was that GABA consumption should help to select relevant information and thus improve performance in both tasks. The RSVP and VS task have diverse backgrounds, which are briefly summarized below.

1.1. Rapid serial visual presentation

By means of RSVP, one of the most widely studied aspects of temporal attention is the attentional blink (AB), a phenomenon in which the second of two visual targets is often missed by observers when both targets occur at a stimulus onset asynchrony (SOA) between 150 and 500 ms (Broadbent & Broadbent, 1987; Raymond, Shapiro, & Arnell, 1992). The challenge of the RSVP task lies in the identification and segregation of relevant targets that are close in temporal succession within a fast stream of consecutive distractors. The failure to process two target stimuli that are close in temporal succession is hypothesized to arise from a limited amount of attentional resources (e.g., Chun & Potter, 1995). In general, processing the first target (T1) is thought to

undermine the proper processing of the second target (T2). The idea of limited cognitive resources has been supported by many previous studies (for a review, see Martens & Wylie, 2010).

Taking this idea one step further, it has been proposed that the blink arises due to an overinvestment in T1 identification, which leaves insufficient attentional resources for the processing of T2 (Olivers & Nieuwenhuis, 2006; Shapiro, Schmitz, Martens, Hommel, & Schnitzler, 2006). Studies show that the AB effect is attenuated when this overinvestment is prevented. For example, extraneous cognitive load during an RSVP task leads to distracting mental activity thereby preventing elaborate processing of T1 and leaving more resources for the identification of the second target (Nieuwenstein, Chun, van der Lubbe, & Hooge, 2015; Zhang, Shao, Zhou, & Martens, 2010). The additional cognitive load presumably leads to a more balanced distribution of attentional resources, thereby preventing the allocation of too many resources towards T1 processing. Further support was obtained by Slagter et al. (2007), who found a positive correlation between P3 size – an event-related potential (ERP) component that is sensitive to (prior) attentional resource allocation – and AB magnitude, providing further support for the hypothesis that T2 identification success is dependent on attentional deployment during T1 processing.

A secondary aspect that has been studied with RSVP is temporal integration, which can be observed when targets succeed each other directly, without intervening distractors, at Lag 1 (Akyürek et al., 2012). Lag 1 is a special case in RSVP, because many studies report Lag 1 “sparing”, a paradoxical improvement of target identification in the shortest Lag condition, where processing time is most limited (Visser, Bischof, & Di Lollo, 1999). This phenomenon may in turn be related to a loss of order information that is most prevalent in the Lag 1 condition, suggesting that the typical increase in identification performance may come at a cost (Hommel & Akyürek, 2005). Akyürek et al. (2012) provided proof that these performance characteristics at Lag 1 are related to the occurrence of temporal integration, a perceptual process by which the successive targets are combined into a single, integrated percept. Thus, next to providing an index of temporal attention and the AB, the RSVP task can also be used to assess temporal integration.

1.2. Visual search

Selection of task-relevant targets within an array of distractors is mediated by spatial attention – the allocation of attentional resources across a visual scene. Particularly in feature-based search tasks, in which the observer is asked to find the targets by virtue of a specific feature (e.g., a diamond shape), or feature combination (e.g., a red diamond), search depends on the similarity of targets and other elements in the display, typically referred to as distractors (Treisman & Gelade, 1980; Wolfe, 1994). When targets are more similar to distractors, they are harder to find. Similarity is defined on the feature level, but also by whether they are defined in the same feature dimension (e.g., color or shape) or not. If the search cannot be resolved simply by looking for anything deviant within a search array (i.e., by singleton search; Bacon & Egeth, 1994), dimensionality strongly determines search efficiency, such that search for targets that are defined by features that belong to the same dimension as those of the distractors is difficult (Müller, Heller, & Ziegler, 1995).

An exemplary task in which such effects have been observed is the dual-singleton task, in which a target is not the only deviant item in a search array of otherwise uniform distractors, but is always presented with another salient item; a “nontarget” (e.g., Akyürek & Schubö, 2011). Here search is defined by a specific feature, such as the color blue, and the nontargets then either share this feature dimension by also having a color, but not the target color (e.g., red), or another salient feature, such as having a different line orientation. Although the different-dimensional feature of line orientation also makes the nontarget salient within the array, target search is much easier than for the same-dimensional trials, leading to shorter reaction times. ERP

components that track the distribution of attention across the visual field, such as the N2pc, also reflect that attention is drawn heavily towards same-dimension nontargets, but not at all to different-dimension ones (Akyürek & Schubö, 2011). Thus, the dual singleton VS task includes dimension-based conditions in which attention is particularly taxed, and ones in which it is not—similar to the lag-based conditions of the RSVP task.

