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Mini-review

Noradrenergic modulation of emotional memory in aging

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Abstract

Interest in the role of the noradrenergic system in the modulation of emotional memories has recently increased. This study briefly reviews this timely line of research with a specific focus on aging. After having identified surprisingly few studies that investigated emotional memory in older adults from a neurobiological perspective, we found a significant interaction between noradrenergic activity and emotional memory enhancement in older adults. This pattern of data are explained both in terms of a top-down modulation of behavioral processes (e.g., changes in priority and individual goals) and in terms of greater activity of noradrenergic system during aging. Altogether, both behavioral and genetic variations studies (e.g., Alpha 2 B Adrenoceptor genotype) have shown that healthy older adults are able to circumvent or minimize the experience of negative emotions and stabilize or even enhance positive emotional experiences. Future studies are highly warranted to better clarify the relationship between noradrenaline and emotional memories in the aging brain.

Keywords: Noradrenergic System, ADRA2B; Emotional Memory, Aging

1. Introduction

The neurobiological processes mediating emotional arousal and memory are highly adaptive and the noradrenergic hormonal system, activated by dangerous or favorable situations (for a review see, Chamberlain et al., 2006), influences later memory consolidation. Research, in this regard, is abundant both with human (see McGaugh et al., 2002 for a review) and animal studies (e.g., Clayton & Williams, 2000). Noradrenaline (NA), a primary noradrenergic neurotransmitter principally released from neurons originating in the Locus Coeruleus (LC) crucially modulates memory during an emotional event (e.g., van Stegeren, 2008; Tully & Bolshakov, 2010 for a review). These neurons project to several brain regions, among which, the hippocampus and amygdala, key regions known to be involved in emotional memory processes (Hu et al., 2007). Noradrenaline release, in fact, has been shown to be involved in emotion enhancement effects (that is, more efficient processing for emotionally charged events compared to neutral events, e.g., Tully & Bolshakov, 2010) via amygdala activation (e.g., van Stegeren et al., 2005, Mather, 2016). Interestingly, such emotional enhancement in cognition can be experienced to different degrees according to age and genotype differences (e.g., Hamann & Canli, 2004).

In terms of age-related differences, numerous studies have shown that older adults focus on emotional information to a greater extent than their younger counterparts and that they can use emotional information during cognitive processing to compensate for their cognitive deficits and/or to regulate emotion towards the positive pole (for a review, see Mather, 2012). In addition, a recent

line of research in the field of noradrenergic neurotransmission has identified a functional deletion variant of ADRA2B as a specific modulator of emotional response (Todd et al., 2013, 2014; Mammarella et al., 2016). The ADRA2B protein is a subtype of alpha 2-adrenergic receptor (a2-AR) mediating biological effects of endogenous catecholamines, adrenaline and noradrenaline (Belfer et al., 2005).

The aim of the present study is to review findings focusing on the noradrenergic modulation of emotional memory in aging in order to foster new interest in the interaction between noradrenergic, genetic variations and emotional memory in the aging brain. Altogether, findings are consistent with the viable hypothesis that the noradrenergic system is involved in promoting flexible behavior and optimize cognitive functions of older adults in relation to contextual variables and individual goals (see Robertson, 2013).

1.1. Emotional memory in aging

Contrary to the well-established decline in cognitive-processing, recent behavioral research suggests that emotion processing in aging is preserved (see Mather, 2016 for a review). In particular, many studies have found age-related differences linked to the valence of emotional information (Mather and Carstensen, 2005). These studies have shown how older adults remember positive information better (positivity effect) than younger adults and have led many cognitive and social psychology researchers (Charles et al. 2003; Kensinger and Schacter 2008) to focus attention on the features that characterize emotional enhancement effects in general and, in particular, positivity effects. Carstensen and colleagues (e.g., Carstensen and Mikels 2005) explained this emotional advantage in terms of an age-related selectivity towards the pursuit of emotional goals. These authors affirmed that the proximity of the end of an individual's life span generates a cognitive shift towards emotion processing, boosting memory processes for emotional information in general and, in particular, for positively connoted meaningful goal-orientated emotional information.

