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Mark S. Mills
University of Nebraska-Lincoln, mark.mills2@huskers.unl.edu

Olivia Wieda
University of Nebraska–Lincoln

Scott F. Stoltenberg
University of Nebraska-Lincoln, sstoltenberg2@unl.edu

Michael Dodd
University of Nebraska-Lincoln, mdodd2@unl.edu

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Emotion moderates the association between *HTR2A* (rs6313) genotype and antisaccade latency

Mark Mills, Olivia Wieda, Scott F. Stoltenberg, and Michael D. Dodd

Department of Psychology, University of Nebraska–Lincoln

Corresponding author — Mark Mills, University of Nebraska–Lincoln, 238 Burnett Hall, Lincoln, NE, USA 68588; *email* mark.mills2@huskers.unl.edu

Abstract

The serotonin system is heavily involved in cognitive and emotional control processes. Previous work has typically investigated this system's role in control processes separately for cognitive and emotional domains, yet it has become clear the two are linked. The present study, therefore, examined whether variation in a serotonin receptor gene (*HTR2A,* rs6313) moderated effects of emotion on inhibitory control. An emotional antisaccade task was used in which participants looked toward (prosaccade) or away (antisaccade) from a target presented to the left or right of a happy, angry, or neutral face. Overall, antisaccade latencies were slower for rs6313 C allele homozygotes than T allele carriers, with no effect of genotype on prosaccade latencies. Thus, C allele homozygotes showed relatively weak inhibitory control but intact reflexive control. Importantly, the emotional stimulus was either present during target presentation (overlap trials) or absent (gap trials). The gap effect (slowed latency in overlap versus gap trials) in antisaccade trials was larger with angry versus neutral faces in C allele homozygotes. This impairing effect of negative valence on inhibitory control was larger in C allele homozygotes than T allele carriers, suggesting that angry faces disrupted/ competed with the control processes needed to generate an antisaccade to a greater degree in these individuals. The genotype difference in the negative valence effect on antisaccade latency was attenuated when trial N-1 was an antisaccade, indicating top-down regulation of emotional influence. This effect was reduced in C/C versus T/_ individuals, suggesting a weaker capacity to downregulate emotional processing of task-irrelevant stimuli.

Keywords: Serotonin, Antisaccade, Emotion, Inhibitory control

Introduction

There is an increased interest in the interplay between emotion and cognition function (Pessoa 2009; Vuilleumier 2005), along with growing recognition that individual differences in these relations may be relevant to fundamental differences in behavior (Kanske 2012) and risk of psychopathology. In particular, there is growing evidence that individual differences in behavioral inhibitory control (Crosbie et al. 2013) and in sensitivity to emotional stimuli (Anokhin et al. 2010) are at least partially heritable and, therefore, represent promising candidate endophenotypes for genetic investigation. Recently, molecular genetic studies have linked polymorphisms in structural genes for serotonin receptors to individual variation in cognitive (Passetti et al. 2003) and emotional (Fisher et al. 2009, 2011) control processes. Although cognition and emotion exert strong influence on each other, research investigating the relationship between serotonin receptors and cognitive functioning on the one hand, and between serotonin receptors and emotion processing on the other, has developed largely in parallel with little crossover, leaving the role of serotonin receptors on the cognition–emotion interface unclear. The goal of the present study, therefore, was to examine whether genetic variation in a polymorphic region of a candidate serotonin receptor plays a role in the impact of emotional stimuli on inhibitory control.

The 5-hydroxytryptamine (5-HT or serotonin) system has long been implicated in a wide array of cognitive, behavioral, and emotional control processes. A role for 5-HT in cognitive functioning, in particular inhibitory control, is suggested by findings of impulse control failure following reductions in 5-HT transmission. For example, 5-HT levels are reduced in patients with mania (Thakore et al. 1996), alcohol-mediated aggression (Coccaro 1989), and suicidal patients with depression (Linnoila and Virkkunen 1992). Such findings are consistent with the notion that 5-HT mediates behavioral inhibition (Soubrié 1986). Studies investigating the molecular mechanisms of such impairments have implicated variation in 5-HT receptors as key, especially the 2A receptor—a G protein-coupled receptor expressed at high levels in the neocortex (including primary motor, supplementary motor, premotor, parietal, and occipital cortices) and prefrontal cortex, and at intermediate levels in the hippocampus, nucleus accumbens, and the hypothalamus (Dwivedi and Pandey 1998; see Aznar

and Klein 2013, for a review). The 5-HT_{2A} receptor has received considerable attention for its implications in executive functioning and risk of disorder (e.g., Gong et al. 2011; Lane et al. 2008; Wingen et al. 2007). This work suggests that 5-HT, through the 5-HT_{2A} receptor, is involved in regulating aspects of cognitive functioning, including inhibitory control (Passetti et al. 2003).

There is also evidence that 5-HT plays a role in emotional control processes (Cools et al. 2008). A role for 5-HT in the processing of emotional stimuli is evident by the fact that selective serotonin reuptake inhibitors have a positive effect in treating major depression and anxiety disorders (Blier and de Montigny 1999), whereas acute tryptophan depletion increases negative emotion (Van der Veen et al. 2007). Furthermore, reductions in 5-HT neurotransmission have been associated with enhanced processing of negative emotional content (Murphy et al. 2002). Neurophysiological studies have shown that the 5-HT system also modulates the responsiveness of the amygdala and connected medial frontal regions to threat-related content. For example, reductions in 5-HT neurotransmission have been associated with enhanced amygdala activation in response to threat-related stimuli (von dem Hagen et al. 2011). Thus, dysfunction in the 5-HT system is associated with impaired emotion processing. Here, too, the 5-HT_{2A} receptor appears key. Bilateral amygdala damage, for example, has been associated with a decrease in 5-HT_{2A} receptors signaling a loss of the capacity to feel fear or stress (Hurlemann et al. 2009). Importantly, recent work has shown that the level of postsynaptic excitatory 5-HT_{2A} receptor binding and density in the medial prefrontal cortex is inversely correlated with threat-related amygdala activity (Fisher et al. 2009, 2011). Taken together, this work suggests that polymorphisms in its structural gene may play a role in individual differences in the interplay between emotion and inhibitory control.