1.3. The present study

Although spatial attention and temporal attention are dissociable in some cases (Coull & Nobre, 1998; Rolke, Festl, & Seibold, 2016), in the current study the predictions with regard to the effects of GABA intake were similar. In general, ingestion of 800 mg of GABA (cf. Steenbergen et al., 2015b) was expected to increase performance in both RSVP and VS tasks by promoting a more balanced distribution of attentional resources and/or by facilitating the filtering of irrelevant information. If GABA is targeting temporal attention, this would be expected to improve (a) target identification and/or (b) target sequencing in the RSVP task, which would be indicated by a reduced AB and fewer order errors at short lags, respectively. If GABA is targeting spatial attention, this would be expected to improve speed and accuracy in the more challenging shared feature dimension condition of the VS task, which could be taken to indicate improved attentional filtering.

2. Method

2.1. Participants

Twenty-four undergraduate psychology students (4 males, mean age = 20.2 years, range 18–24 years) at the University of Groningen participated in the experiment for course credit. This sample size was chosen to match those of previous studies that were conducted with the same tasks (Akyürek & Schubö, 2011; Akyürek et al., 2012). The study was conducted in accordance with the Declaration of Helsinki (2008), and approved by the departmental ethical committee prior to its execution (15078-NE). All participants gave written informed consent. In order to determine eligibility for participation in the study subjects were interviewed via phone with the Mini International Neuropsychiatric Interview (MINI); a short, structured interview screening for various mental and neurological disorders. The MINI interview is often used in clinical and pharmacological research (Sheehan et al., 1998). Subjects could not take part in the study in case of any cardiac, hepatic or renal disorders, any mental disorder, regular use of medication or any kind of drug use three months prior to the study. Hormonal contraception was a requirement for female participants. All participants had a weight between 55 and 70 kg and did not take any kind of food supplements related to the present study. Subjects had normal or corrected-to-normal vision and were asked to come to the lab for two sessions with one week between both sessions. They were reminded multiple times to abstain from smoking, coffee, and food 12 h prior to their visit to the lab. Also, they were asked to abstain from alcohol 24 h before coming to the lab. Sessions were always scheduled early in the morning to counter circadian effects.

2.2. General apparatus

Participants were individually seated in a dimly lit room at a distance of about 60 cm from a 22-in. CRT screen. The screen was driven by a standard personal computer running the Microsoft Windows XP operating system with a refresh rate of 100 Hz in 16-bit color. The experimental tasks were programmed in E-Prime Professional, Version 2.0 (Psychology Software Tools) and responses were logged on a USB keyboard.

2.3. General procedure

As indicated, participants took part in two sessions. Each of the these comprised both the RSVP and VS tasks. Task order was randomized and equally distributed across participants. Before the start of each task, participants had some time to read the instructions and ask questions. At the start of each session, participants were administered an oral dose of either 800 mg of synthetic GABA or 800 mg of microcrystalline cellulose, the latter fulfilling the role of a placebo. Both doses consisted of inconspicuous white powders that were dissolved in 200 ml of orange juice. An independent person not otherwise involved in the study prepared a randomized list that coded for participants to receive either placebo or GABA, and the matching treatment doses. Thus, the administration was carried out in a double-blind fashion.

Studies involving GABA suggest that higher GABA levels are associated with improvements in mood (Brambilla, Perez, Barale, Schettini, & Soares, 2003). To rule out an account of our results in terms of change in affective states participants were asked to rate their mood and arousal on a 9×9 Pleasure \times Arousal grid (Russell, Weis, & Mendelsohn, 1989) with values ranging from -4 to 4 . Furthermore, given that altered GABA levels were found to have an influence on animals' cardiovascular system (Zhang & Mifflin, 2010), the heart rate (HR) of the participants was measured using an electrocardiogram (ECG) device. Measurements took place before the treatment, and 30 min after the GABA or placebo intake. 15 min after the second HR measurement participants started with the RSVP task or the VS task, depending on the order. Upon completion of the session, participants again rated their mood before having their HR measured for the third time.

2.4. RSVP task: Apparatus and stimuli

Fig. 1 illustrates a typical trial example of the RSVP task. The RSVP task was run at a resolution of 1024 by 768 pixels. A light gray (RGB 192, 192, 192) background was maintained throughout the experiment. Stimuli were adopted from Akyürek et al. (2012). Before the start of each trial a fixation cross (“+”), drawn in 18-point, boldface Courier New font appeared at the center of the screen. The ensuing RSVP consisted of black distractor and target stimuli, drawn in the same 52-point font. Distractor stimuli were upper-case letters randomly drawn from the alphabet without replacement. Target stimuli consisted of one or more corners of a square of which each horizontal and vertical sides were 23 pixels long and 7 pixels wide. The entire square was 54×54 pixels in size, which left a gap of 8 pixels between the corners. The area within which the targets were presented was similar in size to the distractors. Possible combinations of T1 and T2 appeared randomly and equally often across trials, but it was ensured that features of T1 did not overlap with the features of T2 within one trial. Eliminating such overlap is essential to be able to measure integration responses, in which the features of both targets are combined into a single reported percept.

2.5. RSVP task: Procedure

The task in each of the two experimental sessions consisted of 320 experimental trials, divided into two blocks, and 20 practice trials that were discarded from further analyses. Participants were offered to take a break between blocks. 100 ms after the start of each self-paced trial, a fixation cross appeared for 200 ms at the center of the screen. The RSVP sequence then commenced, containing 18 stimuli, each with a duration of 70 ms, with a 10 ms blank interval between each stimulus. The stream was followed by another 100 ms delay, before the response screens were presented.

