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The modulating role of ADRA2B in emotional working memory: Attending the negative but remembering the positive

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Abstract
Previous studies found that the ADRA2B gene modulates early perception and attention. Here, we aimed to examine whether ADRA2B polymorphisms also influence emotional working memory and the willingness to implement behaviors (switching affective intonation) in order to avoid negative information, both considered indexes of cognitive–affective flexibility. We examined genotype data collected from 212 healthy females, 91 ADRA2B carriers and 121 non-carriers, and found that carriers showed a positivity bias in working memory. That is, carriers remembered a higher number of positive words compared to negative and neutral words. In addition, although carriers were more unwilling to switch intonation in order to avoid negative information, they showed better recognition memory for words read with a positive intonation. These findings suggest that deletion variants of ADRA2B may show greater levels of cognitive–affective flexibility compared to non-carriers.

Keywords
ADRA2BEmotionWorking memoryWillingness to avoid negative information

1. Introduction

The neurobiological processes mediating emotional arousal and memory are highly adaptive and later memory consolidation is influenced by the noradrenergic hormonal system activated by dangerous and/or favorable situations. Interestingly, such emotional enhancement of cognition may be experienced to different degrees in people due to genotype differences (e.g., Hamann & Canli, 2004). A recent line of research in the field of noradrenergic neurotransmission identified a functional deletion variant of ADRA2B as a potential modulator of emotional encoding processes (Todd et al., 2013, Todd et al., 2014). This intronless gene, located on the 2p13-q13 chromosome, encodes a seven-pass transmembrane protein widely distributed in the human central and peripheral nervous systems. ADRA2B protein is a subtype of alpha 2-adrenergic receptor (a2-AR)

mediating biological effects of endogenous catecholamines, epinephrine and norepinephrine (NE, Belfer et al., 2005). The presence of the ADRA2B functional polymorphism, consisting of an inframe deletion of three glutamic acids residues (301–303) in the third intracellular loop, leads to a small decrease in coupling receptor efficiency (e.g., Makaritsis et al., 1999).

Studies on the interaction between the ADRA2B variant and emotion, with a specific focus on valence effects on attention and memory, present a very complex picture (for a review see Todd et al., 2015). While some studies have found a bias for negative information (e.g., Rasch et al., 2009, Todd et al., 2013), others have detected a general arousal effect highlighting how carriers were sensitive to both positive and negative stimuli (e.g., De Quervain et al., 2007, Li et al., 2013, Todd et al., 2014, Todd et al., 2015, Zoladz et al., 2014).

Several different explanations have been advanced to account for this mixed pattern of findings. As outlined by Todd et al. (2013), it is likely that ADRA2B may interact with other polymorphisms known to be involved in emotional responses, such as the dopamine (DA) and serotonin (5-HT) systems, which may, in turn, affect the direction of valence biases. Indeed, a recent study by Todd et al. (2015) showed that ADRA2B and 5HTTLPR mutually influenced each other in ventromedial prefrontal cortex regions important for evaluating the salience of stimuli. It is, therefore, reasonable to suppose that norepinephrine, dopamine and serotonin all contribute to shaping valence effects.

A complimentary explanation is related to cognitive flexibility, and in particular, cognitive–affective flexibility. Cognitive–affective flexibility depends on several components of executive functions, including Working Memory (WM) and response inhibition, which underlie the ability to flexibly attend to or disengage from situations and/or stimuli according to life experiences, situational demands and individual goals (e.g., Malooly, Genet, & Siemer, 2013). Since the central noradrenergic system is associated with cognitive flexibility (e.g., Aston-Jones and Cohen, 2005, Sara and Bouret, 2012), it may be that ADRA2B carriers show greater levels of cognitive–affective flexibility and assign emotional relevance to any type of salient stimulus, shifting direction bias according to context and responding more flexibly to emotional stimuli that non-carriers.

