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Evidence that baroreflex feedback influences long-term incidental visual memory in men

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Abstract

Sympathetic nervous system (SNS) activity at the time of acquisition is associated with human memory. However, rather than SNS activity per se, it may be afferent baroreflex feedback that is responsible for this effect. A pharmacological design was employed to unload (SNP, sodium nitro-prusside) and load (norepinephrine) baroreceptors. In addition to two placebo periods, epinephrine and esmolol (a peripherally acting β1-blocker) served as control conditions for altered cardiac perception. During drug infusion blood pressure, heart rate, and perception of heartbeat were tested. Twenty-four healthy men were participated. The participants viewed emotional slides while their electromyographic eye blink responses to random noise bursts were measured (affective startle modulation paradigm) to determine potential drug impact on emotional processing. Subjects were not informed that memory testing would take place after 4 weeks. Drugs did not impact startle, thus indicating unbiased emotional processing at the time of acquisition. Norepinephrine had no effect on heartbeat perception, but improved ($p = .002$) recognition memory. SNP ($p = .0001$) increased heartbeat perception but impaired ($p = .038$) recognition memory. Epinephrine, on the other hand, increased heartbeat perception ($p = .0001$) yet did not impair but partially improve memory (effect on high arousing pictures only: $p = .05$). Heartbeat perception in the placebo condition did not correlate with recognition memory (p's $> .5$). We suggest that baroreflex unloading, with subsequent feedback activation of the SNS, impairs long-term incidental visual recognition memory in humans while baroreflex loading enhances it. Further, we propose that these memory effects are neither secondary to cardiac sensations that accompany SNS activation nor to altered emotional picture processing at the time of acquisition.
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1. Introduction

Sympathetic nervous system (SNS) activity influences memory. Blocking SNS activity at the time of stimulus encoding may impair memory (Cahill, Prins, Weber, & McGaugh, 1994; Nielson & Jensen, 1994) while inducing adrenergic arousal during consolidation may improve it (Cahill & Alkire, 2003; Cahill, Gorski, & Le, 2003; Nielson & Jensen, 1994; Nielson, Radtke, & Jensen, 1996). However, an intact brainstem integration center for visceral afferent signals (NTS, Nucleus tractus solitarius) is a prerequisite for this memory improvement (Miyashita & Williams, 2003, 2004; Williams & McGaugh, 1993). This suggests that peripheral sympathetic arousal is transmitted via neural visceral afferents to the NTS to enhance memory. Indeed, stimulation of visceral afferents projecting to the NTS improved memory retention (Clark, Naritoku, Smith, Browning, & Jensen, 1999; Clark et al., 1998).

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Visceral afferent neurotransmission also modifies amygdala functions (Myers & Rinaman, 2002) relevant for memory processes (Miyashita & Williams, 2003). Baroreceptor afferents, too, are visceral afferents, and project to the NTS. They subsequently induce a variety of neurophysiological and neuropsychological effects (Dworkin et al., 1994; Rau & Elbert, 2001). Furthermore, baroreceptor input to the NTS is transmitted to medullar SNS relay and output structures which also project to amygdala neurons involved in memory processes (Roder & Ciriello, 1995), suggesting the potentiality of cardiovascular afferent information to influence memory. However, until now there has been no clear report on whether baroreflex loading and unloading influences memory processes.

One of the difficulties in studying cognitive consequences of baroreflex feedback is that baroreceptor unloading results in SNS activation, which in turn increases cardiac symptoms such as palpitations. But cardiac sensations potentially interfere with the encoding process. Baroreceptor loading has the opposite effect on SNS function, namely a reduction in SNS output (Jonson & Anderson, 1990; Schachinger, Weinbacher, Kiss, Ritz, & Langewitz, 2001). Therefore, comparing baroreceptor loading to unloading may be biased by cardiac sensations. There is no simple way to control for this. However, palpitations may be induced or abolished by peripheral β-adrenergic agonism and antagonism, respectively. Assessing cardiac awareness during either epinephrine or esmolol (a peripheral β1-blocker) infusion periods would then give an indication on whether cardiac sensations have an obscuring effect on the acquisition process.