The three experimental conditions that were analyzed differed in the number of distractors between T1 and T2. T1 appeared either on the fifth or the seventh position of the RSVP stream. T2 succeeded T1 after

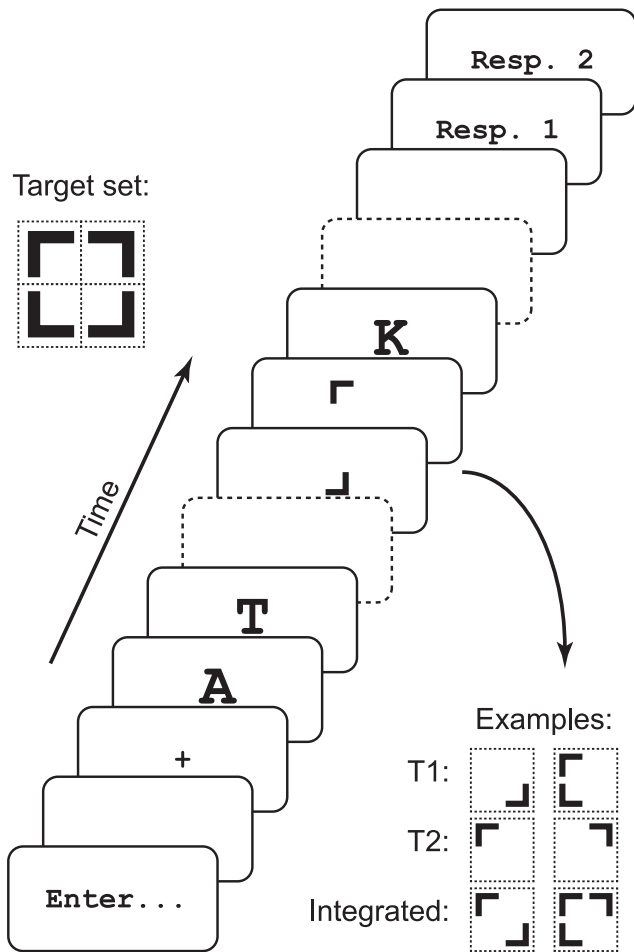


Fig. 1. The rapid serial visual presentation task. Lag is defined by the temporal position of the second target with regard to the first, and the resultant number of distractors in-between. Frames with dashed outlines represent a variable number of letter distractors. Trial-wise examples of first and second target stimuli and their associated integration responses are shown on the bottom right. Dotted outlines were not presented to the participants and are shown for illustration only. Resp. = response; T1 = first target; T2 = second target.

either 0, 2, or 7 distractors, referred to as Lag 1, 3, or 8 respectively. Each of these conditions occurred 100 times. There were also 20 trials in which there was no T2. Participants were nonetheless always asked to first identify T1 and then T2. Each target figure was identified by pressing the specified keys in a previously instructed order on the numeric keypad. The upper left corner corresponded to the 4 key, the upper right corner to the 5 key, the lower left corner to the 1 key, and the lower right corner to the 2 key. Thus, participants reconstructed the first and second target figure they perceived by pressing the corresponding keys. By pressing Enter, they finished their response. In case they had not seen a target, they were informed they could simply press Enter immediately, leaving the relevant prompt empty.

2.6. RSVP task: Design

Statistical analyses were performed in SPSS using a 2 × 3 repeated measures analysis of variance (ANOVA) with GABA consumption (placebo or GABA) and T1-T2 lag (1, 3, or 8) as within-subjects variables. If the assumption of sphericity was violated Greenhouse-Geisser epsilon correction was applied. For the analysis of T1 and conditional T2 accuracy (i.e., T2|T1), correct report order was required for the target(s) to be considered fully correct. Order errors and integrations were analyzed separately. Order errors constituted cases in which T2 was reported as T1 and vice versa, with the target identities as such

