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Dissecting perception and memory-driven imagery by boosting GABA-ergic neurotransmission

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ABSTRACT

Flanking lateral masks enhance or weaken the detection of a low-contrast visual target. This effect depends on the target-to-mask distance. An improvement of stimulus detection can also be observed when participants imagine (i.e., retrieve from memory) the previously presented masks. In this double-blind, placebo-controlled study, we show that the gamma-aminobutyric acid-A ($GABA_A$) receptor agonist alprazolam disrupts perceptual but not imagery enhancement of contrast detection in individuals with generalized anxiety and adjustment disorder. The weakened target detection at short target-to-mask distances became more pronounced after the administration of the GABA-agonist in both perception and imagery conditions. Healthy control participants did not differ from individuals with generalized anxiety and adjustment disorder receiving placebo. These results indicate that perception and imagery can be dissociated by boosting GABA-ergic neurotransmission. Further studies are warranted to investigate this effect in healthy individuals.

1. Introduction

The notion of "seeing in the mind's eye" or visual imagery, which refers to an active and intentional reconstruction and visualization of images in our inner world, has been the subject of intense debate since the work of Aristotle and Plato on *Phantasia*, and, in close conjunction with the emergence of memory traces, imagery may have a cardinal role in the birth of western culture (Thomas, 2014). A fundamental open question is how perception, imagery, and memory interact during human cognition.

Recently, it has been emphasized that early visual areas play a multifaceted role in the representation of information, including stimulus-driven perception, top-down generation of images that have not been perceived before (mental imagery), and the maintenance or retrieval of previously seen pictures (visual working memory, internally directed attention, and retrieval of long-term memory traces) (Gazzaley & Nobre, 2012; Harrison & Tong, 2009; Kay et al., 2008; Klein et al., 2000; Kosslyn & Thompson, 2003; Kosslyn, Thompson, & Ganis, 2006; Mesulam, 2008; Pasternak & Greenlee, 2005; Pylyshyn, 2002; for a review of early findings on brain activation and mental imagery, see Roland & Gulyás, 1994). Using multivariate analysis to decode the information from neuronal activity, as revealed by functional magnetic resonance imaging, Albers et al. (2013) showed that stimulus identity could be reconstructed from neuronal activity patterns in early visual areas when the participant imagined the stimulus or maintained that in working memory. The neuronal activity patterns accompanying imagery and working memory were very similar to that measured during stimulus-driven visual perception, suggesting that early visual areas serve as a general "dashboard" for bottom-up and top-down processes (Albers et al., 2013; for a review of new behavioral and imaging methods in mental imagery research, see Pearson, 2014).

It has long been recognized that visual perception is specifically modulated by gamma-aminobutyric-acid (GABA), a major inhibitory neurotransmitter in the visual cortex (Iversen, Mitchell, & Srinivasan, 1971; Pettigrew & Daniels, 1973). Studies using pharmacological interventions in humans showed that the $GABA_A$ receptor agonist lorazepam disrupted early-stage "filling-in", which is critical for the integration of local contours (Beckers et al., 2001; Giersch, 1999; Giersch et al., 1995). Consistent with these findings, studies applying magnetic resonance spectroscopic measurements in early visual areas confirmed the role of GABA in perceptual integration of target and surround (orientation-specific surround suppression) (Yoon et al., 2010). Furthermore, GABA agonists have been shown to reduce visual awareness (van Loon et al., 2012) and to change contents of consciousness during bistable per-

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ception (van Loon et al., 2013). In the light of these results, it is plausible to hypothesize that GABA agonists affect not only perceptual integration, but they also have an impact on mental imagery.

Ishai and Sagi (1995, 1997) designed an elegant paradigm to show that early-stage visual perception and imagery have common mechanisms. Specifically, they asked observers to detect a low-contrast visual target (Gabor patch) flanked by two lateral masks (Fig. 1). This is a basic scenario during which local visual detectors interact to obtain a primitive "shape" (Kovács & Julesz, 1994). As expected (Polat & Sagi, 1993), collinear flankers placed in a particular distance from the target enhanced target detection. Strikingly, a similar decrease in target detection threshold was observed when participants imagined the previously presented masks (Ishai & Sagi, 1995, 1997). This suggests that physically presented and imagined flankers are both able to influence the detection of target stimuli.

