Cognitive enhancement : toward the integration of theory and practice

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Chapter five

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

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Abstract

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 priorities 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, randomized, 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.

1. Introduction

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 priorities and cascade different actions (Mückschel, Stock, & Beste, 2014). 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 (Verbruggen, Schneider, & Logan, 2008; Stock, Arning, Epplen, & Beste, 2014). The general consensus is that action cascading processes rely on fronto-striatal networks (Humphries, Stewart, Gurney, 2006; Bar-Gad, Morris, & Bergman, 2003; Redgrave, Prescott, & Gurney, 1999; Beste, Dziobek, Hielscher, Willemssen, & Falkenstein, 2009; Beste et al., 2012; Ravizza, Goudreau, Delgado, & Ruiz, 2012; Cameron, Watanabe, Pari, & Munoz, 2010; Willemssen, Falkenstein, Schwarz, Müller, & Beste, 2011). 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 (Humphries, Stewart, Gurney, 2006; Bar-Gad, Morris, & Bergman, 2003; Plenz, 2003). GABA plays a pivotal role in information encoding and behavioral control (Adler, Finkes, Katabi, Prut, & Bergman, 2013), in the regulation of motor functions (Chase & Taminga, 1979; Will, Toniolo, & Brailowsky, 1988; Boy et al., 2010), and in motor learning (Stagg, Bachtiar, & Johansen-Berg, 2011; Floyer-Lea, Wylezinska, Kincses, & Matthews, 2006). More importantly, GABA also seems involved in action selection (Bar-Gad, Morris, & Bergman, 2003) and response inhibition processes occurring in the frontal-striatal networks (Bari & Robbins, 2013; Quetscher et al., 2015).

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 (2014) 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) concentrations in the brain, improved response selection functions during action cascading, compared to sham stimulation (Steenbergen et al., 2015). In contrast, Stock, Blaszkewicz, and Beste (2014) showed that high-dosage alcohol, an unselective GABA-ergic agent (Ticku, 1990), impaired action selection. Taken together, these findings indicate a critical role of GABA in the neuromodulation of action cascading processes and suggest that increased (Yildiz et al., 2014; Steenbergen et al., 2015), but not too high (Stock, Blaszkewics, & Beste, 2014), 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 (Haig et al., 2001; Rizzo et al., 2001) 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 (2002), 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 (Knudsen, Poulsen, & Paulson, 1988; Bassett, Mullen, Scholz, Fenstermacher, & Jones, 1990), a more recent study with rats has shown that the administration of GABA alone

increased brain GABA concentration, when compared to untreated rats (Shyamaladevi, Jayakumar, Sujatha, Paul, & Subramanian, 2002). In addition, the synthetic GABA-like agent gabapentin, which mimics the chemical structure of GABA, leads to an overall increase in central GABA levels (Errante, Williamson, Spencer, & Petroff, 2002) and a recent study using 7-T MRS reported an increase in GABA concentration in the visual cortex of healthy participants after gabapentin administration (Cai et al., 2012).

In the present study, action cascading was assessed by means of a well-established stop-change paradigm (Verbruggen, Schneider, & Logan., 2008), 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, signaling 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 Figure 1; Mückschel et al., 2014). 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 (Bar-Gad, Morris, & Bergman, 2003; Redgrave, Prescott, & Gurney, 1999; Bari & Robbins, 2013; Quetscher et al., 2014; Yildiz et al., 2014; Steenbergen et al., 2015), 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 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 (Lowan, 1984; Logan, 1994). 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 (Boy et al., 2010; Quetscher et al., 2014; Groenewegen, 2003; Draper et al., 2014), 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 (Steeter et al., 2010; Brambilla, Perez, Barale, Schettini, & Soares, 2003) and current mood-state is reckoned to affect cognitive-control processes (Schuch & Koch, 2014; van Steenbergen, Band, & Hommel, 2010), 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 (Russel, Weiss, & Mendelsohn, 1989), 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 (Zhang & Mifflin, 2010). 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).