Although, some researchers have found inconsistent evidence regarding the positivity effect (e.g., Gru¨hn, Smith, & Baltes, 2005), a large corpus of data confirms an emotional enhancement effect in older adults' memory (e.g., Reed, Chan, & Mikels, 2014; Kalenzaga et al., 2016). A neurophysiological explanation of this pattern of data posits that this emotional enhancement effect is due to the fact that age-related changes in regions to be associated with emotion processing including the ventromedial prefrontal cortex (PFC), anterior cingulate gyrus, and temporal pole (Satpute & Lieberman, 2006; Kalisch et al., 2006) are less pronounced compared to other regions involved in cognitive processing. Aging has also been shown to affect amygdala activity in a peculiar manner. In fact, older adults show enhancements in amygdala engagement in response to positive stimuli and reductions in amygdala activity in response to negative stimuli (Mather et al., 2004; Wright et al., 2006).

1.2. Noradrenaline and emotional memories

Evidence for the role of NA in the modulation of emotional memory in aging comes from the convergence of three lines of research. First, the central noradrenergic system is associated with cognitive flexibility (e.g., Aston-Jones & Cohen, 2005; Sara & Bouret, 2012) and with the hypothesis that NA is involved in cognitive reserve (e.g., by disease compensation, disease modification, or a combination of both, see Robertson, 2013; see also Mather & Harley, 2016). In particular, 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). In particular, Aston-Jones & Cohen (2005) clarified the role of LC-NA function in optimizing task performance (exploitation), disengagement from a current task and 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-NA 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 gain rewards or to change a negative stimulus to a positive one. In particular, Bouret & Richmond (2015) showed that the activity of LC neurons reflects both expected reward and action. These explanations may account for the older adults' tendency to prefer positive information in their behavioral and cognitive performance. Mather et al. (2015) showed, in fact, that arousal-induced NA release from the LC biases perception and memory in favor of salient, high priority representations at the expense of lower priority representations. Given that priority depends on a series of bottom-up and top-down mechanisms (e.g., stimulus features and goal-relevant information, e.g. Beck & Kastner, 2009), one can also assume that these high priority representations can be biased in favor of positive information relevant for healthy older adults' wellbeing. For example, numerous eye-tracking studies (e.g. Isaacowitz et al., 2006, 2009) showed that gaze preferences in older adults are biased toward positive and away from negative stimuli. These findings have been interpreted as reflecting older adults' motivation to regulate their emotions and optimize their current feeling state (see also Sara, 2009 for a similar assumption).

Second, genetic variants involved in noradrenergic signaling have been shown to contribute to individual differences in emotional memory. In particular, genetic factors likely mediate the effects of noradrenaline release in the amygdala and a functional deletion polymorphism in the α-2B adrenoceptor gene (ADRA2B) has recently been linked to emotional memory (e.g., Mammarella et al., 2016). ADRA2B deletion results in reduced receptor functionality and this genetic variation leads to potentiation of central noradrenergic transmission, since the receptor's major role is the presynaptic inhibition of NA release. Behaviorally it has been shown that deletion carriers have enhanced memory for emotional material and it was suggested that this effect is due to an emotional

arousal-induced activation of noradrenergic neurotransmission (de Quervain et al., 2007). A series of behavioral studies, in fact, have found that deletion carriers tend to show a general emotional enhancement effect in long-term memory tasks such as free-recall for emotional pictures (de Quervain et al., 2007; Zoladz et al., 2014), recognition for emotional faces (Li et al., 2013) and recognition for emotional scenes (Todd et al., 2014). fMRI data also suggest that deletion carriers exhibit increased neural activity in the amygdala during encoding of emotional pictures (Rasch et al., 2009).