Among polymorphisms in the structural gene for the 5-HT_{2A} receptor (*HTR2A*, 13q14.2), one that has received considerable attention for its role in both cognitive and emotional control processes is a single nucleotide polymorphism (SNP) at codon 102 (rs6313; either thymine, T, or cytosine, C). It is a synonymous substitution that does not alter amino acid sequence but is associated with differential mRNA and 5-HT_{2A} receptor protein expression (Polesskaya and Sokolov 2002), and is in complete linkage disequilibrium with a promoter polymorphism (rs6311; Smith et al. 2013). Therefore, rs6313

represents a candidate gene polymorphism of interest. The C allele of rs6313 is associated with low gene expression. Homozygosity for the C allele (i.e., C/C genotype) is associated with characteristic features of several psychiatric disorders, in particular, impaired cognitive function (e.g., Becker et al. 2004; Üçok et al. 2007; Vyas et al. 2012). For example, previous work has found that individuals with the C/C genotype make more errors than those with the T/_ genotypes (i.e., T/C or T/T genotypes) on a test of behavioral control (Bjork et al. 2002). Although this work supports the presence of functional genetic variants in the 5-HT_{2A} receptor in patient populations, the role that functional genetic variants in the 5-HT_{2A} receptor play in cognition and risk of disorder within the normal population is unclear. Here, we examine whether rs6313 genotype plays a role in behavioral response inhibition (the ability to suppress actions that are no longer behaviorally relevant or contextually appropriate), as measured via oculomotor response within a modified antisaccade task. To our knowledge, this is the first investigation of antisaccade performance with the rs6313 polymorphism.

The antisaccade task (Hallett 1978) is a widely used measure of oculomotor response inhibition and a key tool for health professionals in testing for frontal lobe dysfunction. In this task, a peripheral onset stimulus is presented to one side of a central fixation stimulus (usually something innocuous like a "+" sign) and participants are cued either to look toward (prosaccade) or away (antisaccade) from it. It is generally assumed that prosaccades are elicited exogenously (reflexively or effortlessly) in response to the peripheral onset, whereas antisaccades are generated endogenously (volitionally or effortful) by actively inhibiting the prosaccade and executing a saccade to the mirror location. Correct performance on antisaccade trials, therefore, is thought to require at least two intact subprocesses: inhibition of a reflexive prosaccade and generation of an effortful antisaccade. As these processes take time to unfold on antisaccade trials and are not required on prosaccade trials (given that prosaccades are elicited exogenously), antisaccade latencies tend to be considerably longer than prosaccade latencies. Furthermore, as a failure to inhibit or cancel the reflexive prosaccade on an antisaccade trial will result in an erroneous saccade toward the peripheral onset, there tend to be more antisaccade errors (i.e., erroneous prosaccade on antisaccade trials) than

prosaccade errors (i.e., erroneous antisaccade on prosaccade trials). A general inhibitory deficit, therefore, would be evident by difficulty performing antisaccades (i.e., slow and/or error prone antisaccades). Accordingly, if the C/C genotype is associated with a general inhibitory deficit, then these individuals should exhibit slower and/or more error prone antisaccades compared with T allele carriers (i.e., T/T or T/C).

To investigate the impact of a distracting (i.e., task-irrelevant) emotional stimulus on oculomotor control processes, the antisaccade task was modified to include either a happy, angry, or neutral facial expression as the central fixation stimulus (as opposed to a "+" sign). Distraction challenges our ability to maintain focus on goal-relevant information, and emotional stimuli are particularly potent distractors that can capture attention and reallocate processing resources (Hansen and Hansen 1988), which can in turn impair performance on measures of cognitive function. Previous work, for example, has shown reduced performance on measures of response inhibition following presentation of task-irrelevant emotional stimuli (Dennis et al. 2008; Kalanthroff et al. 2013; Padmala et al. 2011; Pessoa et al. 2012; Sagaspe et al. 2011; Verbruggen and De Houwer 2007), presumably because emotional stimuli capture attention automatically, interrupting or competing with ongoing activities and leaving fewer resources available for effortful control (Kanske 2012; Pessoa 2009). As a result, performance may be impaired on tasks that do not require the processing of emotional stimuli. For individuals with trait-level impairments in inhibitory control, such as C allele homozygotes, this implies there may be even more resources available to spill over to emotion processing and so even greater emotional interference might be expected relative to those with a T allele. Thus, an inhibitory deficit may also be reflected in a failure to resist disruption or interference from the task-irrelevant emotion stimulus, which would be evident by slower antisaccades when the central fixation stimulus was emotional in nature (happy or angry face) compared with neutral.

In the standard antisaccade task, removing the central fixation point before presentation of the peripheral onset stimulus (gap trials) tends to shorten saccadic latencies relative to leaving it on during onset presentation (overlap trials), a phenomenon referred to as the *gap effect* (Saslow 1967). The gap effect is thought to reflect the tendency to keep the eyes on a currently fixated stimulus, which competes with

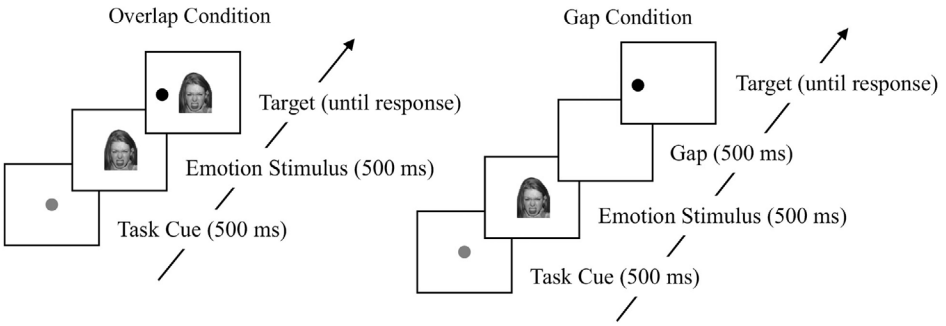

Fig. 1. Example trial sequence for overlap (*left*) and gap (*right*) trials. Every trial started with 500-ms task cue (the *color* which indicated whether a prosaccade or an antisaccade was required), followed immediately by an emotional stimulus that was presented for 500 ms. In overlap trials, the onset target was presented, while the emotional stimulus was still present. In gap trials, the emotional stimulus was removed and a blank screen was presented for 500 ms before target presentation.