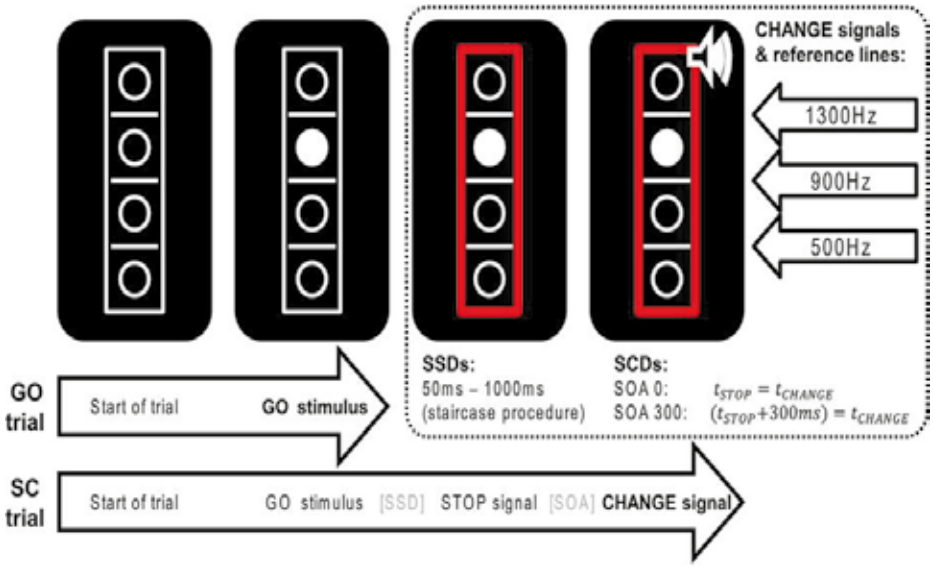

Figure 1. Schematic illustration of the stop-change paradigm. GO trials end after the first response to the GO stimulus (bold). In contrast, Stop-Change trials end after the first response to the CHANGE signal (bold). The stop-signal delay (SSD) between the onset of the GO stimulus and the STOP signal was adjusted using a staircase procedure described in the Method section. 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.

2. Method

2.1. 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 behavioral 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 (Sheehan et al., 1998; Colzato & Hommel., 2008; Colzato, Ruiz, van den Wildenberg, & Hommel, 2011). 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, randomized, 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 (2008) and Colzato, Jongkees, Sellaro, and Hommel

(2013), 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.

2.2. Apparatus and procedure

All participants were tested individually. Upon arrival, participants were asked to rate their mood on a 9 × 9 Pleasure × Arousal grid (Russel, Weiss, & Mendelsohn, 1989) 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; Abdou et al., 2006) 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.

2.2.1. Stop-Change paradigm

The experiment was presented on an LG Flatron 776FM 16 inch monitor (refresh rate of 60 Hz), controlled by an Asus laptop running on an Intel Core i3-3217U processor. Presentation software (Neurobehavioral Systems, Inc., Berkeley, CA) was used for stimulus presentation and data collection. The stop-change (SC) paradigm was adapted from Yildiz, Wolf, and Beste (2014), and Dippel and Beste (2015), see Figure 1.

Each trial consisted of the presentation of a white rectangle (on a black background) of 55 × 16 mm in the center 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). 250 ms after the onset of each trial, one of the circles was filled white, as such becoming the GO target stimulus. Sixty-seven percent of all trials were GO trials, which constituted the GO condition. In this condition, participants were expected to indicate, with their right index and middle finger, whether the target was located above or below the middle horizontal reference line. If the target was located above the middle reference line, participants were supposed to press the outer right key using the right middle finger ("above" judgment). If the target was located below the middle horizontal reference line, participants were supposed to press the inner right key with the right index finger ("below" judgment). All stimuli remained visible until the participant responded. In case of RTs longer than 1000ms, a "Quicker!" sign would appear above the rectangle until the participant responded.

