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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.

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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 and 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 and 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 and 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 and 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 pos-

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itive 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 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., Grühn et al., 2005), a large corpus of data confirms an emotional enhancement effect in older adults' memory (e.g., Reed et al., 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 and 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 and Cohen, 2005; Sara and 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 and 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 et al., 2013). In particular, Aston-Jones and 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 and 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 and 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 and 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)