the signal to generate a saccade in the overlap condition. If the centrally fixated stimulus is no longer present at the time of onset presentation, then there is no competition and the saccade can be generated more quickly (Fischer and Weber 1993). Accordingly, emotional interference may be especially evident by the presence of a gap effect (shorter latencies on gap versus overlap trials) on antisaccade trials. Support for this idea comes from a previous study in which a larger gap effect was observed for task-irrelevant fearful versus neutral faces (West et al. 2011). On overlap trials, the task-irrelevant stimulus is presented concurrently with the target and therefore may need to be inhibited before an antisaccade can be executed (see Fig. 1). In contrast, on gap trials, the task-irrelevant stimulus is removed prior to target presentation and therefore does not need to be inhibited. Thus, if the C/C genotype is associated with a general inhibitory deficit, then those with that genotype should show a larger antisaccade gap effect than those carrying a T allele, regardless of the content of the task-irrelevant stimulus. However, to the extent that task-irrelevant emotional stimuli are particularly disruptive to ongoing processing, then the genotype difference in the antisaccade gap effect should be selectively larger for emotional versus neutral stimuli.

Methods

Participants

Healthy undergraduates from the University of Nebraska-Lincoln participated in exchange for course credit (N = 116; 64 % female; 86 % white; mean age = 20.23 years). All participants had normal or corrected- to-normal vision, were naïve to the purpose of the study, and were informed of their rights of participation according to the University of Nebraska–Lincoln Institutional Review Board.

Genotyping

Participants donated buccal cells, from which DNA was extracted using the PureGene kit, (Qiagen, Venlo, Netherlands). The rs6313 SNP of the *HTR2A* was genotyped using a StepOnePlus Real-Time PCR system, TaqMan SNP Genotyping Assay (C___3042197_1_; Life Technologies, Carlsbad, CA) per manufacturer's instructions. Allele frequencies were consistent with the HapMap CEU population (C = .61, T = .39), and genotype frequencies (C/C = 39 %, C/T = 44 %, T/T = 17 %) were in Hardy–Weinberg equilibrium (χ^2 = .71, p > .05).

Apparatus

Stimuli were displayed on a Pentium IV PC with VGA monitor (85 Hz) in a dimly lit, sound-attenuated testing room. Participants were seated approximately 44 cm from the monitor. Eye movements were recorded using an SR Research Ltd. EyeLink II system (Mississauga, Ontario, Canada), which has high spatial resolution and a sampling rate of 500 Hz. Thresholds for detecting the onset of saccadic movements were accelerations of 8000°/s^2, velocities of 30°/s, and distances of .5° of visual angle. Movement offset was detected when velocity fell below 30°/s and remained at that level for 10 consecutive samples. Each participant underwent a nine-point calibration procedure followed by a nine-point calibration accuracy test. Calibration was repeated if any point was in error by more than 1° or if the average error for all points was greater than .5°. Viewing was binocular, but only the dominant eye was recorded.

Procedure

Participants completed two blocks of 72 trials. Blocks were identical with the exception of a gap manipulation. In one condition, a central emotional stimulus remained present during target presentation (overlap condition), whereas in the other condition it was removed prior to target presentation (gap condition). An example trial sequence for overlap and gap trials is shown in Fig. 1. A trial began with presentation of a 500-ms task cue at fixation (green or red circle), which indicated whether the current trial required a prosaccade or an antisaccade. An emotional face (angry, happy, or neutral) then replaced the cue for 500 ms, followed by a peripheral onset target appearing 5° or 10° either to the left or right fixation.[1] Participants were instructed to look toward the target (prosaccade) or away from the target (antisaccade) depending on the task cue (green = toward; red = away).

Data analysis

The extent to which saccade (prosaccade or antisaccade), gap (gap or overlap), emotion (angry, happy, or neutral), and genotype (C/C or T/_) predicted task performance was examined—separately for saccade latencies and errors—in a sample of 16,704 saccades, which were nested within 144 trials and within 116 subjects and where trials and subjects were crossed (given that each subject responded to each trial). A saccade was defined as an eye movement with an amplitude > 3°. The latency of the first correct saccade was defined as the interval between target presentation and the initiation of a saccade. An error was defined when the first saccade was directed toward the target (in antisaccade trials) or away from the target (in prosaccade trials). Anticipations (latencies < 100 ms) and late saccades (latencies > 800 ms) were discarded (5.4 %), as were error trials in latency models (15.6 %). After all exclusions, 13,107 saccades remained for analysis of saccade latencies and 15,801 saccades remained for analysis of saccade errors. Data were analyzed via general (latency)

1. Emotional face stimuli were selected from the NimStim set of facial expressions (Tottenham et al. 2009). Model IDs were the following: happy (01F_HA_O), angry (01F_AN_O), neutral (01F_ NE_C).

and generalized (errors) linear mixed models with subjects and trials specified as crossed random effects (Baayen et al. 2008; Hoffman 2014) and by-subject random slopes for within-unit manipulations (Barr et al. 2013).[2]

Results

Errors

Figure 2 shows the mean probability of an error in each gap, genotype, and emotion condition, plotted separately for antisaccades (left panel) and prosaccades (right panel). As expected, there was a significant main effect of saccade, $F(1, 110) = 124.96$, $p < .001$, such that the probability of an error was greater in antisaccade ($M = .20$, $SE = .013$) versus prosaccade ($M = .07$, $SE = .006$) trials. There was also a trend toward a greater probability of error in overlap ($M = .13$, $SE = .009$) versus gap ($M = .11$, $SE = .008$) trials, $F(1, 104) = 3.46$, $p = .067$. No other effects were significant.