In the present study, we investigated how perceptual and imagery processes are modulated by $GABA_A$ receptor agonist benzodiazepines. This pharmacological manipulation has been shown to alter perceptual organization in humans (Beckers et al., 2001; Giersch, 1999; Giersch et al., 1995). Given that early perception and imagery are thought to have shared mechanisms, we hypothesized that GABA agonists would disrupt both perception and imagery in the lateral masking task of Ishai and Sagi (1995, 1997).

We assessed individuals with mild psychological difficulties with the assumption that they did not differ from healthy participants at baseline contrast detection and lateral masking. This assumption was tested by the inclusion of a healthy control group. The assessment of patients instead of healthy volunteers was an unavoidable methodological limitation, because we had no allowance to administer GABA agonists to healthy people.

2. Methods

2.1. Participants

We recruited the participants at the National Institute of Psychiatry and Addiction, Budapest and Szeged, Hungary. The healthy control group comprised individuals from the hospital staff. Altogether, we had three experimental groups: (1) individuals with generalized anxiety disorder (GAD) ($n = 20$), (2) adjustment disorder (AD) ($n = 20$), and (3) healthy control volunteers ($n = 15$) (Table 1). AD (stress-response syndrome) is diagnosed when an individual is not able to cope with or adapt to stressful life events, but the diagnostic criteria of major psychiatric disorders are not fulfilled (e.g., mild, clinically sub-threshold depression or anxiety).

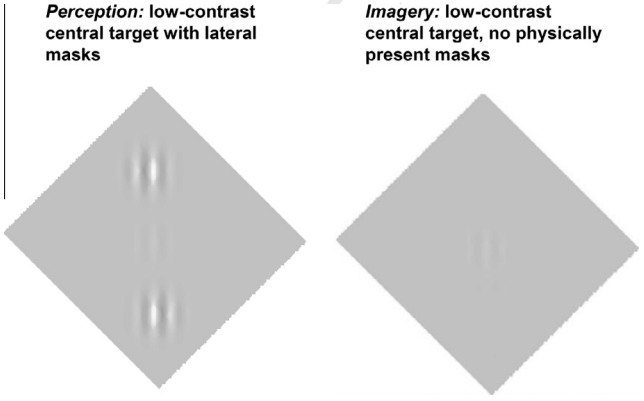

Fig. 1. Illustration of Gabor stimuli from the perception task when lateral masks were present and imagery task when the masks were physically absent.

Table 1
Demographic characteristics of the participants.

	HC ($n = 15$)	GAD ($n = 20$)	AD ($n = 20$)
Age (years)	32.6 (8.0)	34.7 (6.0)	31.5 (7.3)
Gender (male/female)	7/8	9/11	9/11
Education (years)	13.6 (3.7)	12.7 (4.7)	12.3 (4.3)
HAM-D	–	12.4 (5.7)	8.7 (4.8)
HAM-A	–	5.9 (3.8)	6.9 (4.2)

Data are mean (standard deviation) with the exception of gender. HC – healthy control, GAD – generalized anxiety disorder, AD – adjustment disorder, HAM-D – Hamilton Rating Scale for Depression (0–7: no depression, 8–15: mild,>15: severe), HAM-A – Hamilton Rating Scale for Anxiety (0–5: no anxiety, 6–15: mild,>15 severe). The three experimental groups did not differ in age, gender ratio, and education (two-tailed t tests and chi-square tests, $p > 0.2$).

AD is characterized by depressed mood, anxious symptoms, or disturbances in conduct (American Psychiatric Association, 2013).

The patients did not receive any pharmacological treatment before the experiment. The severity of anxiety and depression was evaluated with standard clinical scales (Hamilton, 1959, 1960), and the diagnosis was established by trained and supervised clinical psychiatrists according to standard criteria (American Psychiatric Association, 2013). We included patients because we were not allowed to administer benzodiazepines to healthy people. Two separate groups with different disorders (GAD and AD) were tested to explore whether the results are replicable across different disorders. The characteristics of the participants are summarized in Table 1. The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional ethics board. All participants gave written informed consent.

2.2. Randomization and pharmacological intervention

Experiments were conducted between 9 and 11 a.m. GAD and AD patients were randomized using the RANUNI module of SAS (Statistical Analysis System) (SAS Institute Inc., Cary, NC). Half of them received placebo (lactose), and half of them received the $GABA_A$ receptor agonist alprazolam according to standard clinical protocols (Rickels & Rynn, 2002). The oral dose of alprazolam was 0.02 mg/kg. We chose this dose because it is equivalent to that of lorazepam, which is the most frequently applied GABA agonist in visual experiments (Beckers et al., 2001; Schatzberg, Cole, & Debattista, 2010). However, lorazepam was not available in Hungary at the time of the experiment, and alprazolam exhibits several advantages in clinical practice regarding its side-effect profile (Schatzberg, Cole, & Debattista, 2010). We performed the experiment at the estimated peak plasma concentration of alprazolam (1.5 h following administration) (Schatzberg, Cole, & Debattista, 2010). Healthy control individuals were tested at baseline without placebo or alprazolam administration.