The present study examines the effect of the ADRA2B polymorphism on performance in affective versions of two different cognitive tasks in ADRA2B carriers and non-carriers. Our aims were two-fold. First, we investigated whether ADRA2B carriers show specific valence effects in WM. In particular, WM reflects the ability to temporarily maintain relevant valenced information (the capacity function) for later processing (inhibition, updating, monitoring, linking information to semantic knowledge, etc., Baddeley, 2000). Thus, WM performance may index how goal-relevant information processing may change according to the task at hand. Furthermore, increasing behavioral evidence indicates that WM functions are involved in emotion processing (e.g., Kensinger & Corkin, 2003). Thus, exploring the influence of ADRA2B polymorphism on affective WM may have implications for genotype-related effects and emotion processing studies as well (e.g., Hofmann, Schmeichel, & Baddeley, 2012). To this end, we used a modified version of the Operation Working Memory Span (O-span) Test for emotional words (adapted from Turner & Engle, 1989) for two reasons. On one hand, this recall-based task has been shown to entail concurrent processing and short-term storage demands coupled with an attentional control component to limit interference between processing and storage (e.g. Mammarella, Borella, Carretti, Leonardi, & Fairfield, 2013). The span, in fact, requires participants to solve a series of math equations (processing function), while trying to remember a set of semantically unrelated

but valenced words (maintenance function). In addition, because of its span "structure", the task becomes more difficult as the number of words increases. On the other hand, these WM functions are sensitive to different motivational goals (e.g., emotional focus linked to well-being, reactivation of autobiographical events) that may accrue during the task at hand and, consequently, change the direction of valenced biases. For example, older adults showed better WM for positively valenced words compared to younger adults in line with their classical preference for positively charged information processing in attention and memory (e.g., Mammarella et al., 2013, Mather and Carstensen, 2005). If ADRA2B carriers' tendency to focus attention on negative information extends to WM functions as well, we expect genotype-related differences in terms of a negativity bias during the WM task as well. Such results would lend support to and extend results from previous studies about carriers' preference for negative information (e.g., Rasch et al., 2009, Todd et al., 2013). Differently, no valence effects or a positivity bias in carriers would lend support for the hypothesis that carriers assign emotional connotation to stimuli more flexibly and shift direction bias according to task demands.

Second, we designed an auditory comprehension task that involved a brief story read and recorded with two different intonations: a negative and a positive one. During listening, participants could choose to switch from the negative to positive version of each sentence. We adopted this manipulation in order to study participants' flexibility and/or willingness to implement behaviors in order to avoid listening to negative information since NE has also been linked to functions that would influence switching or acting to avoid negative information.

In particular, Aston-Jones and Cohen (2005) clarified the role of locus coeruleus (LC)–NE function in optimizing task performance (exploitation) and disengagement from a current task and a search for alternative behaviors (exploration). In particular, they proposed that this system is responsive to ongoing evaluations of task utility (that is, the costs and benefits associated with performance), provided by input from frontal structures. When utility comes less, changes in LC–NE tonic activity withdraw support for task performance, facilitating other forms of behaviors that are useful for exploring alternative sources of reward.

In addition, several recent studies (e.g., see Bouret & Richmond, 2015) show that noradrenergic neuronal responses might also be related to motivation and especially to willingness to act to gain a reward or, is in our case, to act in order to change a negative stimulus to a positive one. In particular, Bouret and Richmond (2015) showed that the activity of LC neurons reflects both expected reward and action. Neuron firing patterns suggest that they are activated in relation to the energy needed to respond to behaviorally significant events as a function of the current behavioral state, anticipated actions and corresponding outcomes. These findings are also in line with hypothesis of an interaction between the LC–NE system and the DA system. For example, Belujon & Grace, 2015) highlighted that the dopamine system is likely to be involved in motivation and attention processes underlying behavioral responses to relevant stimuli, whether aversive or rewarding, pointing to a relationship between the NE system and DA system in order to adapt to challenging situations.

Finally, we developed a yes–no recognition memory test in which a series of old words (words heard in the paragraph) were mixed with new words (never heard) that followed the listening comprehension task to investigate participants' memory for words from different affective intonations according to the shifts each participant made from a negative to a positive intonation.

Our predictions were as follows. If ADRA2B genotype effects are characterized by a robust negativity bias across different encoding tasks (Todd et al., 2013), we expect carriers to show a decrease in their willingness to implement behaviors to avoid sentences read with a negative intonation indexed by an inferior number of shifts to the positive prosody compared to controls. We expect this negativity bias to extend to recognition memory as well. However, if carriers are able to flexibly respond to emotional stimuli, we expect to observe behavioral differences between carriers and non-carriers, for example, a decreased willingness to act to avoid a negative information and no valence effects or even positive biases during the recognition memory task in the deletion group only.