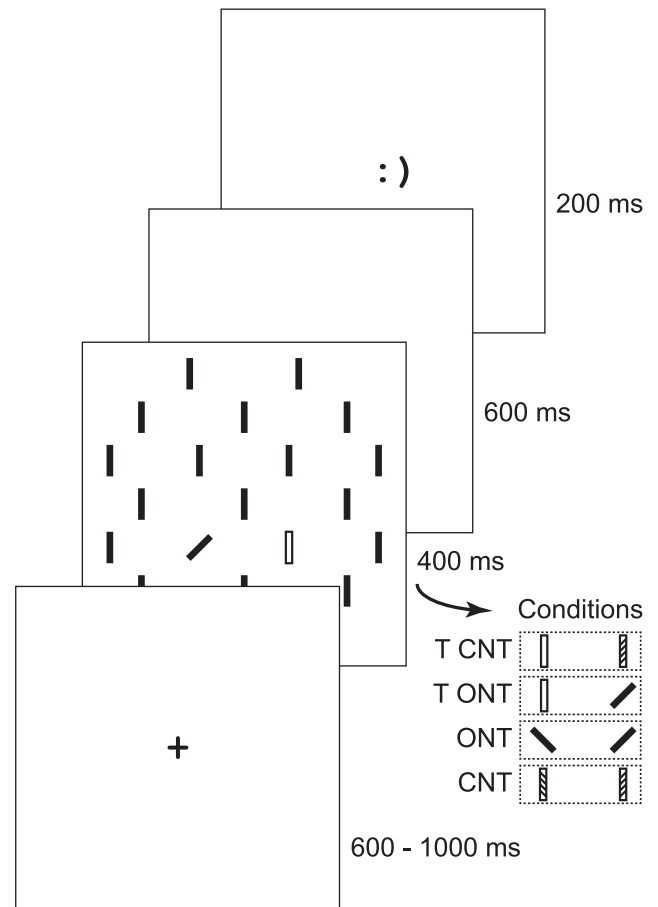


Fig. 2. The visual search task. Target presence and nontarget feature dimension conditions are depicted on the bottom right. Target and nontarget pairs always appeared on different sides of the search array. Targets were defined by color, while nontargets either had another color, or a different orientation (non-vertical). T CNT = target and color nontarget; T ONT = target and orientation nontarget; CNT = two color nontargets; ONT = two orientation nontargets.

being correct. An integration response was only counted if it matched exactly the features of both targets combined, and if it was entered in a single response prompt, while leaving the other prompt empty.

2.7. VS task: Apparatus and stimuli

Fig. 2 illustrates the visual search task. The VS task was presented at a resolution of 800 by 600 pixels. A white background was maintained throughout the experiment. Each trial started with the presentation of a fixation cross (“+”), drawn in 18-point, boldface Courier New font. Stimuli consisted of 21 vertical line segments that were 30 pixels long and were presented at the center of the screen in a circular array with 50 pixels between each stimulus. For each line segment a random displacement jitter of 0–5 pixels in both horizontal and vertical directions was used. Each trial consisted of black vertical line segments and either one target line (vertical line in the target color) and one nontarget line (either a black tilted line or a vertical line in a nontarget color), or two nontargets (two lines of different orientations or two vertical lines in different nontarget colors). Possible colors were red, green, and blue (pure single channel RGB values). Possible orientations (other than vertical) were implemented by a 10-pixel displacement of the line endpoints (~48° tilt), either to the left or right.

2.8. VS task: Procedure

Each of the two experimental sessions consisted of one practice

block of 32 trials that were excluded from further analyses and 2 sets of 3 experimental blocks of 96 trials, for a total of 576 experimental trials. Before the start of a new block, participants were told which color they should attend to in the following trials, which was different between blocks and counterbalanced. Between the two sets of blocks, there was another explicit opportunity to pause. Trials were evenly distributed over four experimental conditions, crossing target presence with feature dimension; comprising a color target with a color non-target (T CNT), a color target with an orientation non-target (T ONT), two color non-targets (CNT) and two orientation non-targets (ONT). Because color was the task-relevant dimension, the T CNT and CNT trials made up the shared feature dimension condition, and the T ONT and ONT trials made up the different dimension condition. Targets appeared randomly but equally often on the left and right side of the visual field. Nontargets appeared on the other side, and this visual hemi-field balancing was maintained when two nontargets appeared.

At the start of each trial a fixation cross appeared for 600–1000 ms at the center of the screen. Immediately after, the search array was shown for 400 ms and followed by a blank screen for 600 ms. In response to the array, and within the total interval of the search array and the blank (i.e., 1000 ms), participants had to indicate whether the target was present or absent by pressing the '1' key on the numeric keypad if the target was present among the line segments and '2' when it was not. Depending on the accuracy of the response, positive or negative feedback, “:)” or “:(”, was provided for 200 ms, and the next trial commenced.

2.9. VS task: Design

The analysis approach was identical to the RSVP task, except that the design was now a $2 \times 2 \times 2$ repeated measures ANOVA, with GABA consumption (placebo or GABA), target presence (present or absent) and nontarget feature dimension (same or different) as within-subjects variables. Both response accuracy and reaction time were analyzed. Trials with missing responses or reaction times lower than 100 ms were discarded from all analyses, and reaction times were analyzed for correct trials only.

2.10. Data availability

The behavioral data, as well as the analysis scripts used, are publicly available from the Open Science Framework repository with the identifier s2w97 (<https://osf.io/s2w97>; doi: 10.17605/OSF.IO/S2W97).

3. Results

3.1. RSVP task

As can be seen in the top left panel of Fig. 3, simple target detection was not affected by GABA intake, as the analysis of T1 identification accuracy revealed. There was no main effect of GABA, and no interaction with lag (F 's < 1). Lag by itself had a pronounced effect, as is commonly observed in this version of the task (e.g., Akyürek et al., 2012), $F(1.1, 26) = 217.08$, $MSE = 0.03$, $p < .001$, $\eta_p^2 = 0.9$: At Lag 1, accuracy was much lower (30.5%) than at Lag 3 (74.3%) and Lag 8 (81.4%).