2.3. Stimuli and procedure

We previously modified the procedure of Polat and Sagi (1993) to fit for patient populations (Kéri et al., 2005a, 2005b; Must et al., 2004). The present experiment is an extended version of the perceptual task including an imagery component (Ishai & Sagi, 1995, 1997). In the perception condition, the contrast threshold was measured for a foveal target Gabor patch flanked by two lateral Gabor masks (Fig. 1). An imagery task followed the perception task during which the previously seen masks were not physically present, and participants were asked to imagine them.

Stimuli were presented on an NEC MultiSync PA301W monitor (NEC, Itasca, IL), controlled by a Dell XPS workstation. The display area subtended 10° by 10° from a viewing distance of 150 cm. The

mean display luminance was 50 cd/m^2. The Michelson-contrast of the masks was 40% with a Gaussian envelope size of 0.15°.

The trial was initiated by the participant who pressed a key. There were four subsequent phases during a trial: a no-stimulus (0.5 s), a first stimulus (90 ms), a second no-stimulus interval (1 s), and a second stimulus (90 ms). A session included nine alternating blocks (50 trials/blocks) of perception followed by imagery. The target-to-mask distance was 0, 3, or 6λ. Each block included one target-to-mask distance. The order of blocks was randomized. Each block of perception was followed by the corresponding imagery block during which participants were asked to imagine what they had just seen. The participant was asked to indicate which of the stimulus periods contained the target by pressing two different keys. The contrast threshold of the target was measured by a staircase method as described previously (Polat & Sagi, 1993; Q4 Kéri et al., 2005a, 2005b). Threshold changes in perception and imagery conditions were calculated relatively to the baseline when an isolated target was presented with two peripheral crosses.

The delay between perception and imagery tasks was either 0 min (immediate presentation of the imagery task after the perception task) or 5 min. We included an immediate and a delayed condition in order to test how sensory traces established during the perception task were stored in memory and how they could be retrieved during the imagery condition.

The current paradigm differed from the original task of Ishai and Sagi (1995, 1997). In order to shorten the procedure, we used only three critically relevant target-to-mask distances (0λ: peak inhibitory effects of the masks on the target; 3λ: peak excitatory effects of the masks on the target; 6λ: negligible effects of the masks on the target). Second, we eliminated the control condition during which an isolated target patch was presented after the perception task but participants were not requested to imagine the masks. Note, however that this control condition is not the same as the separate baseline condition when the target is presented in the absence of Gabor flankers (only two peripheral high-contrast crosses are presented). Threshold changes are compared to the latter baseline condition (Ishai & Sagi, 1995, 1997). This simplification was necessary because many participants were not able to stay on the original task (i.e., the procedure was too long).

2.4. Statistical analysis

The STATISTICA 11 (StatSoft, Inc., Tulsa), Prism 6 (GrpahPad, Inc., La Jolla), and SAS (Statistical Analysis System) (SAS Institute Inc., Cary, NC) software packages were used for data analysis. Contrast threshold data were log-transformed. Analyses of variance (ANOVAs) were performed to compare experimental groups (within-subjects factors: target-mask distance and delay between perception and imagery tasks). Tukey Honestly Significant Difference (HSD) tests were applied for post hoc analysis. The level of statistical significance was set at $\alpha < 0.05$.

3. Results

3.1. Perception

An ANOVA was conducted on the log-contrast threshold elevation data. We first compared individuals receiving placebo and the GABA-agonist alprazolam. The within-subjects factors were delay (0 and 5-min delay period between perception and imagery) and target-to-mask distance (0, 3, and 6λ). The ANOVA revealed a significant main effect of placebo vs. alprazolam group ($F(1,38) = 58.32$, $p < 0.001$, $\eta^2 = 0.61$) and a significant interaction between group and target-to-mask distance ($F(2,76) = 17.59$, $p < 0.001$, $\eta^2 = 0.32$). This two-way interaction was further explored with Tukey HSD tests. As shown in Fig. 2, there was a significant threshold elevation at 0λ in the alprazolam group compared with the placebo group ($p < 0.01$). It is also evident from Fig. 2 that at 3λ the enhancing effect of masks was not observed in the alprazolam group, whereas it was detectable in the placebo group. The difference between individuals receiving placebo and alprazolam was significant at 3λ ($p < 0.001$). At 6λ, threshold elevation was similar in both groups ($p > 0.5$). Finally, the results were highly similar at both delay intervals (ANOVA main effect of delay, $p > 0.5$) (Fig. 2).