2. Method

2.1. Ethics statement

The study was approved by the Departmental Ethics Committee of the University of Chieti. In accordance with the Declaration of Helsinki, all participants gave their written informed consent prior to their inclusion in the study.

2.2. Participants

The sample size of the present study was established following the typical effect size (η2) of .07 of genetic correlates of memory's studies (e.g., Rasch et al., 2009). We required 90 participants per genotype for a behavioral study. In line with the finding that 30% of the White population show the ADRA2b deletion variant, we recruited 300 right-handed native Italian speakers from an undergraduate pool of students from the University of Chieti for credit in a second year psychology course. Participants were females between the ages of 19 and 25 (mean age 20.6). Participants reporting a history of significant head injuries, stroke, epilepsy and/or learning disabilities were excluded. Eleven participants were excluded because they could not be genotyped for ADRA2b. A subset of participants with previous or current diagnosis or treatment for anxiety and depression, revealed by a self-report demographic questionnaire, were further excluded from the analysis due to potential associations between anxiety/depression and ADRA2B (Gibbs, Lee, & Kulkarni, 2013) leaving a total of 212 female participants. Only females were tested because a recent study reported by Zoladz et al. (2014) showed that ADRA2B deletion variant may selectively predict stress effects on memory in females, potentially underlying gender-related differences and stress effects on learning. In this study, we expected ADRA2B polymorphisms effects in memory to be magnified by recruiting females only.

2.3. Materials

2.3.1. Affective operation span

We adopted a modified version of the Operation Working Memory Span (O-span) Test for emotional words (adapted from Turner & Engle, 1989). The O-span requires participants to solve a series of math equations (processing function) while trying to remember a set of semantically unrelated words (maintenance function). Participants saw one equation/word string at a time, centered on a computer monitor. For each trial, participants read the equation aloud, decided whether the given solution was true or false and then read the following word aloud. Immediately after reading the word, the next equation–word string was presented. The task was self-paced. The equation–word strings were presented in sets of three to six items. Three question marks in the center of the monitor cued the participants that the set was complete and to recall the words in the correct order of presentation.

Sets from three to six equation–word strings were constructed for each affective valence (positive, negative and neutral). Two trials for each set size were presented. Additionally, in order to ensure that participants were not trading off between solving the equations and remembering the words, an 85% accuracy criterion on the math equations was required for all participants. The experimenter transcribed accuracy for math equations on a dedicated protocol. Two training trials preceded the task. Stimuli for the operation span task consisted in 36 math equations and 36 target words. Words were selected from the Italian standardization of the ANEW (Montefinese, Ambrosini, Fairfield, & Mammarella, 2014). The 12 positive words had a mean valence of 7.8 (1.5) and a mean arousal level of 5.9 (2.8), the 12 negative words had a mean valence of 2.4 (1.8) and a mean arousal level of 5.9 (2.7). Finally the 12 neutral words had a mean valence of 5.5 (1.9) and a mean arousal level of 2.7 (2.3). The order of the valenced set was counterbalanced across participants. For the psychometric properties of this task see previous studies (e.g., Mammarella et al., 2012, Mammarella et al., 2013).

2.3.2. Listening comprehension task and recognition

We created a single short story using 31 neutral target words. The target words were selected from the Italian version of the ANEW (Montefinese et al., 2014) and had the following characteristics: mean frequency of use, 127.4 (SD = 97.9), mean valence of 5.07 (SD = 0.28) and mean arousal 5.03 (SD = 0.45). The story was read by a professional actor and recorded in two versions that differed in affective intonation. One version was read with a positive intonation and one with a negative intonation.

In order to stress the difference between positive and negative emotions, the positive intonation recording resulted in the story being read in a higher pitch, while the negative intonation recording resulted in the story being read in a lower pitch. This is in line with previous studies showing that auditory items are typically perceived as positively charged if presented in a higher pitch, while they are perceived as negative if presented in a lower pitch (e.g., Weger, Meier, Robinson, & Inoff, 2007).