2. Latency models were estimated within SAS PROC MIXED using restricted maximum likelihood estimation and Satterthwaite denominator degrees of freedom. The latency model included random intercepts for mean differences between subjects, $-2\Delta LL(1) = 798.0$, $p < .001$, and between trials, $-2\Delta LL(1) = 30.1$, $p < .001$, as well as random slopes for mean differences across subjects in the effects saccade, $-2\Delta LL(2) = 577.7$, $p < .001$, gap, $-2\Delta LL(3) = 130.2$, $p < .001$, and their interaction, $-2\Delta LL(5) = 126.3$, $p < .001$. Given that accuracy is a dichotomous outcome (correct or incorrect saccade), for analysis of errors, a generalized linear function modeling the logit of the probability of an errant saccade was selected. Parameter estimates, therefore, are on a logit scale, which is unbounded and symmetric around zero. A logit of zero means that a saccade was equally likely to be incorrect as correct—i.e., a logit of zero is equivalent to a probability p of .50, where $p = \exp(\text{logit})/(1 + \exp(\text{logit}))$. To facilitate interpretation, we transformed the mean logit of an error in each condition back onto the probability scale for plotting purposes (Fig. 2) using the equation above. Error models were estimated within SAS PROC GLIMMIX using pseudo-maximum likelihood estimation and Satterthwaite denominator degrees of freedom. The model included random intercepts for mean differences between subjects, $-2\Delta LL(1) = 2133.9$, $p < .001$, and trials, $-2\Delta LL(1) = 84.7$, $p < .001$, as well as random slopes for mean differences between subjects in the effects saccade, $-2\Delta LL(2) = 824.1$, $p < .001$, and gap, $-2\Delta LL(3) = 135.4$, $p < .001$.

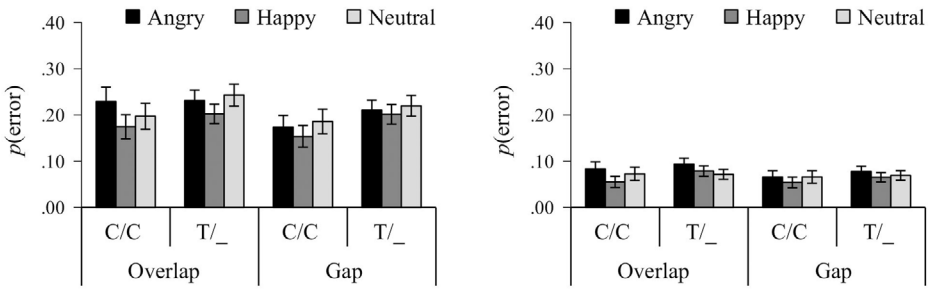

Fig. 2. Mean probability of an error, *p*(error), in each gap (overlap, gap), emotion (angry, happy, neutral), and genotype (C/C, T/_) condition, plotted separately for antisaccades (*left panel*) and prosaccades (*right panel*). *Error bars* represent ±1 standard error.

Latency

Figure 3 shows mean saccade latency in each gap, genotype, and emotion condition, separately for antisaccades (left panel) and prosaccades (right panel). As expected, there was a significant main effect of saccade, $F(1, 109) = 191.06$, $p < .001$, such that saccade latency was longer on antisaccade ($M = 386$, $SE = 4.7$) versus prosaccade trials ($M = 308$, $SE = 4.6$). There was also a significant main effect of gap, $F(1, 111) = 4.95$, $p = .03$, such that saccade latency was shorter on gap ($M = 343$, $SE = 4.0$) versus overlap trials ($M = 351$, $SE = 4.1$). The gap effect (overlap minus gap) was significant in prosaccade trials ($M = 16$, $SE = 3.9$, $t = 4.16$, $p < .001$) and was significantly larger than the gap effect in antisaccade trials ($M = .49$, $SE = 4.1$), evident by a significant saccade by gap interaction, $F(1, 107) = 7.75$, $p < .01$. The gap

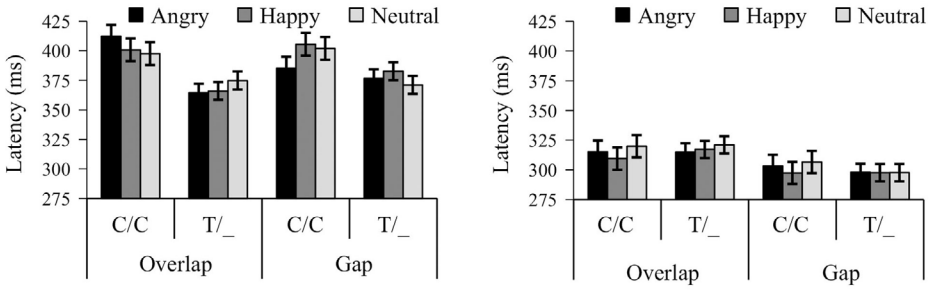

Fig. 3. Mean saccade latency in each gap (overlap, gap), emotion (angry, happy, neutral), and genotype (C/C, T/_) condition, plotted separately for antisaccades (*left panel*) and prosaccades (*right panel*). *Error bars* represent ±1 standard error.

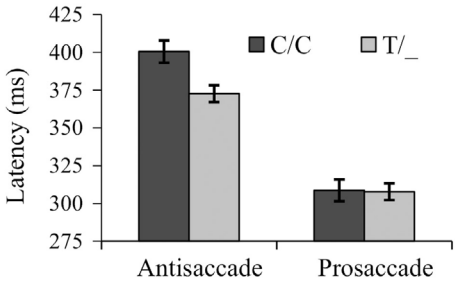

Fig. 4. Mean saccade latency in antisaccade and prosaccade trials for each genotype (C/C and T/_). Mean values are displayed above *each bar*. *Error bars* represent ±1 standard error.

effect in antisaccade trials was not significant (t = .28, p = .78). Regarding effects of genotype, there were two main findings. The first was a significant saccade by genotype interaction, $F(1, 107) = 5.37$, p = .02, indicating that the genotype effect differed between pro- and antisaccades (Fig. 4). Whereas antisaccade latencies were significantly longer in those with C/C versus T/_ genotypes (t = −2.86, p < .01), prosaccade latencies did not differ between genotypes (t = −.09, p = .92). This pattern supports the hypothesized inhibitory deficit in C allele homozygotes. Moreover, as prosaccade latencies did not differ between genotypes, this indicates that C allele homozygotes have an intact reflexive saccade system.

The second was a significant gap by emotion by genotype interaction, $F(2, 140) = 4.89$, p = .01. As can be seen in Fig. 5, the gap effect for angry faces was significantly larger in those with C/C versus T/_ genotypes (M = 17.1, SE = 8.7, t = 2.03, p = .048), suggesting that the inhibitory deficit in C allele homozygotes was exacerbated in the presence of threat. The gap effect did not differ significantly between

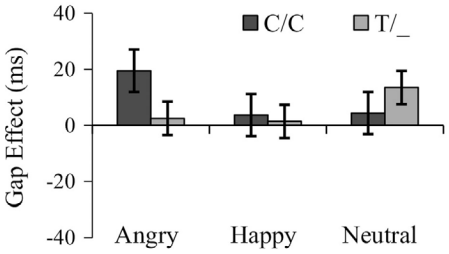

Fig. 5. Mean gap effect (latency in overlap trials minus latency in gap trials) for each emotion (angry, happy, neutral) and genotype (C/C, T/_). *Error bars* represent ±1 standard error.