To test the possibility that individuals with GAD and AD, who were randomized to placebo and alprazolam, differed from healthy individuals, we performed a separate ANOVA including the healthy control and placebo groups. This ANOVA revealed no significant differences between the two groups and no significant interactions (all p-values from the ANOVA > 0.2) (Fig. 2).

3.2. Imagery

We conducted an ANOVA for the imagery condition with the same design as used in the perception condition. There was a significant main effect of placebo vs. alprazolam group ($F(1,38) = 14.83$, $p < 0.001$, $\eta^2 = 0.28$). The interaction between group and target-to-mask distance was also significant ($F(2,76) = 13.10$, $p < 0.001$, $\eta^2 = 0.25$). As shown in Fig. 3, the main effect and the two-way interaction were due to the significant threshold elevation at 0λ ($p < 0.001$), which was consistently observable at both delay periods. In both placebo and alprazolam groups, however, there was a significantly decreased threshold at 3λ relative to 0λ and 6λ ($p < 0.05$), which indicates a reliable facilitation effect.

As in the case of perception, there was no significant difference between healthy individuals and participants receiving placebo (ANOVA main effect of group, $p > 0.2$) (Fig. 3).

3.3. Contrast threshold for isolated Gabor patches

When contrast threshold was measured in the absence of lateral masks, participants belonging to different experimental groups

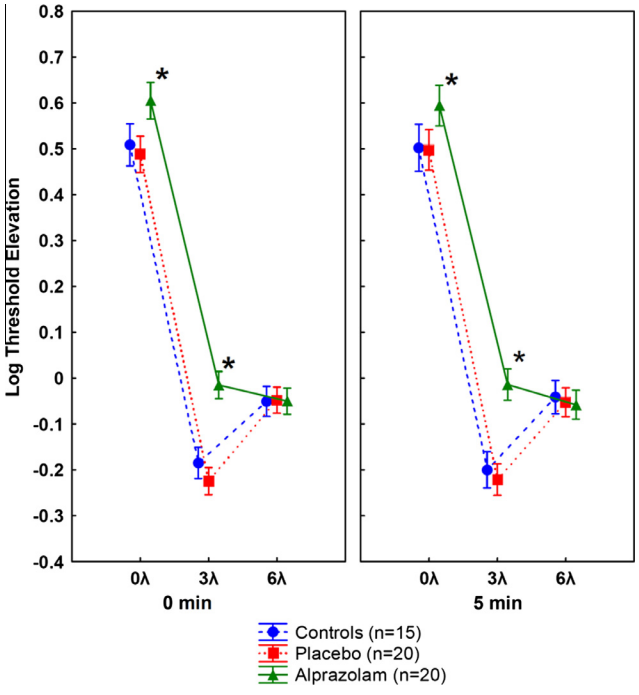

Fig. 2. Results from the perception task. Mean log-threshold elevation in healthy controls, individuals receiving placebo and alprazolam. Error bars indicate 95% confidence intervals. *$p < 0.01$ (Tukey HSD post hoc tests).