Conditional T2 accuracy (T2|T1) is shown in the top right panel of Fig. 3. It was also affected by Lag, $F(1.4, 32.1) = 67.31$, $MSE = 0.029$, $p < .001$, $\eta_p^2 = 0.75$, showing a steady increase in accuracy for longer lags, averaging 52.6% at Lag 1, 72.4% at Lag 3, and 86.3% at Lag 8—evidence of the AB. There was no main effect of GABA ($F < 1$), but the interaction term was significant, $F(2, 46) = 6.21$, $MSE = 0.005$, $p < .005$, $\eta_p^2 = 0.21$. Accuracy at Lag 3 was 5.7% higher after GABA consumption than after the placebo, while at both Lag 1 and 8, performance was not improved, but slightly lower (−4.2% and −1.2%,

respectively). Two-sided permutation tests (50,000 repetitions) on the differences at the blink-sensitive lags did not reveal significant differences ($p < .28$ at Lag 1 and $p < .13$ at Lag 3), but the GABA effect at Lag 3 was significantly different from both Lag 1, $p < .02$, and Lag 8, $p < .05$, Bonferroni-corrected.

Integration frequency is shown in the bottom left panel of Fig. 3. Integrations were affected by Lag, $F(1, 23.2) = 40.59$, $MSE = 0.041$, $p < .001$, $\eta_p^2 = 0.64$. As expected, integrations were frequent at Lag 1 (24.5%), but not at Lag 3 (2.3%) and Lag 8 (0.9%). GABA did not have a main effect ($F < 1$), and did not interact with Lag either ($F < 1.3$).

Order reversal frequency is shown in the bottom right panel of Fig. 3. Order reversals, like integrations, were affected by Lag, $F(1.2, 27.5) = 25.74$, $MSE = 0.001$, $p < .001$, $\eta_p^2 = 0.53$. Reversals were more frequent at Lag 1 (5%) than at Lag 3 (2.3%) and Lag 8 (0.8%). Although GABA did not have a main effect ($F < 1.6$), it did interact with Lag, $F(2, 46) = 5.7$, $MSE = 0.001$, $p < .006$, $\eta_p^2 = 0.2$. At Lag 1, GABA consumption reduced reversal frequency by 2%, compared to a slight increase of 0.6% at Lag 3, and a negligible difference at Lag 8 of 0.1%. Permutation tests of the means showed that the difference between GABA and placebo at Lag 1 was significant, $p < .03$. The GABA effect at Lag 1 also differed significantly from that at Lag 3, $p < .02$, but did not survive Bonferroni correction at Lag 8, $p < .12$.

3.2. VS task

Accuracy in the visual search task is shown in the top panel of Fig. 4. Accuracy was affected both by target presence, $F(1, 23) = 9.93$, $MSE = 0.002$, $p < .004$, $\eta_p^2 = 0.3$, and feature dimension, $F(1, 23) = 60.55$, $MSE = 0.001$, $p < .001$, $\eta_p^2 = 0.73$. Accuracy was lower when a target was present (93.8%) than when it was not (96%), and lower when feature dimension was shared with the nontarget (94%), than when it was not (95.8%). Target presence and feature dimension showed a marginal interaction, $F(1, 23) = 2.95$, $MSE = 0.001$, $p < .1$, $\eta_p^2 = 0.11$, suggesting that the dimension effect might have been slightly more pronounced when a target was absent (2.4%) than when it was present (1.1%). GABA did not have a main effect ($F < 1$) and was not involved in any interaction (F 's < 1.1).

Reaction times in the visual search task are shown in the bottom panel of Fig. 4. Once again, effects of target presence, $F(1, 23) = 15.01$, $MSE = 1178.686$, $p < .001$, $\eta_p^2 = 0.4$, and feature dimension, $F(1, 23) = 79.24$, $MSE = 121.502$, $p < .001$, $\eta_p^2 = 0.78$, were obtained. Participants responded faster to target-present trials (348 ms) than to target-absent ones (367 ms). Different feature dimension trials also resulted in faster responses (351 ms) than shared dimension ones (365 ms), as expected. The two stimulus variables also interacted, $F(1, 23) = 9.79$, $MSE = 144.379$, $p < .005$, $\eta_p^2 = 0.3$: The dimensional effect was larger when the target was absent (20 ms) than when it was present (9 ms). Neither the main effect ($F < 1$) nor any interaction involving GABA was significant (F 's < 1.8).

3.3. Mood, arousal, and heart rate

Mood, arousal and heart rate were significantly affected by time $F(2, 92) = 9.1$, $MSE = 1.03$, $p < .001$, $F(1.73, 79.6) = 8.84$, $MSE = 1.65$, $p < .001$, and $F(1.7, 78.16) = 42.59$, $MSE = 51.82$, $p < .001$, respectively. Importantly, there was no significant interaction effect between time and treatment for all three measures (F 's < 1.1). Table 1 provides an overview of all measurements across all time points.