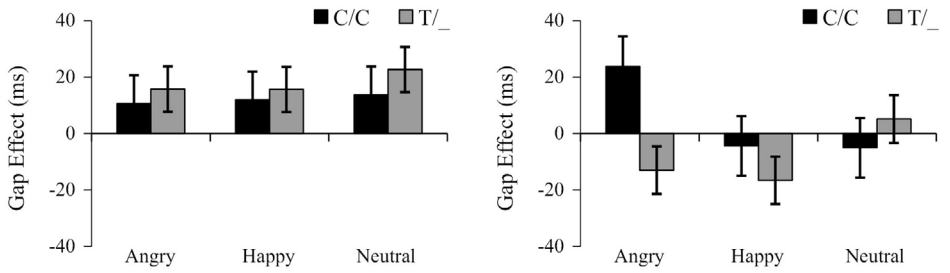

Fig. 6. Mean gap effect (latency in overlap trials minus latency in gap trials) for each emotion (angry, happy, neutral) and genotype (C/C, T/_) in prosaccade (*left panel*) and antisaccade (*right panel*) trials. *Error bars* represent ±1 standard error.

genotypes for happy (M = 2.1, SE = 8.54, t = .24, p = .81) or neutral faces (M = −11.0, SE = 9.3, t = −1.19, p = .24). This pattern was qualified by a significant saccade by gap by emotion by genotype interaction, $F(2, 210) = 3.02$, p = .048, indicating that genotype differences in the effect of emotion on the gap effect differed between antisaccades and prosaccades. The gap by emotion by genotype interaction was significant for antisaccades, $F(2, 172) = 6.01$, $p < .01$, but not prosaccades, $F < 1$. As can be seen in Fig. 6, the genotype difference in the gap effect for angry faces was larger for antisaccades than for prosaccades (M = −45, SE = 16.9, t = −2.69, $p < .01$). The genotype difference in the gap effect for happy faces was also larger for antisaccades than for prosaccades, though the difference was not significant (M = −20, SE = 16.2, t = −1.26, p = .21). In contrast, the genotype difference in the gap effect for neutral faces did not differ at all between antisaccades and prosaccades (M = .97, SE = 15.0, t = .06, p = .95).

To summarize, relative to those with a T allele, C allele homozygotes exhibited intact reflexive control (no effect of genotype on prosaccade latencies) but deficient inhibitory control. This inhibitory deficit in C allele homozygotes was evident by a) longer antisaccade latencies relative to T allele carriers, reflecting generally greater difficulty inhibiting a reflexive prosaccade response and executing an effortful antisaccade, and b) a larger gap effect in antisaccade trials with an angry distractor relative to T allele carriers (i.e., antisaccade performance was slowed for those with the C/C genotype when the angry face remained on the screen to a greater extent than for those carrying a T allele), suggesting that the general inhibitory deficit was exacerbated in the presence of threat-related content.

A number of studies have shown that the disruptive effect of emotional stimuli can be attenuated by top-down processes (Cohen et al. 2011; Kalanthroff et al. 2013; Pessoa et al. 2012; Sagaspe et al. 2011; Verbruggen and De Houwer 2007; see also, Cohen and Henik 2012), leading to the suggestion that activation of the executive network attenuates the emotional system. The idea in these studies is that strong trace representations of emotional stimuli disrupt/ compete with top-down attention mechanisms devoted to goal-directed behavior. Thus, the present genotype difference in the effect of emotion on the gap effect in antisaccade trials may not be driven solely by threat processing (such as enhanced capture by threat and/or reduced ability to disengage from threat in C/C versus T/_ genotypes) but also by reciprocal interactions between activation of top-down inhibitory control and emotion processing. In particular, it is possible that executive influence on emotional processing exists that results from a top-down regulatory mechanism which reduces emotional influence when the task requires conflict resolution processes. We examine this possibility next.

Sequential analysis

The sequential analysis uses only part of the data—trials that fit to a particular sequence (antisaccade trials in the overlap condition). If inhibitory control attenuates activation in amygdala, then we would expect to find enhanced inhibitory control on trials that follow antisaccade trials, reflecting the fact that sequential activation of top-down inhibitory control mechanisms attenuates amygdala activity, resulting is less competition and, consequently, faster antisaccades. Accordingly, this account predicts that emotional influence in a given trial (trial N) should be modulated by activation of the conflict resolution process in the previous trial (trial N-1). Specifically, the difference between trials with angry and neutral faces in trial N should be decreased after an antisaccade in trial N-1 compared with a prosaccade in trial N-1.

Figure 7 shows mean antisaccade latency in trial N as a function of trial N-1 saccade (N-1 antisaccade, N-1 prosaccade) for each genotype in trials with angry or neutral distractors (left panel); also shown is the negativity effect (angry minus neutral) by genotype for trial N-1 anti- and prosaccades (right panel). Figure 8 shows the same, but for

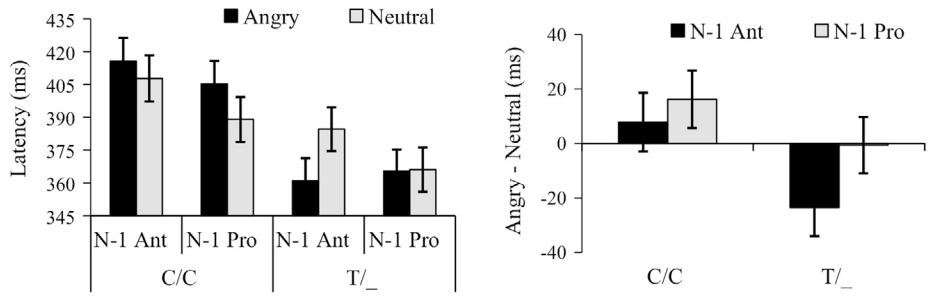

Fig. 7. The *left panel* shows mean antisaccade latency in trial N as a function of trial N-1 saccade (N-1 antisaccade, N-1 prosaccade) for each genotype (C/C, T/_) in angry and neutral distractor trials (*left panel*). The *right panel* shows the mean negativity effect (angry minus neutral) by genotype for trial N-1 anti- and prosaccades. *Error bars* represent ±1 standard error.