The affective content of stimulus information plays an important role in memory processes: emotional materials are remembered better. Thus, for the purpose of the current study, validated visual materials of defined valence (pleasant, unpleasant) and arousal (high and low arousing) categories (Lang, Öhman, & Vaitl, 1988) were taken from the International Affective Picture System (IAPS). These stimuli have been used in memory research before (Bradley, Greenwald, Petry, & Lang, 1992; Cahill & Alkire, 2003; Cahill et al., 2003; Nava, Landau, Brody, Linder, & Schachinger, 2004). Theoretically, drugs may interfere with the emotional evaluation during the encoding process and so obscure memory effects. To investigate if such a mechanism is present, affective acoustic startle modulation (Lang, Bradley, & Cuthbert, 1990; Vrana, Spence, & Lang, 1988) was assessed as a non-verbal, biology-based paradigm to describe emotional processing of stimuli at the time of acquisition.

2. Methods

The research protocol was approved by the local ethics committee. All participants signed informed consent. Both the pharmacological design and detailed physiological response data have already been published elsewhere (Schachinger et al., 2001). Twenty-four male volunteers aged from 18 to 35 years participated in the study. All had normal findings in a physical examination, routine blood chemistry, and hematology, as well as standard electrocardiography. Only non-smokers without evidence or history of any illicit drug use were accepted. Participants were asked to refrain from alcohol or caffeine-containing beverages the night before the experiment as well as during the experimental days. All experiments took place in a psychophysiological laboratory. The temperature was 22 °C; the light was dimmed manually during investigations.

2.1. Pharmacological procedures

On the acquisition day, a small venous line for drug infusions was placed in the forearm. The experiment was divided into two parts of 4.5 h duration each, one lasting from 8:30 AM to 1:00 PM, the other from 1:30 to 6:00 PM. During the first part—the 'baroreceptor loading and unloading set'—norepinephrine (peripheral α-adrenergic stimulation, to a lesser extend also β-adrenergic stimulation), sodium nitro-prusside (SNP, vasodilatation), and a control placebo (saline) infusion were administered consecutively. During the second part—the 'β-adrenergic set'—further placebo, epinephrine (peripheral β-adrenergic stimulation, to a lesser extend also α-adrenergic stimulation), and esmolol hydrochloride (β1-blockade) were given. Following a balanced cross-over design, half of the subjects started with the 'baroreceptor set' and half with the 'β-adrenergic,' respectively. Within each set the succession of drug periods was such that for six consecutive subjects each infusion period was equally often the first, second, and third intervention. Thus, within each set potential sequence effects were counterbalanced. Each infusion period lasted 90 min with the first 10–15 min being used to titrate doses so that for every individual a ±15% change of blood pressure and/or heart rate was achieved. Once defined, the infusion dosages (norepinephrine: $64 \pm 4\,\mathrm{ng\,kg^{-1}\,min^{-1}}$; SNP: $77 \pm 4\,\mu\mathrm{g\,min^{-1}}$; epinephrine: $61 \pm 3\,\mathrm{ng\,kg^{-1}\,min^{-1}}$; esmolol: $169 \pm 9.4\,\mu\mathrm{g\,kg^{-1}\,min^{-1}}$) were kept constant. The infusion was followed by a 10–30 min washout period.

2.2. Visual memory, acquisition, and testing

Six sets of pictures were presented, each containing 54 slides with standardized valence and arousal ratings (Lang et al., 1988). During each infusion period a different set of slides was used, so that each subject saw each set of pictures only once. Across subjects, each set of pictures was shown equally often during each infusion period. Slides were presented for 6 s, with 4 s interslide

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