Besides GO trials the task also included stop-change (SC) trials, which constituted the remaining 33% of the trials. Like a GO trial, a SC trial began with the presentation of a white rectangle with 4 vertically aligned circles separated by 3 horizontal reference lines. Again, 250 ms after the onset of the trial, one of the circles would turn white. For this condition however, a STOP signal (a red rectangle replacing the previous white frame) was presented after a variable stop signal delay (SSD). This STOP signal requested participants to try to inhibit the right-handed response to the GO stimulus and remained on the screen until the end of the complete trial. The SSD was initially set to 250 ms and was adapted to each participant's performance by means of a staircase procedure. This procedure yields a 50% probability of successfully inhibiting the GO response. In 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 current trial. In case of an incorrect response to a SC trial (if any of the above criteria were not met), the SSD

was adjusted by subtracting 50 ms from the SSD of the current trial. SSD values were set not to exceed a value of 1000 ms or to fall below a value of 50 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 (Verbruggen et al., 2008; Cai et al., 2012).

Irrespective of successfully or unsuccessfully inhibiting the GO response, every stop signal was combined with one of three possible CHANGE stimuli. The CHANGE stimuli consisted of a 100 ms sine tone presented through headphones at 75 dB SPL. This tone could be high (1300 Hz), medium (900 Hz) or low (500 Hz) in pitch, and indicated which of the horizontal lines need to be used as a reference line for this trial. That is, 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 Figure 1). All three reference lines were used with equal frequency. Participants were required to make the appropriate CHANGE response with index or middle finger of the left hand. The left middle finger had to be used to press the outermost left key, and the left index finger for the innermost left key. Which button the participant had to press depended on the location of the white circle and the tone presented. In case the target was located above the newly assigned reference line, an outer left key press (left middle finger; above judgement) was required; in case the target circle was located below the newly assigned reference line, a left inner key press (left index finger; below judgement) was required. RTs for the stop-change trials were measured from the onset of the CHANGE stimulus. In the case of a RT-SCD longer than 2000 ms, a "Quicker" sign was presented above the rectangle until the participant responded. Notably, half of the trials in the SC condition, consisted of a STOP signal and a CHANGE stimulus being presented simultaneously (stimulus onset asynchrony (SOA) of 0 ms, SCD0), whereas in the other half of the trials, there was a stop change delay (SCD) with a SOA of 300 ms (SCD300 condition) between the STOP and CHANGE stimuli. 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.

2.3. Statistical Analyses

Mood (pleasure and arousal), HR, DBP and SBP were analyzed 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.

3. 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 behavioral parameters for the stop-change paradigm separately for the GABA and placebo group.

Table 1. Behavioral parameters for GABA and Placebo groups (mean ±SEM).

	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

Significant difference between the two conditions; **p<0.05

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% (Verbruggen et al., 2008). For this reason, only error rates in the GO condition were analyzed. The analysis revealed no group effect, $t(28) = 1.49$, $p = .148$. The analysis of the SSRT (Verbruggen et al., 2008) 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.

Table 2. Mean heart rate values (in beats per minute), systolic (SBP) and diastolic (DBP) 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. Mean±standard error of the mean.

	T1		T2		T3	
	GABA	Placebo	GABA	Placebo	GABA	Placebo
Heart rate	74±4	82±4	68±2	74±2	66±2	67±2
SBP	116±4	118±4	115±4	117±4	109±3	119±3
DBP	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

4. 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 (Verbruggen, Schneider, & Logan, 2008). Indeed, we observed that the administration of a low dose of synthetic 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 (Humphries, Stewart, Gurney, 2006; Plenz, 2003; Bar-Gad, Morris, & Bergman, 2003; Redgrave, Prescott, & Gurney, 1999; Yildiz et al., 2014).

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 (Boy et al., 2010; Quetscher et al., 2014; Groenewegen, 2003; Draper et al., 2014). 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 (Bar-Gad, Morris, & Bergman, 2003; Redgrave, Prescott, & Gurney, 1999).

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 (Stock, Blaszkewicz, & Beste, 2014). 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 (Shyamaladevi, Jayakumar, Sujatha, Paul, & Subramanian, 2002), 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).