4. Discussion

The present study provides evidence that oral ingestion of 800 mg of GABA can improve attentional performance, compared to a placebo condition, in the absence of arousal- and/or mood-related effects. Through an interaction between Lag and GABA condition, an

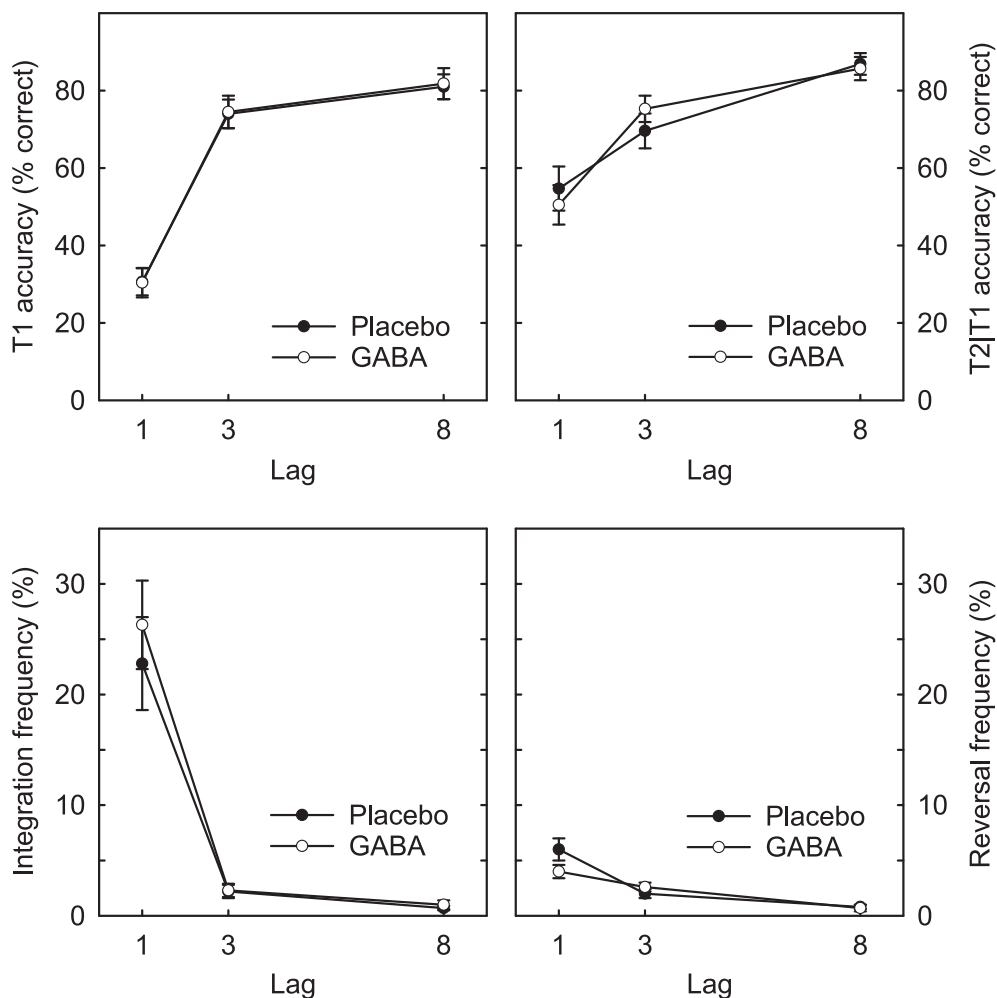


Fig. 3. Performance in the rapid serial visual presentation task as a function of the lag between targets. The top left panel shows the identification accuracy of T1 (% correct). The top right panel shows the identification accuracy of T2 (% correct), given that T1 was identified correctly. The bottom left panel shows the frequency (%) of trials in which the integration of both targets was reported. The bottom right panel shows the frequency (%) at which the two targets were reported correctly, but in reversed order. Black symbols represent the placebo condition and white symbols the GABA condition. Error bars represent ± 1 standard error of the mean.

attenuation of the AB deficit at Lag 3 was apparent, although a direct comparison of the means was unreliable. There was furthermore a significant decrease in order errors at Lag 1. Notably, temporal integration rates at Lag 1 were unaffected. Spatial attention, as measured in the visual search task, also appeared insensitive to GABA, both in terms of reaction time and response accuracy. The effects of GABA thus seemed limited to temporal attention only.

In line with previous research, our findings thus support the notion that the inhibitory neurotransmitter GABA plays an important role in the regulation of attention (Paine et al., 2011). The currently observed role of GABA in temporal attention fits with the recent observation of a negative relationship between GABA levels in the right prefrontal cortex and the size of the AB (Kihara, Kondo, & Kawahara, 2016). It also fits with the hypothesis that excessive attention directed to T1 identification, possibly due to lower levels of inhibition, leads to a larger AB (Martens & Wyble, 2010). When this overinvestment in target identification is diminished by increased inhibition due to higher GABA levels, attentional performance might improve, and this prediction is supported by our data. Thus, when targets succeed in close temporal proximity, as in the Lag 3 condition, GABA may act to suppress the excessive deployment of attention towards the identification of the first target and may thereby promote the redistribution of attentional resources to the identification of the second.