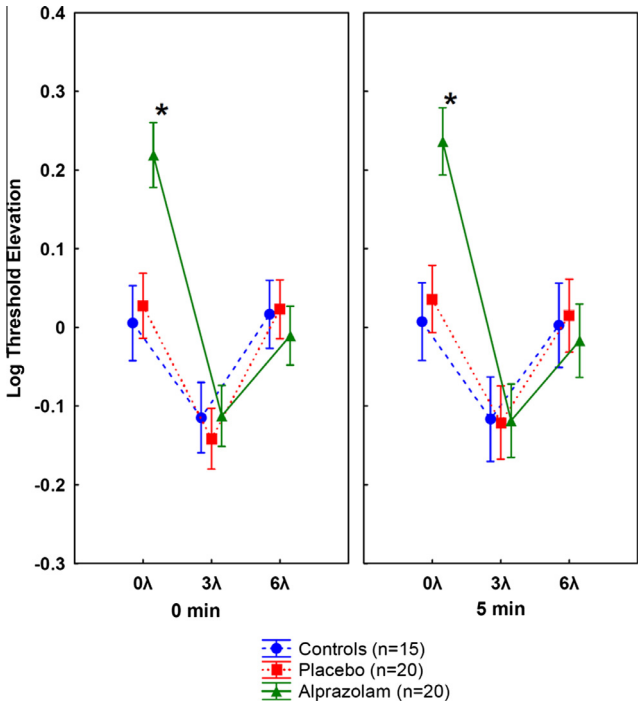

Fig. 3. Results from the imagery task. Mean log-threshold elevation in healthy controls (HCs), individuals receiving placebo and alprazolam. Error bars indicate 95% confidence intervals. *$p < 0.01$ (Tukey HSD post hoc tests).

performed similarly (healthy controls: 7.5%, SD = 2.7; placebo: 7.2%, SD = 3.3; alprazolam: 7.9, SD = 3.5) ($p > 2$, all pairwise comparisons).

3.4. Effect of baseline anxiety and depression

We found no significant correlations between threshold elevation and anxiety/depression ($-0.1 < r < 0.1$, $p > 0.5$). There was no significant difference between individuals with GAD and AD ($p > 0.5$).

4. Discussion

The results of the present study did not confirm the main hypothesis: the GABA agonist alprazolam disrupted peak facilitation at 3λ in the perception but not in the imagery task. Inhibition at 0λ target-to-mask distance was enhanced by the GABA agonist in both perception and imagery tasks. From a broader perspective, these results indicate that perception and memory-driven imagery can be dissociated at the behavioral level by pharmacological manipulation. Although the neuronal underpinnings of imagery and perception are thought to be similar, including the activation of early visual areas under many experimental conditions (Kosslyn & Thompson, 2003; see also Roland & Gulyás, 1994 and Dulin et al., 2008), Hume's proposition (1740, 1978) that percepts (*impressions*) and images (*ideas*) are substantially similar has not been empirically confirmed (Thomas, 2014). The currently accepted general framework of top-down modulation of sensory cortical areas, i.e., during working memory and imagery, claims that the prefrontal and parietal control regions re-instantiate neural activity in sensory cortex that was originally elicited when the item was processed during stimulus-driven perception (Gazzaley & Nobre, 2012; Kosslyn, Thompson, & Ganis, 2006; Mesulam, 2008; Pasternak & Greenlee, 2005). However, recent research provided evidence for some neuronal differences between perception and imagery. Specifically, Johnson and Johnson (2014) found that the fusiform face area (FFA) contained item-specific information during the perception of natural scenes, which was not evident during the imagery (retrieval and maintenance) of the same scenes.

The finding that the pharmacological facilitation of GABA-ergic neurotransmission dissociated perception and imagery is consistent with the results of Giersch and Vidailhet (2006) who demonstrated intact perceptual priming (completion of fragmented pictures of everyday objects) and impaired visual contour processing in long-term lorazepam users. In some respects, the completion of fragmented pictures may require mental imagery of intact objects.

The task of Ishai and Sagi (1995, 1997) is not a strictly defined imagery task, because it does not include the generation of images not been seen before. Instead, this task is based on the memory trace and retrieval of lateral masks exposed during the perception task (a memory-driven imagery task). Ishai and Sagi (1995) showed that reducing the number of trials in the perception blocks diminished the facilitation effect in the subsequent imagery task. This suggests that a minimum number of stimulus repetitions are indispensable to establish a memory trace. In addition, this memory trace is maintained at least for 5 min available for retrieval in a subsequent imagery task to produce a facilitation effect (Ishai & Sagi, 1995). GABA agonists seem to disrupt the perceptual facilitation effects of masks during bottom-up processing, but they do not impair the creation, storage, and retrieval of memory traces of masks. In addition, when the masks are retrieved during the imagery task, they produce a facilitation effect on target detection, which suggests that this top-down process is dissociable from bottom-up perception and is not influenced by GABA. These effects are not a trivial consequence of sedation because sedation induced by alprazolam is regularly associated with impaired top-down memory retrieval (Verster & Volkerts, 2004). Imagery during the effect of GABA-agonists may be similar to fully reconstructed conscious images while dreaming (Nir & Tononi, 2010), but in the latter case, the retrieval of internal representations are not voluntary and intentional in contrast to memory-guided imagery.