Finally, while some studies (e.g., Shibata et al., 2006; Mei et al., 2015) have suggested an age-related decline in LC neurons and LC is usually the first site exhibiting Alzheimer's disease pathology (Braak et al., 2011), others have shown that noradrenergic system activity increases in older compared to younger adults, both peripherally and in the central nervous system (Featherstone et al., 1987; Lawlor et al., 1995; Supiano et al., 1990). Wang et al. (2013) also demonstrated that concentrations of cerebrospinal fluid NA are higher in older adults than younger ones (Elrod et al., 1997; Raskind et al., 1999). In addition, Seals and Esler (2000) reviewed a series of studies that support the interpretation of increases in total NA spillover as evidence for elevated central sympathetic nervous system activity with human aging. Differently, Matthews et al. (2002) showed that the LC is typically damaged in AD and a significant reduction was seen in the medial temporal cortical noradrenaline concentration in patients with Alzheimer’s disease (see Cristy et al., 2016). Generally speaking, this stronger noradrenergic activity may explain stronger emotion enhancement effects in healthy aging and reduced or null effects of emotion in cognitive processing of Alzheimer’s Dementia patients (e.g., Mammarella et al., 2013).

Although extensive evidence indicates that the noradrenergic system modulates emotional memory in healthy younger adults, to our knowledge the relationship between noradrenaline system and memory modulation in healthy older adults has not been thoroughly examined. A primary goal of the present brief review was to examine whether there are studies supporting an interaction

between noradrenergic response and emotional memory processes in aging and whether genetic variations may be associated to a tentative hypothesis about a noradrenaline contribution to positivity effects in aging.

2. Literature search criteria

We conducted a comprehensive literature search in a variety of electronic databases before the 15th of March 2016 (PubMed, PsychInfo, and Web of Science) to identify relevant studies. Key search words were," "noradrenergic," "noradrenaline (norepinephrine)", "ADRA2B", "emotional memory," "aging," Search was limited to journals published in English and to empirical research. Thus, editorials, letters, and commentaries were not included. In addition, reference lists from the retrieved articles were screened to identify additional papers. Articles were included for review if they met the following criteria:

(1) The review was based on human studies that involved older adults. Participants were both healthy older participants and older adults with cognitive impairments resulting from neurodegenerative diseases, e.g., Alzheimer's disease. Since our review aimed to assess the relationship between the noradrenergic system, aging and emotional memory, only animal studies that could help to clarify this interaction were included: we identified only two studies;

(2) The construct of emotional memory may include a combination of different processes. Provided that emotion was involved (emotion regulation, manipulation of emotional content of stimuli, manipulation of emotional context, mood induction, etc.), all studies were included.

Altogether, we reviewed 7 studies.

2.1. Studies on noradrenergic modulation of emotional memory in aging

Nielson & Jensen (1994) is one of the first studies to focus on the relationship between NA, memory and aging. These researchers tested a group of older adults who were chronically taking beta-receptor antagonist medications to control hypertension. In particular, 20 younger adults, 22

normotensive older adults, 21 older adults taking either calcium-channel blockers or angiotensin-converting enzyme inhibitors to control hypertension and 21 older adults taking beta-blocker antihypertensive medications took part in the study. A moderate level of muscle-tension-induced arousal was elicited by having subjects squeeze a hand dynamometer during encoding and recall of highlighted (salient) words in short 200-word paragraphs. Younger adults, healthy normal older adults and those taking non-beta-blocker medications showed enhanced words recall as a result of the arousal manipulation. However, older adults taking beta-receptor-antagonist medications showed no effect. These findings support the hypothesis that the noradrenergic system is likely to modulate memory for salient emotional information in aging as well.

In another study, Segal et al. (2012) tested 31 healthy older adults (69 ± 2 y), and 23 (71.4 ± 2.4 y) patients with mild cognitive impairment (MCI). This study compared the relationship between exercise-induced noradrenergic activation and memory in MCI patients and healthy age-matched controls. Participants were randomly assigned to either the exercise condition or the sedentary condition and were tested in a two-day session. The first day measured VO2 max (an index of gas exchange) using a stationary bike. On the second day, after a 15-min acclimation period, a baseline saliva sample was taken. Participants subsequently viewed a series of 20 mild emotionally positive pictures but were not informed about a subsequent memory test. A second saliva sample was taken immediately after the study phase. After picture presentation, participants either exercised for 6 min at 70% VO2 max, or rested (sedentary group). Additional saliva samples were taken immediately after exercise or rest, 10 min, 30 min, and 50 min later. One-hour after the exercise, participants were asked to free-recall pictures. Results indicate that post-learning, acute exercise both activates the noradrenergic system similarly in MCI patients and controls and significantly enhances memory in both groups.