It is interesting to note that we found evidence for a role of GABA in the identification and the sequencing of targets but not in target integration. The integration of target-related information across time (i.e., temporal integration) is one form of sensory integration, which also includes the matching of input from different modalities, and at a

different level, also the combination of different features within-modality (e.g., shape and color). Past studies have shown that a deficit in GABA can cause disruptions in both attentional and sensory integration processes, which have also been observed in psychiatric disorders (Paine, Cooke, & Lowes, 2015). For example, schizophrenia is associated with GABAergic abnormalities (Lewis, Hashimoto, & Volk, 2005), and a key symptom of schizophrenia is the experience of hallucinations, which has been attributed to a pathological over-integration of sensory stimuli (Talpos, Riordan, Olley, Waddell, & Steckler, 2015). More specifically, diminished GABA levels are thought to reduce evoked gamma oscillations and in turn, to minimize neural synchrony, resulting in abnormally frequent integration of sensory input (Paine, Slipp & Carlezon Jr, 2011). Coincidentally, schizophrenia patients also tend to have increased AB magnitude (Li et al., 2002). Although only correlational in nature, these studies underline the possible impact of GABA concentrations on (visual) integration processes. In the present study, however, integration was unaffected (perhaps because the current dosage was too small), precluding an interpretation in terms of integration-related processes.

The decrease in order errors at Lag 1 may therefore rather originate from altered attentional dynamics. One mechanism that has been proposed to cause order errors at Lag 1 is precedence or prior entry (Olivers, Hilkenmeier, & Scharlau, 2011; Reeves & Sperling, 1986; see also Shore, Spence, & Klein, 2001; Titchener, 1908; Vibell, Klinge, Zampini, Spence, & Nobre, 2007), by which a stimulus that is more strongly attended to also appears to have occurred earlier in time. According to at least one theory (Olivers & Meeter, 2008), the onset of T1 might trigger an attentional boost, in an attempt to enhance the

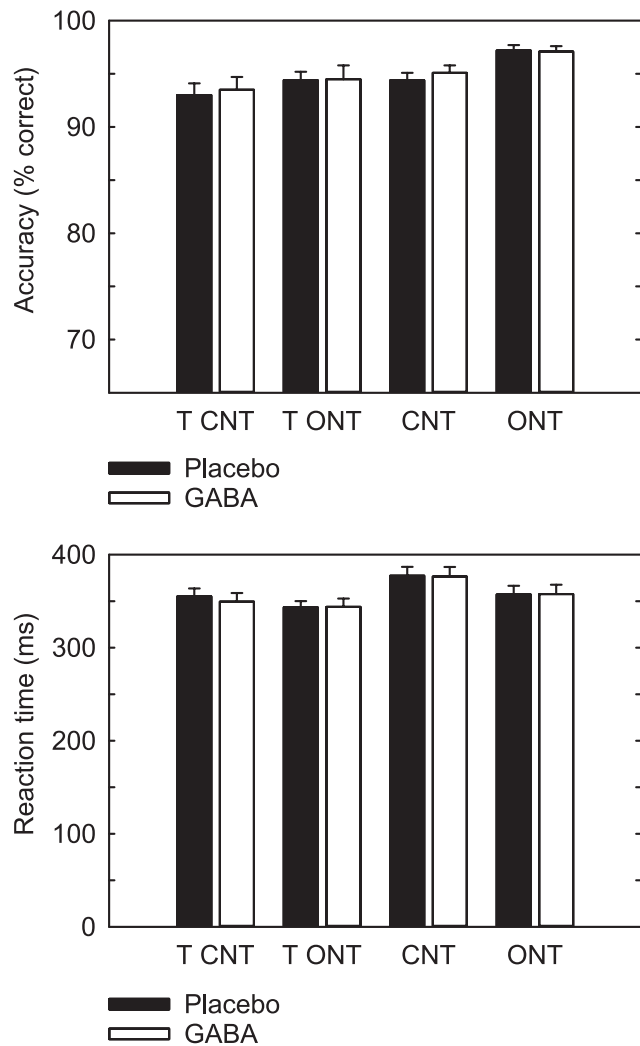


Fig. 4. Performance in the visual search task, plotted for each of the target presence and nontarget feature dimension conditions. The top panel shows response accuracy (% correct), and the bottom panel shows reaction time (ms).

perception of that target, but which lags by about 100 ms, thereby arriving in time only for the Lag 1 item—in this case T2. Because T2 thus enjoys attentional priority, it is reported first, with an order error resulting. A reduced tendency to invest attention into T1, as might result from GABA consumption, could thereby lessen the delayed boost effect on T2, and diminish the frequency at which order errors occur.