In addition, an independent group of 30 participants rated the two versions according to valence on a 7 point-scale (from 1 = absolutely negative to 7 absolutely positive). The intonation was effective in changing the direction of the rating as participants rated the story as more positive (M = 6.4, SD = .70) when the actor read the story with a positive intonation, more negative one (M = 2.1, SD = .74) with a negative. To test participants' comprehension, we asked them to respond to 5 multiple choice questions about the story. For the recognition memory test, the 31 studied words were mixed with 20 new words matched for all characteristics to old words to create a list of 51 items. Participants listened to the list of words read by the experimenter and answered "yes" if they thought they had heard the word during the story or "no" if they felt it was new.

2.4. Procedure

Participants first completed the affective O-span and subsequently listened to a brief story. Participants were instructed to pay attention to what the story was about. They were also told that they could choose to change the affective intonation of the story and listen to the story with a positive intonation whenever they wanted by pressing a key on the keyboard. Each sentence of the story began with a negative intonation for all participants. This was done because we were interested in studying participants' willingness to act in order to avoid listening to negative information. If the participant chose to listen to the sentence in a positive prosody, the intonation changed and remained positive until the end of the sentence. That is, participants had to stick with

the positive intonation till the end of the sentence. We presented this task as a comprehension study so participants did not know that a recognition memory test would follow. Participants listened to the story through a pair of Bose headphones. The story lasted about 70 s.

The recognition phase began after a 3 min interval during which participants completed the Pattern Comparison Test (Salthouse, Babcock, & Shaw, 1991). To be sure that participants listened to the story, they were engaged in a brief comprehension test first and then in the recognition memory task. For the comprehension test, participants answered 5 multiple choice questions based on inferential processing by marking the correct response based on their understanding of the story they had just listened to. After answering the comprehension questions, participants were presented with a surprise yes–no recognition memory task.

2.5. Scoring

2.5.1. Affective O-span

As a WM measure, we considered the proportion of correctly words by valence recalled regardless of serial position.

2.5.2. Listening comprehension task and recognition

We considered the proportion of shifts towards positive intonation made by each participant. Recognition, instead, was measured as HITs-FAs for words per affective intonation. Given that participants were told that they could freely choose to switch from the negative to positive intonation, the encoding phase differed between participants. Accordingly, recognition memory data should be treated with caution. To reduce these confounding effects, recognition scores were calculated individually for each participant as the ratio between the number of words each participant correctly recognized in the positive or negative intonation and the total number of words that were listened to in the positive or negative intonation calculated according to the number and position of shifts made by each participant.

2.6. Genetic analysis

Genomic DNA was isolated from buccal swabs using the NucleoSpin Tissue kit (Macherey-Nagel, Düren, Germany) according to manufacture instructions. PCR reaction was carried out in a final volume of 25 µl mixture using AmpliTaqGoldTMpolymerase. The forward primer, 5-AGAAGGAGGGTGTTTGTGGGG-3, and reverse primer, 5-ACCTATAGCACCCACGCCCCT-3, were employed, with an annealing temperature of 58 °C. This PCR reaction generated 200 and 209 base pair PCR products respectively for the Glu301–Glu303 deletion and wild type alleles. PCR products were resolved on a 4% Amresco (Solon, OH) Super Fine Resolution agarose gel stained with ethidium bromide. A PCR reaction which contained no DNA was performed as a negative control. In line with previous studies (e.g., Todd et al., 2013, Todd et al., 2014) homozygote and heterozygote ADRA2B carriers were treated as a single group due to the low number of homozygotes.

A significance level was set at $p < .05$. We were primarily interested in studying the influence of ADRA2B on emotional WM performance. Consequently, mixed-model analyses of variance (ANOVAs) were run on O-span data (old words reported regardless of order) with Valence (positive, negative and neutral) as repeated measures factor and Group (ADRA2B carriers vs. non-carriers) as the between-subjects factor. Second, we report the number of switches from negative to positive tone and the recognition memory data as HITs-FAs. For the recognition data, we used

proportional scores. Since comprehension was designed as a control task to ensure correct encoding, we did not include these data. There were no differences between the two groups.