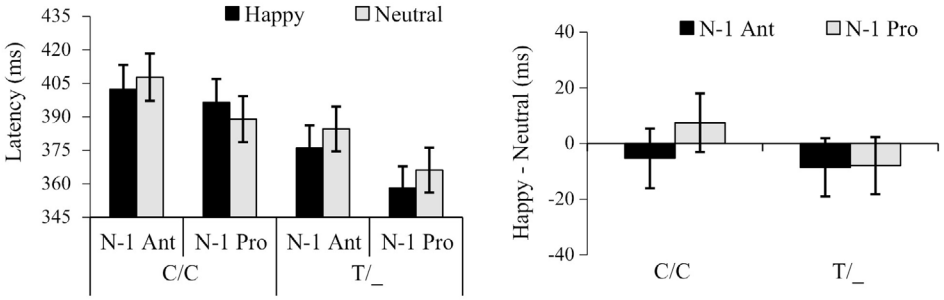

Fig. 8. The *left panel* shows mean antisaccade latency in trial N as a function of trial N-1 saccade (N-1 antisaccade, N-1 prosaccade) for each genotype (C/C, T/_) in happy and neutral distractor trials (*left panel*). The *right panel* shows the mean positivity effect (happy minus neutral) by genotype for trial N-1 anti- and prosaccades. *Error bars* represent ±1 standard error.

happy and neutral distractors. Conflict adaptation is reflected by a reduced (i.e., less positive) effect of emotion in trial N when trial N-1 was an antisaccade (conflict) trial. In those with the C/C genotype, the negative valence effect (angry minus neutral) on antisaccade latencies appears to be reduced (less positive) when trial N-1 was an antisaccade versus prosaccade, suggesting that activation of the executive network attenuated the emotional system. In those with T/_ genotypes, the negative valence effect on antisaccade latencies also appears to be reduced (less positive) when trial N-1 was an antisaccade versus prosaccade. Note that for those with the C/C genotype, antisaccades still appear slower than prosaccades. Also, trial N antisaccades

still appear slower for angry versus neutral faces—the effect is simply attenuated when trial N-1 was also an antisaccade. This means that the sequential effect did not improve executive performance but rather only attenuated the deleterious effect of emotional processing on executive performance.

There was a significant main effect of trial N-1 saccade, $F(1, 90) = 5.22$, $p = .03$, such that antisaccade latency on trial N was faster when trial N-1 was a prosaccade ($M = 379$, $SE = 5.8$) than an antisaccade ($M = 390$, $SE = 5.9$). There was also a significant main effect of genotype, $F(1, 101) = 10.25$, $p = .01$, such that antisaccade latency on trial N was slower in C/C ($M = 402$, $SE = 8.6$) versus T/_ ($M = 367$, $SE = 6.5$) individuals. The emotion by genotype interaction was also significant, $F(2, 75) = 3.7$, $p = .03$. For the C/C genotype, the effect of emotion was marginally significant, $F(2, 73) = 2.95$, $p = .052$. The mean latency of trial N antisaccades was significantly slower for angry ($M = 410$, $SE = 8.4$) than neutral ($M = 397$, $SE = 9.3$) distractors, $t(170) = 1.99$, $p = .05$. The mean latency of trial N antisaccades was also slower for angry than happy ($M = 398$, $SE = 8.7$) distractors, $t(173) = -1.87$, $p = .069$, though not significant. The mean latency of trial N antisaccades did not differ significantly between neutral and happy distractors, $t(165) = .15$, $p = .88$. For T allele carriers, the effect of emotion was significant, $F(2, 76) = 2.18$, $p = .04$. There was a trend toward faster trial N antisaccades with angry ($M = 362$, $SE = 7.1$) versus neutral ($M = 373$, $SE = 7.8$) distractors, $t(71) = -1.64$, $p = .09$. The mean latency of trial N antisaccades was nonsignificantly faster for angry than happy ($M = 366$, $SE = 7.3$) distractors, $t(68) = .40$, $p = .69$. There was a trend toward faster trial N antisaccades with happy versus neutral distractors, $t(67) = -1.71$, $p = .08$. The difference between angry and neutral distractors was significantly different between those with the C/C genotype ($M = 12$, $SE = 9.3$) and those with T/_ genotypes ($M = -11.1$, $SE = 7.5$), $t(74) = 2.43$, $p = .02$. The difference between happy and neutral distractors did not differ significantly between those with the C/C genotype ($M = 1.3$, $SE = 9.2$) and those with T/_ genotypes ($M = -8.2$, $SE = 7.4$), $t(81) = .64$, $p = .52$. The difference between angry and happy distractors was nearly significantly different between those with the C/C genotype ($M = -11.7$, $SE = 9.4$) and those with T/_ genotypes ($M = 2.9$, $SE = 7.4$), $t(80) = 1.95$, $p = .051$.

In sum, sequential analysis indicated that recruitment of executive processes attenuated emotional influence such that emotional

influence in a given trial was diminished following a conflict (antisaccade) response in the previous trial. Moreover, this conflict adaptation effect was smaller in the C/C versus T/_ individuals, suggesting that top-down regulation of emotional processing was more difficult for C allele homozygotes. In any case, this top-down regulation mechanism did not eliminate the impact of angry faces, suggesting that two separable control systems may regulate responses in the present emotional antisaccade task, one reactive (threat) and one self-regulative (effortful control).