Our behavioral data might provide a primer for electrophysiological, functional neuroimaging, and animal studies to explore the neuronal bases of these memory traces and the mechanism of dissociable perceptual and retrieval processes. At the network level, a key factor may be the differential modulation of temporal properties of neurons. We speculate that GABA-induced synchronization at specific frequency ranges may have distinct effects on perception and imagery (i.e., altered temporal properties of neuronal groups may result in perceptual dysfunctions but intact retrieval of memory traces) (Elliot et al., 2000; Elliott, Giersch, & Seifert, 2006).

The GABA agonist also had a shared effect on perception and imagery, that is, the enhancement of inhibition at small target-to-mask distances. This suggests that GABA plays a critical role in this inhibitory effect. It is intriguing that Ishai and Sagi (1995) failed to find interference suppression between target and masks in the imagery condition when they were overlapping. The authors interpreted it as a lack of the classic Perky effect (Craver-Lemley & Reeves, 1992; Waller et al., 2012), probably because the stimuli in their simple detection task had no meaning. The present results indicate that the Perky effect can be induced even in the case of simple stimuli during a detection task if the GABA-ergic neurotransmission is boosted.

Although benzodiazepines are considered as a homogeneous group of compounds stimulating $GABA_A$ receptors, the effect of individual drugs on perception may be substantially different. Beckers et al. (2001) showed that whereas lorazepam markedly impaired perceptual integration, the effect of diazepam did not dif-

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fer from that of the placebo. We used alprazolam, one of the most commonly prescribed anxiolytic medications, which had a substantial effect on perceptual integration. Alprazolam is similar to lorazepam regarding its high affinity to $GABA_A$ receptors (Schatzberg, Cole, & Debattista, 2010). Nevertheless, it remains to be demonstrated that alprazolam also has a detectable effect in classic tasks of perceptual integration (Giersch, 1999). Lorazepam prolongs visual information processing (Giersch & Herzog, 2004), and its long-term use leads to decreased contrast sensitivity (Giersch et al., 2006). In the single alprazolam administration paradigm, we did not detect decreased contrast sensitivity when an isolated target was presented, which is against its non-specific dampening effect on visual perception. However, alprazolam may have a detrimental influence on threshold decrease in the lateral masking paradigm by slowing down the flankers' effects. Polat and Sagi (2006) showed that excitation develops slowly, whereas inhibition is rapid and follows stimulus onset and offset.

It is also interesting to note that, in healthy individuals, collinear interactions induce a high false alarm rate at the critical 3λ target-to-mask distance during a Yes/No detection task (Polat & Sagi, 2007). Zomet et al. (2008) showed that this high false alarm rate is significantly less pronounced in hospitalized patients with major depressive disorder. Moreover, the authors also found that those patients who received lower doses of benzodiazepines displayed a more similar performance to that of the healthy control subjects (Zomet et al., 2008). Lower false alarm rate in patients can be explained by reduced excitation between neurons and weaker lateral interactions, which is consistent with our results regarding the effects of GABA-agonist benzodiazepines.

A critical limitation of the present study is that we demonstrated the GABA-related dissociation between perception and imagery in individuals with GAD and AD and not in healthy volunteers. Given that GABA-ergic neurotransmission displays alterations in mental disorders characterized by anxiety and depression (Möhler, 2012), one may claim that the results are due to these specific disease features and cannot be generalized to healthy individuals. Although this possibility cannot entirely be excluded, several aspects of these findings should be taken into account. First, at baseline, there was no significant difference among HCs and individuals with GAD and AD. Second, depressive and anxiety symptoms did not correlate with visual variables. Third, and most importantly, the effect of alprazolam was replicated in GAD and AD, two disorders with substantially different clinical profiles (American Psychiatric Association, 2013): while GAD is a chronic anxiety disorder, AD is a mild, stress-related manifestation of anxiety and depression, which regularly exhibits rapid remission spontaneously or after a short therapeutic intervention. Most of the individuals with AD are healthy with transient psychological difficulties. In this respect, our methodological opportunities were limited because we were not allowed to use lorazepam in healthy individuals, which is the most optimal paradigm to obtain comparable results in the literature.

In conclusion, the results of this study provide evidence that perception and imagery are dissociable at the level of early vision. The pharmacological enhancement of GABA-ergic neurotransmission disrupts lateral facilitation during perception, but not during the retrieval of memory traces that have a contextual effect on perception. These results must be replicated in an independent group of healthy individuals, and the exact neurobiological mechanisms must be uncovered.

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