3. Results

3.1. Genotype and demographic data of participants

A group of 212 subjects were available for analysis. Homozygosity for the Glu301–Glu303 deletion was detected in 20 participants; 71 subject were heterozygote while 121 were homozygote reference (see Fig. 1). The ADRA2B genotype frequencies were in Hardy Weinberg equilibrium ($\chi 2$ test p value >0.05). Participants were divided into two groups according to their ADRA2B genotype (91 carriers vs 121 non-carriers). Groups were matched in terms of age and education as well as general short term memory (measured with the forward and backward digit spans of the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981) and current mood (measured with the Positive and Negative Affective Scale, PANAS, Watson, Clark, & Tellegen, 1988). Table 1 presents the demographic data of participants.

Table 1. Neuropsychological and demographic characteristics of carriers and controls.

	Carriers (91)		Controls (121)	
	M	*SD*	*M*	*SD*
Age	20.80	2.51	20.38	1.79
Education (in years)	15.11	1.10	15.00	0.69
Digit span forward	6.85	1.56	6.63	1.68
Digit span backward	5.34	1.94	5.82	1.64
PANAS pos	30.15	5.79	31.32	5.87
PANAS neg	21.44	6.69	21.37	6.70

3.2. Data analysis

We carried out a first analysis on affective O-span data. A 2 (Group: carriers vs. controls) × 3 (Valence: positive vs. negative vs. neutral) mixed analysis of variance (ANOVA), with the last factor as a within participant factor, on the proportion of correct recall regardless of position as the dependent measure, revealed a main effect of valence, $F(2, 420) = 65.27$, $p < .001$, $\eta 2 = .24$. Post-hoc tests showed that participants remembered more positive words than negative and neutral words and more negative words than neutral ones. Finally, the analysis showed a significant Valence × Group interaction, $F(2, 420) = 3.67$, $p < .05$, $\eta 2 = .02$. Post-hoc tests confirmed that carriers remembered more positive words than controls while there were no difference for negative and neutral words. Table 2 shows the mean proportions of recall for positive, negative and neutral words.

Table 2. Mean proportions (with standard deviations) of correct recall for Valence (positive vs. negative vs. neutral) and Group (carriers vs. controls).

	Carriers (91)		Controls (121)	
	M	*SD*	*M*	*SD*
Positive words	.84	(.01)	.78	(.01)
Negative words	.77	(.01)	.77	(.01)
Neutral words	.70	(.02)	.68	(.01)

In order to investigate whether they shift away less often from processing negative information, we carried out a second analysis on listening comprehension and recognition data. A first analysis carried out on the mean proportion of shifts revealed a main effect of Group, $F(1, 210) = 115.19$, $p < .001$, $\eta 2 = .35$ since carriers made fewer shifts than controls indicating their general tendency not to act to avoid a negative intonation. Finally, a 2 (Group: carriers vs. controls) × 2 (Prosody: positive vs. negative) mixed analysis of variance (ANOVA), with the last factor as a within participant factor, on the proportion of correct recognition, calculated as HITs-FAs, revealed a significant main effect of prosody, $F(1, 210) = 26.43$, $p < .001$, $\eta 2 = .11$, because accuracy was better with a positive intonation than with a negative intonation. Finally, the 2-way interaction between Group and Prosody was also significant, $F(1, 210) = 34.80$, $p < .001$, $\eta 2 = .14$. Post-hoc tests revealed that the valence of prosody influenced content memory in carriers and controls in different manners. Carriers recognized more words with a positive vocal prosody than controls, while emotional prosody did not influence recognition in controls. Table 3 shows the mean proportions of shifts, comprehension and recognition for Group (carriers vs. controls) and Prosody (positive vs. negative).

Table 3. Mean proportions (with standard deviations) of shifts, comprehension and correct recognition for Prosody (positive vs. negative) and Group (carriers vs. controls).