Discussion

The present study investigated whether emotional influence on inhibitory control is modulated by the rs6313 polymorphism of the 5-HT_{2A} receptor gene. Inhibitory control was measured with the antisaccade task. Participants were cued to make a saccade either toward (prosaccade) or away from (antisaccade) a peripheral onset stimulus. As expected in this task, antisaccade latencies were longer than prosaccade latencies, reflecting the time needed to inhibit or cancel the reflexive prosaccade response triggered by the peripheral onset and to execute an effortful (anti)saccade in the opposing direction (i.e., inhibitory control). Importantly, we found that rs6313 genotype modulated this effect (Fig. 3), consistent with the hypothesis that this polymorphism is linked to individual differences in inhibitory control. Specifically, antisaccade latencies were significantly longer in C allele homozygotes than in T allele carriers. This finding is congruent with previous findings obtained using other executive tasks (e.g., Becker et al. 2004; Bjork et al. 2002; Üçok et al. 2007; Vyas et al. 2012) and suggests that inhibition of a prosaccade response was impaired or more effortful in C allele homozygotes relative to T allele carriers. At the same time, prosaccade latencies were not significantly affected by rs6313 genotype (Fig. 2). Lack of emotion and genotype effects on prosaccades indicate that the genotype difference in antisaccade latency was not due to individual differences in overall speed of response but rather to individual differences in inhibitory control. This finding reinforces the idea that these two factors (genotype and emotion) impact inhibitory control given that such control is not required to make a prosaccade. Thus, whereas those with the C/C genotype have relatively

weaker effortful behavioral control than those with a T allele, reflexive control appears spared. To our knowledge, this is the first investigation of antisaccade performance with the rs6313 polymorphism.

Emotional influence on inhibitory control was examined by presenting a task-irrelevant emotional stimulus (happy, angry, or neutral facial expression) at central fixation and varying whether the peripheral onset was presented, while the emotional stimulus was present (overlap trials) or just after the emotional stimulus had been removed (gap trials). Saccade execution on overlap trials, therefore, stood to benefit from suppression of emotional distractors, at least to the degree that saccade execution is effortful (i.e., antisaccade trials). This was not the case, however, on gap trials, given that the emotional stimulus is removed prior to target presentation and therefore does not need to be inhibited. Thus, the difference between overlap and gap trials measures the additional time needed to execute a saccade due to emotional interference. We found that latencies in antisaccade trials with angry distractors were prolonged on overlap versus gap trials to a greater extent for individuals with the C/C genotype relative to individuals with T/_ genotypes (Fig. 6). This finding is consistent with the notion that threat-related stimuli capture attention and receive prioritized processing, which draws attention away from executive resources needed for inhibitory control, thereby resulting in impaired inhibitory control. Thus, the genotype difference in the gap effect in antisaccade trials with angry distractors reinforces the presence of an inhibitory deficit in the C allele homozygotes and suggests further that this deficit was exacerbated in the presence of threat-related content.

Relative to neutral faces, greater interference was observed for angry versus happy distractors, which corroborates previous studies showing that positive stimuli elicit less attention than negative stimuli do, thereby producing less interference (Baumeister et al. 2001). A motivational aspect might also account for this finding. The prioritization of the processing of negative stimuli may be driven by the protection of the self, as negative stimuli quickly signal the potential for danger in the environment and prepare the organism to face such danger by interrupting or slowing ongoing behavior and mental processes (Öhman and Mineka 2001). Thus, on overlap trials, angry faces may have “froze” the reflexive prosaccade response which, in turn, speeded antisaccade responses. In contrast, on gap trials, the

angry face was not present to "freeze" the prosaccade response and, consequently, antisaccade responses were not speeded and thus were slower relative to overlap trials. Likewise, it has been suggested that the presence of positive stimuli serves as signals to safety and opportunity and thus facilitates or energizes ongoing motor behavior (Depue and Lenzenweger 2001; Gray 1987; Mills et al. 2014). Thus, motor inhibition may have been facilitated when acting within the context of a negative stimulus (overlap trials), whereas motor execution may have been facilitated when acting within the context of a positive stimulus (overlap trials).

Interestingly, although it might be anticipated with a 500-ms temporal asynchrony separating offset of fixation stimulus and onset of peripheral onset that a gap effect might not be observed, the gap effect in antisaccade trials for T allele carriers was in the opposite direction of what would be expected (Fig. 6). Specifically, antisaccades were faster on overlap than gap trials; however, this was found only with emotional distractors. When the fixation stimulus was a neutral face, T allele carriers did not show a gap effect. This could be indicative of emotional stimuli improving inhibitory control for these individuals. It has been suggested that low-intensity emotional stimuli improve inhibitory control, whereas high-intensity emotional stimuli impair inhibitory control (Pessoa 2009). In this view, low-intensity emotional stimuli improve inhibitory control by recruiting but not completely consuming processing resources (or at least not consuming them to the same degree as high-intensity emotional stimuli), leaving available more resources than would be for neutral stimuli. These leftovers are then available for other processes, such as inhibitory control. As a result, effortful control is strengthened, leading to faster antisaccades in trials with low-intensity emotional stimuli (overlap trials with happy distractors) than without (gap trials). If inhibitory control is deficient to begin with, however, which appears to be the case with C allele homozygotes, then greater resource availability may not make much difference. Thus, C allele homozygotes did not show a gap effect in trials with happy distractors, whereas T allele carriers showed a reversed gap effect. On the flipside, if an individual is sensitive to threat, which also appears to be the case with C allele homozygotes, then even mild threat might consume resources needed for inhibitory control. Thus, C allele homozygotes showed a gap effect in trials with angry distractors, whereas T allele carriers did not.

In addition, we found that activation of executive processes in trial N-1 attenuated emotional influence in trial N such that emotional influence in trial N was diminished following a conflict (antisaccade) response in trial N-1 (Figs. 7 and 8). A number of studies have shown that the disruptive effect of emotional stimuli can be attenuated by top-down processes (Cohen et al. 2011; Kalanthroff et al. 2013; Pessoa et al. 2012; Sagaspe et al. 2011; Verbruggen and De Houwer 2007), leading to the suggestion that activation of the executive network attenuates the emotional system. In support, neuroimaging studies have found decreased activation in brain regions considered to process emotional stimuli. Specifically, executive processes, namely selective attention, have been shown to attenuate activation in brain regions associated with emotional processing, namely the amygdala (Blair et al. 2007; Etkin et al. 2006; Hart et al. 2010; Hariri et al. 2000; Liberzon et al. 2000; Mitchell et al. 2008; Vuilleumier 2005). During conflict the amygdala is modulated by the prefrontal cortex (Ongur and Price 2000), anterior cingulate cortex (Bishop et al. 2004), orbitofrontal cortex (Blair et al. 2007), and frontoparietal regions (Mitchell et al. 2008). These findings suggest that attentional processes can modulate the activation of brain regions that are involved in emotional processing via top-down regulatory brain circuits. If inhibitory control similarly attenuates activation in amygdala, then we would expect to find enhanced inhibitory control on trials that follow the requirement to make an antisaccade, reflecting the fact that sequential activation of top-down inhibitory control mechanisms attenuates amygdala activity, resulting is less competition and, consequently, faster antisaccades.