These two studies, together with numerous behavioral studies about emotion enhancement effects in aging (e.g., for a review Mather, 2012), suggest that the noradrenergic system is involved

in the emotional memory of older adults and, more interestingly, that it may play a role in the generation of positivity effects in their cognitive processing. The rationale being as follows. First, there are studies illustrating the important contribution of noradrenaline release in the basolateral amygdala during encoding according to the valence of learning conditions (e.g., Young & Williams, 2010; 2013). Second, older adults show greater amygdala activation for positive pictures than for neutral pictures, whereas this pattern does not occur for younger adults (e.g., Mather et al., 2004).

In this regard, Fridman et al. (2011) tested a group of 65 older adults (32 Holocaust survivors, and 33 comparison respondents). Age ranged from 71 to 84 years. Participants were engaged in a social stress task that included both social-evaluative threats (speaking in the presence of a critical audience) and lack of control (an arithmetic task that is impossible to complete within the time constraints). In particular, the Trier Social Stress Test (Kirschbaum et al., 1993) combines social-evaluative threat and an uncontrollable situation, which is consistently associated with a significant cortisol increase in saliva and blood. Participants were asked to convince university experts that their grandchild deserved a scholarship and were given 5 minutes to prepare for their talk without written notes. After the 5-min. speech, participants were asked to serially subtract the number 13 from 2,083 as fast and accurately as possible and that their results would be evaluated by the university experts. Cortisol reactivity to stress was measured three times following the stressful procedure: 20, 30, and 40 min. after the onset of the test. The authors found no difference between Holocaust survivors and participants in the comparison group if they were ADRA2b deletion carriers (as measured by their cortisol reactivity to the task) independently of time sampling. Differently, wildtype ADRA2B carriers showed higher diurnal cortisol levels than participants in the comparison group. This study indicates that the ADRA2B gene moderates traumatic memories of survivors, helping changing the valence of memories from the negative to the positive pole. Older adult deletion carriers somehow showed higher levels of emotion regulation.

In line with this finding, a study Ryff et al. (2004), tested 135 older women (age range: 61-91) screened for biomarkers of wellbeing, among them, NA.

In particular, overnight urinary adrenaline and noradrenaline samples were taken. Wellbeing was measured with a structured self-report 14-item scale based on six dimensions (self-acceptance, purpose in life, personal growth, positive relations with others, environmental mastery, and autonomy). The authors found a positive correlation between NA and an increased sense of autonomy. Given that this component is an index of one's strength to follow personal convictions, the authors highlighted the role that NA may play in regulating stress-related conditions.

It is worth noticing that the study presented in the next paragraph found genetic variations linked to emotional enhancement effects in memory only in healthy aging. In particular, Koutroumani et al. (2013) tested a total of 119 older adults with Alzheimer's disease, 95 with Mild Cognitive Impairment (MCI) and 97 healthy older controls. ADRA2B genotypic frequencies differed significantly among the three groups. More specifically, a high prevalence of deletion carriers was observed in the control group (43.9%), while in AD and MCI groups, deletion carriers were less frequent (27.7% and 29.5% respectively).

Similar results are reported in animal studies. In this regard, Luo et al. (2015) found that NA played a key role in the formation of hippocampal synaptic plasticity and emotional memory in aged rats. The authors used a fear-conditioning test commonly used to study fear-/emotion based learning and memory in rats. In particular, rats were habituated in a training chamber before fear conditioning (habituation). Then, the rats were presented with 6-foot shock pairings (1 s) and moved to another chamber. To assess contextual fear memory, rats were placed into the same conditioning chamber 24 h later and observed for 3 min (test). Contextual memory was assessed by measurement of time spent freezing. Conditioned freezing was defined as immobility, except for respiratory movements. The authors found that the age-related deficit in emotional memory was linked to a decrease in NA level, which impaired the long-term potentiation of the hippocampus

during fear conditioning. In addition, acute administration of NA improved emotional memory in aged rats.