This attentional account of the order effect at Lag 1 might seem paradoxical with regard to the overall performance level, because target identification rates at Lag 1 were relatively low. As has been observed previously, our version of the RSVP task does not produce Lag 1 sparing, where performance is higher than would be expected at short lag (Visser et al., 1999), even though close variants of the task can do so (Akyürek et al., 2012). The AB is thus in full effect at this lag. The

decrease in order errors does help performance at Lag 1, but the effect is too small to counter the blink deficit. This may reflect a late locus of the GABA effect, such that the detection and identification of T1 are not affected, but rather the consolidation in working memory. By the time consolidation is underway, a T2 presented at Lag 1 may already have gone by. Thereby GABA would only affect later blink lags, such as the current Lag 3. There is prior ERP evidence that the AB is related to a bottleneck in working memory consolidation (Akyürek, Leszczyński, & Schubö, 2010; Vogel, Luck, & Shapiro, 1998). It would be interesting to examine this interpretation in more detail by looking at the amplitude of ERP components related to attention and working memory, such as the N2pc and P3, as a function of GABA consumption.

Another important observation from our study is that GABA affected temporal, but not spatial attention. Results from the animal study by Petersen et al. (1987) showed that manipulations of GABA levels in a specific region of the brain (i.e., the pulvinar nucleus) altered performance in a cued visual attention task. The authors found that GABA agonists (i.e., functional enhancers) led to a slowing of attention shifting towards the contralateral direction while GABA antagonists (i.e., functional inhibitors) elicited the opposite effect: Shifting of attention to the contralateral visual field was more rapidly accomplished. This modulation suggests that visual search performance in the current study should also have been modulated by GABA in the present study (positively or negatively), but this was not observed.

One possible explanation for this lack of an effect is that although GABA plays a general role in the responsiveness of cortical neurons to visual stimuli (e.g., Katzner et al., 2011), it may play a more important role in the maintenance than in the encoding of spatial memories (Cullen, Dulka, Ortiz, Riccio, & Jasnow, 2014). This may have contributed to our finding that GABA intake did not affect performance in the visual search task, because responses to the stimuli had to be given immediately, so that performance did not rely on memory maintenance. Conversely, in the RSVP task, due to the ongoing masking caused by the distractor stream, and the fact that responses had to be delayed until the prompts appeared, memory effects might have had more opportunity to contribute.

Alternatively, it is possible that the temporal attention task poses a more difficult perceptual task, requiring rapid feature identification and segregation in the context of an ongoing stream of irrelevant items. Kolasinski et al. (2017) proposed that levels of cortical GABAergic tone may specifically affect perceptual performance when more complex processing is required. Interestingly, in the task used by Kolasinski and colleagues, a (tactile) temporal order judgment was used as a performance measure. In the current task, even though an explicit order judgment was not asked for, a spontaneous reduction in order errors was observed after GABA ingestion—similarly to our present findings. The currently observed modulation of T2 identification accuracy that seemed to occur at Lag 3 specifically could also be viewed as another case in which maximal demands were placed on the observers, which would fit with the difficulty hypothesis of Kolasinski et al. (2017).

Finally, it must be noted that there is in general much controversy in the literature regarding the effects of oral GABA intake (Boonstra et al., 2015). Different experimental methodologies and GABA administration methods have led to uncertainties as to whether an oral dose of GABA can succeed in crossing the blood-brain barrier, a semipermeable

Table 1 Mean and standard deviation of mood, arousal and heart beats per minute at all time points for both treatment conditions.

	Before treatment		After treatment		End of experiment	
	GABA	Placebo	GABA	Placebo	GABA	Placebo
Mood	1.13 (SD 1.51)	1.08 (SD 1.53)	2.13 (SD 1.23)	1.79 (SD 1.18)	1.29 (SD 1.4)	1.38 (SD 1.44)
Arousal	-0.5 (SD 1.72)	-1.04 (SD 1.73)	-0.79 (SD 1.02)	-0.63 (SD 1.41)	-1.5 (SD 1.32)	-1.75 (SD 1.48)
Heart rate	85 (SD 14)	80 (SD 13)	78 (SD 11)	72 (SD 10)	73 (SD 10)	68 (SD 10)

membrane that separates the circulating blood from the brain parenchyma, and permitting only small molecules to pass through. The blood-brain barrier protects the brain from particles, toxins and ion abnormalities absorbed by our blood through ingestion; a barrier which might thereby well block GABA as well. In this context it should be acknowledged that cognitive effects of GABA intake might also be mediated by its ability to increase the secretion of growth hormone (GH) from the pituitary gland (Müller, Locatelli, & Cocchi, 1999), which is not protected by the blood-brain barrier. Although evidence of acute effects is limited, GH deficits in patients have been related to impairments in certain cognitive functions (Falletti, Maruff, Burman, & Harris, 2006), suggesting an indirect, alternate route by which orally ingested GABA might act.

However, in view of the compatibility with earlier results (Steenbergen et al., 2015a, 2015b), the present findings do give further credence to the idea that oral ingestion does allow GABA to reach the brain and exert direct effects on cognition, which in the present case were specific to temporal attention. The beneficial nature of these effects furthermore suggests that GABA levels in the brain did not reach a level high enough to become suboptimal through an excess of functional inhibition (Pezze et al., 2014). The current study could therefore serve to encourage further research on the cognitive effects of GABA consumption and studies on the possibilities provided by GABA-based cognitive enhancement.

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