Accordingly, this account predicts that emotional influence in a given trial (trial N) should be modulated by activation of the conflict resolution process in the previous trial (trial N-1). Specifically, the difference between trials with angry and neutral faces in trial N should be decreased after an antisaccade in trial N-1 compared with a prosaccade in trial N-1. The present sequential analysis supported this prediction. In particular, the recruitment of executive processes attenuated emotional influence such that emotional influence in a given trial was diminished following a conflict (antisaccade) response in the previous trial. Moreover, this conflict adaptation effect was reduced in the C/C versus T/_ genotype, suggesting that top-down regulation of emotional processing was more difficult in C allele homozygotes. Thus, consistent with previous work (Cohen et al. 2011), we found

that executive influence on emotional processing resulting from top-down regulation reduced emotional influence when saccade execution required conflict resolution processes. Importantly, however, this top-down regulation mechanism did not eliminate the impact of angry faces, which implies that two separable control systems may regulate responses in the present emotional antisaccade task, one reactive (threat) and one self-regulative (effortful control).

Previous work implicates a corticolimbic circuit composed of structural and functional connections between the amygdala and regions of the medial prefrontal cortex, including the anterior cingulate cortex, in generating and regulating behavioral and physiological responses to threat-related stimuli (Hariri et al. 2006; Pezawas et al. 2005; Phelps et al. 2004; Quirk et al. 2003). Regions of the medial prefrontal cortex are involved in the integration and subsequent regulation of stimulus-driven amygdala response, partly via glutamatergic projections to populations of GABAergic neurons within the amygdala (Likhtik et al. 2005; Quirk et al. 2003). Importantly, 5-HT_{2A} receptors are instrumental in determining 5-HT modulation of this corticolimbic circuit (Fisher et al. 2011). The anatomical localization of this receptor within prefrontal cortex positions it to mediate effectively the effects of 5-HT signaling on corticolimbic circuit dynamics. Variability in the structure and function of this corticolimbic circuitry have been associated with individual differences in personality measures, reflecting sensitivity to environmental threat and related risk of psychopathology (Buckholtz et al. 2008; Etkin et al. 2004; Pezawas et al. 2005; Shin et al. 2005). Neuroimaging studies in humans have mapped individual differences in amygdala reactivity to biologically salient environmental stimuli (e.g., facial expressions of threat) onto variability in 5-HT signaling within this corticolimbic circuitry (Bigos et al. 2008; Fisher et al. 2009; Hariri et al. 2002; Pezawas et al. 2005). However, the role of specific 5-HT receptor signaling pathways in mediating these effects is not fully understood (Holmes 2008). A strongly reactive amygdala might provide the signal of threat/distress that could easily allow speeded responses to events that stimulate overlapping neural activation. In the case of overlap trials, this may result in rapid engagement of attentional resources to the angry face. The engagement of attention on the angry face should in turn leave fewer resources available to execute an effortful (anti)saccade and result in slowed saccade latencies relative to trials where angry face is removed (gap trials).

Attentional resource theories emphasize the importance of available resources for solving a cognitive conflict. In contrast, attentional breadth theories emphasize the impact of negative information on attentional allocation. These theories claim that negative stimuli narrow attention and hence reduce interference of distracting or irrelevant information (Derryberry and Tucker 1994; van Steenbergen et al. 2011). In the present study, then, negative stimuli may narrow attentional focus and, therefore, make peripheral targets more difficult to detect since they would fall outside the focus of attention. In contrast, positive stimuli may broaden attentional focus and, therefore, make peripheral targets easier to detect since they would fall within the focus of attention.

In sum, the present results demonstrate that relative to T allele carriers, C allele homozygotes exhibited deficient inhibitory control, evident by longer antisaccade latencies (reflecting a general inhibitory control deficit) and by a larger antisaccade gap effect in the presence of threat-related content (reflecting a specific inhibitory control deficit driven by threat). This leads to the notion that a specific 5-HT_{2A} receptor signaling pathway is involved in mediating these effects. In addition, we observed a genotype difference in the effect of emotion on conflict adaptation, suggesting that a separate 5-HT_{2A} receptor signaling pathway is involved in top-down regulation of emotional processing. Thus, the genotype difference in the effect of emotion on the gap effect in antisaccade trials was not driven solely by threat processing (such as enhanced capture by threat and/ or reduced ability to disengage from threat in C/C versus T/_ genotypes) but also by reciprocal interactions between activation of top-down inhibitory control and emotion processing. Accordingly, two separable control systems, one reactive (threat) and one self-regulative (effortful control), are implicated in performance in the present emotional antisaccade task.

The present results should be considered in light of two limitations. First, effects of emotion were investigated with only three different facial expressions. Faces displaying other emotions as well as other types of emotional stimuli should be investigated in future research. Second, the present design did not contain a no-face condition, meaning our baseline comparison for emotional faces was a neutral face. As it is well established that attention is biased toward faces per se regardless of their emotional content, it is unclear whether the present results reflect a pure effect of emotional content or an interaction of emotional and biological significance.

In conclusion, the present study demonstrated that rs6313 genotype is associated with individual differences in inhibitory control more generally, as well as with individual differences in the effect of emotion on inhibitory control. These findings are consistent with evidence that variation in this gene may play a role in risk of schizophrenia, a disorder for which antisaccade performance and emotion regulation are considered to be endophenotypes (Greenwood et al. 2011). In contrast to the relatively consistent findings in the schizophrenia literature, the extent and nature of antisaccade deficits in other psychiatric populations is less clear. Most disorders associated with 5-HT_{2A} receptor functioning are complex genetic disorders, yet known genetic variants account for only a small portion of the estimated disease risk, leaving substantial "missing heritability" (Manolio et al. 2009). A greater understanding of genetic variants with functional consequences in key risk genes marks a crucial step forward in characterizing this missing heritability. Finally, as the results of the current study and others implicate variation at rs6313 on the impact of emotion on inhibitory control, and to some extent on the impact of top-down regulation of emotional processing, future work using neuroimaging may help to further characterize the biological circuits involved. Though provisional, the present findings suggest that at least two potentially separate pathways may be involved, one reflexive and one effortful.

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