	Carriers (91)		Controls (121)	
	M	*SD*	*M*	*SD*
Shifts	.39	(.01)	.53	(.01)
Comprehension	.74	(.02)	.71	(.02)
Positive prosody	.72	(.02)	.60	(.02)
Negative prosody	.46	(.03)	.62	(.02)

4. Discussion

The general aim of the study was to determine whether the ADRA2B polymorphism has a modulating effect on two affective versions of cognitive tasks, that is, a WM task and a listening comprehension and recognition task thought to index their cognitive–affective flexibility. Results can be summarized as follows. First, we observed comparable general WM and recognition performance across groups. Second, with regards to the influence of ADRA2B polymorphism and valence effects, we found, a positivity bias of the gene on behavioral performance both for the WM span and the recognition memory task. In particular, our study highlighted two relevant findings.

First, ADRA2B carriers were able to focus on positive information at the level of WM representations. Second, during auditory comprehension, ADRA2B carriers were less likely to adopt behaviors to change a negative stimulus to a positive one, but later recognized a higher number of positive words.

Altogether these valence effects add to the hypothesis that ADRA2B deletion variant is characterized by a flexible sensitivity to salience that may vary across tasks rather than an overall negativity bias across contexts or simply a global response to arousal as previously thought. It is possible that, although ADRA2B carriers tend to focus their attention on negative information or show a reduced willingness to change a negative information to a positive one (as, for example, shown during auditory comprehension), they are still able to flexibly recruit additional encoding controlled processes to diminish the impact of negative information in favor of positive ones on their short-term recall and recognition.

At a first glance, our results seem to vary from previous studies (e.g., Rasch et al., 2009, Todd et al., 2014) which showed that affective ratings predict later memory or that, generally speaking, greater amygdala responses to arousing stimuli predict better memory for those stimuli. However, the focus of our investigation was on valence effects rather than arousal (in the present study the level of arousal was comparable across stimuli). With some respects, our results are in line with the De Quervain et al. (2007) who did not find any difference between positive and negative valence in their memory task nor an arousal effect. Furthermore, in Rasch et al.'s (2009) study negative pictures had higher levels of arousal compared to positive and neutral ones. Second, differences across studies may be due to differences in study material. Here we used verbal material, while the majority of previous studies used affective pictures. As outlined by Kensinger, Anderson, Growdon, and Corkin (2004), visual material is typically richer in contextual details compared with verbal material. Consequently, enhanced perceptual vividness for negative high arousing information and better memory for this type of information may be the results of pictorial material and high arousal level of pictures.

However, the fact that carriers still show a decrease in the willingness to act to avoid negative information during auditory comprehension, suggest that their early encoding processes are more sensitive to negative information compared to positive information independently of arousal. However, they flexibly respond to goal-relevant information and task demands and favor the processing of positive information during later processing.

Although the current study did not directly examine the effects of ADRA2B on the time course of emotional processing, future neuroimaging research (e.g., using EEG or MEG) may help better clarifying the temporal window of valenced biases in carriers.

The present study, however, is not without limitations, especially with regards to the task that evaluated participants' willingness to act to avoid negative information. For example, intrinsic auditory features of the story may have influenced our results. For instance, Todd et al. (2015) showed that ADRA2B carriers show higher sensitivity to visual features such as contrast than non-carriers, suggesting that a similar pattern may occur in the auditory domain as well, that is, sensitivity to specific acoustical features could influence performance of carriers. In addition, one can argue that the story always began with a negative intonation and that without another condition in which participants start by hearing the positive version of the story and can switch to the negative one, it is difficult to know whether the switch rates are affected by valence. Future studies should thus adopt a more controlled methodology to better compare acoustical features across positive and negative condition and include a positive and negative beginning.

Finally, in line with Hewitt's policy (2012) concerning the replicability of genetic studies, our primary interest was on the influence of ADRA2B on emotional WM and recognition. Analysis of observed power suggest a robust level of replicability of our two-way interaction between ADRA2B and valence in WM (.68) and a high level of replicability for our recognition data (.92). Nevertheless, it has to be acknowledged that behavioral studies have generally relied on exploration of single candidate gene effects and that genome wide association studies (GWAS) are more informative.

Our results together with those from previous studies (Todd et al., 2015), thus support the hypothesis that the ADRA2B polymorphism has a different impact on different cognitive tasks,

signaling greater level of cognitive–affective flexibility. This influence was expressed in a positivity bias during WM processing and recognition and in a reduction of avoiding negative information in an auditory task. This ultimately suggested the importance of the noradrenergic system for the management of emotional processes.