The hypothesis that emotional memory is mediated by NA release in aged animals seems to also be supported by Tanaka (1999) who reported stronger long-term effects of NA release in aged rats compared to younger ones. In particular, this study adopted an immobilization stress condition paradigm, in which rats were stressed by immobilization with a wire mesh for 1hr. The author found that the level of MHPG-S04, a major metabolite of NA in the rat brain, was very high in aged rats even 6 and 24 hrs. after release from immobilization compared to younger rats.

In sum, these findings ragarding older adults, like those with healthy younger adults (e.g., Cahill et al., 1994), point to a strong relationship between NA and emotional memory. However, the peculiar aspect relies on older adults' tendency to amplify this interaction given priority to positively-charged information. In the following concluding section, we discuss potential pitfalls and several emerging approaches.

3. Discussion

Emotional memory enhancements are now a recognized hallmark of healthy cognitive aging (e.g., Mather, 2012). The effect of emotion on memory has been widely associated with the efficiency of the noradrenaline system in the younger adults. Our study aimed to review a series of data that confirmed this relationship in the aging brain as well. We were surprised that, although behavioral emotional memory studies rapidly increased in the last 5 years, the same cannot be said for neurobiological explanations (in terms of noradrenaline system involvement) of these emotion enhancement effects. Recently genetic studies about the role of ADRA2B in emotional memories also pointed to a strong contribution of NA to emotional memories. The few studies that we reviewed suggested a significant relationship between NA and emotional memory in healthy aging,

whereas other studies with cognitively impaired patients showed no such link (e.g., Koutroumani et al., 2013).

This relationship is in line with the hypothesis that regulating emotions requires cognitive control mechanisms to selectively attend and remember positive information (e.g., Mather, 2016).

In particular, as stated in the Introduction, Mather et al. (2015) showed that NA release from the LC influence the stimulus processing priority in a scene. Given that priority depends on a series of perceptually- and conceptually-driven mechanisms (e.g., stimulus features and goal-relevant information, e.g. Beck & Kastner, 2009), one can also assume that, as we age, priority becomes generally biased in favor of positive information. However, only older adults with efficient cognitive processes are more effective at implementing emotional strategies for their wellbeing (e.g., engaging in more conceptually-based elaboration of stimuli towards the positive pole). In fact, Fridman et al. (2011) found that only older ADRA2B deletion carriers were able to somehow change the valence of their negative memories. In addition, high prevalence of deletion carriers has been found in healthy aging (e.g., Koutroumani et al., 2013). In line of new studies that point to the involvement of NA in cognitive-affective flexibility and cognitive reserve (e.g., Robertson, 2013; see also Mather & Harley, 2016), it seems reasonable to assume that NA may play a crucial role in emotion regulation processes in general, and in positivity effects in memory, in particular, in the aging brain.

Although this review draws mainly on NA, research has investigated effects of neurotransmitters on emotional memory of older adults, namely, the dopamine (DA) and serotonin (5-HT) systems. A recent study with younger adults by Todd and colleagues (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 NA, DA and serotonin all contribute to shaping valence effects in the aging brain as well (e.g., Di Rosa et al., 2015).

To conclude, a convergence of perspectives across the behavioral approaches and neuroscience supports the hypothesis that important contributions to the explanation of emotion enhancement effects of cognitive aging are likely to emerge from research that takes into account the neurobiological underpinnings of such effects and, in particular, the role that NA may play during the formation of emotional memories. Although we found few studies and findings may appear inconclusive, we hope that the evidence briefly reviewed here underscores the need for future research in this field.

Conflict of interest

The authors declared no potential conflict of interest regarding publication of this manuscript.

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