

Brief communication

Facilitation of learning by social-emotional feedback in humans is beta-noradrenergic-dependent

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ABSTRACT

Adaptive behavior in dynamic environments critically depends on the ability to learn rapidly and flexibly from the outcomes of prior choices. In social environments, facial expressions of emotion often serve as performance feedback and thereby guide declarative learning. Abundant evidence implicates beta-noradrenergic signaling in the modulatory influence of emotion on declarative learning. It is currently unclear whether a similar mechanism also mediates a guidance of declarative learning by social-emotional feedback administered in the form of facial expressions. We therefore conducted a double-blind randomized placebo-controlled trial to test the effects of a 40-mg single oral dose of the non-specific beta-noradrenergic antagonist propranolol in a behavioral task that required gradual declarative learning of item–category associations from either social-emotional (happy vs. angry faces) or nonsocial (green vs. red color signals) trial-by-trial feedback. As predicted on the basis of our previous experiments, learning from social-emotional feedback was more effective than learning from nonsocial feedback in placebo-treated subjects. This advantage of social-emotional over nonsocial feedback was abolished by propranolol treatment. Propranolol had no effect on learning during the nonsocial feedback condition. Our findings suggest that a facilitation of declarative learning by social-emotional feedback critically involves signaling via beta-noradrenergic receptors.

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1. Introduction

Converging evidence from behavioral-pharmacological, neuropsychological, and functional MRI (fMRI) studies shows that enhanced declarative (explicit) learning of emotional material in humans is both amygdala- and β -noradrenergic-dependent (Cahill, Babinsky, Markowitsch, & McGaugh, 1995; Cahill, Prins, Weber, & McGaugh, 1994; Strange & Dolan, 2004; Strange, Hurlemann, & Dolan, 2003; van Stegeren et al., 2005). However, one of the key foundations for successful learning is the enhancement of learning of neutral material by social-emotional feedback provided during social interactions with other individuals (Dashiell, 1930; Gates & Rissland, 1923).

The most prevalent form of social-emotional feedback is the human face, and substantial evidence indicates that both positive

and negative facial expressions of emotion are important for adapting performance either in terms of a continuation or an adjustment of the current behavior (Blair, 2003). The tremendous ecological relevance of social-emotional feedback in declarative learning is best illustrated in social referencing, i.e. the ability of a child to use the mother's facial expressions of emotion to navigate through and acquire declarative (and nondeclarative) knowledge about the world (Frith & Frith, 2007). A central question is therefore whether the same amygdala- and β -noradrenergic-dependent mechanisms involved in a declarative memory enhancement for emotional stimuli also mediate the beneficial influence of social-emotional reinforcement on encoding of neutral stimuli.

In a recent neuropsychological experiment, we used a social-emotional (happy and angry faces) vs. nonsocial (green and red circles) reinforcement learning paradigm to show that social-emotional feedback in both male and female healthy human subjects significantly enhanced performance (Hurlemann et al., 2010a). Furthermore, in two monozygotic twin patients with selective bilateral amygdala calcification damage due to congenital Urbach–Wiethe disease this social-emotional feedback effect on declarative learning was absent but they were unimpaired compared with healthy controls when nonsocial feedback was provided

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(Hurlemann et al., 2010a). We have also shown in a double-blind randomized placebo-controlled fMRI study that treatment with a 40-mg single oral dose of the nonspecific β -noradrenergic antagonist propranolol significantly reduces basolateral amygdala (BLA) responses to both neutral and emotional faces (Hurlemann et al., 2010b). In the present double-blind randomized placebo-controlled trial, we therefore combined the same reinforcement learning paradigm with the administration of a 40-mg single oral dose of propranolol to test whether or not the amygdala-dependent facilitation of declarative learning by social-emotional feedback requires signaling via β -noradrenergic receptors. We hypothesized that β -noradrenergic receptor blockade with propranolol would specifically abolish an augmentation of learning by social-emotional feedback, while leaving unaffected the ability to learn from nonsocial feedback.

2. Methods

2.1. Participants

Thirty-two healthy right-handed adults ($n=16$ females, mean \pm SD age 23.8 ± 1.1 years; $n=16$ males, mean \pm SD age 24.1 ± 2.3 years) volunteered after giving written, informed consent. The study had full ethical approval and was carried out in compliance with the latest revision of the Declaration of Helsinki. Subjects were determined to be free of current or past physical (including respiratory or allergic illness), neurological (including daltonism) or psychiatric disorders (including alcohol, nicotine or drug abuse) by medical history and diagnoses according to the Structured Clinical Interviews for DSM-IV axis I disorders (SCID-I) and axis II disorders (SCID-II). Volunteers were naive to prescription-strength psychoactive medication (including propranolol) and had not taken any over-the-counter psychoactive medication in the past 4 weeks. Neuropsychological screening included the MWT-B (Mehrfachwahl-Wortschatz-Intelligenztest) (Lehrl, 1995) to estimate verbal IQ based on lexical decisions, the RAVLT (Rey Auditory Verbal Learning Test) (German adaptation by Helmstaedter, Lendt, & Lux, 2001; Rey, 1941) to assess verbal learning and memory, and the TMT (Trail Making Test) (Raitan, 1958) to examine motor speed and visual attention. Facial emotion recognition was assessed with the FEEST (Facial Expressions of Emotions: Stimuli and Test) (Young, Perret, Calder, Sprengelmeyer, & Ekman, 2002). Two-sample t -tests confirmed no significant baseline (pretreatment) between-group difference in any measure (all p -values > 0.05 ; Table 1).

2.2. Experimental design

The rationale of this study was to show the β -noradrenergic dependency of a social-emotional facilitation of feedback-guided learning in a double-blind ran-

Table 1

Listed are the demographic and neuropsychological characteristics of the placebo- and propranolol-treated groups. Two-sample t -tests showed no significant baseline (pretreatment) between-group difference in any measure (all p -values > 0.05).

Characteristic	Placebo ($n=16$) raw score (SD)	Propranolol ($n=16$) raw score (SD)	p -Value
RAVLT			
Trials 1–5 ^a	61.31 (6.15)	62.88 (6.96)	0.506
Trial 5 ^b	14.06 (1.00)	14.44 (0.89)	0.271
Trial 6 retention ^b	12.81 (1.97)	13.38 (1.89)	0.417
Trial 7 delayed recall ^b	13.50 (1.51)	13.81 (1.52)	0.563
DST ^c	21.69 (3.65)	21.00 (3.61)	0.596
MWT-B ^d	30.31 (3.34)	30.19 (3.76)	0.922
FEEST			
Happy ^e	7.94 (0.25)	7.88 (0.34)	0.559
Sad ^e	6.06 (0.93)	6.31 (0.70)	0.398
Disgust ^e	3.81 (1.64)	4.00 (1.59)	0.745
Fear ^e	5.50 (1.63)	5.88 (1.20)	0.465
Anger ^e	7.13 (1.02)	6.88 (1.47)	0.521
Surprise ^e	6.81 (1.17)	6.56 (1.09)	0.537

RAVLT, Rey Auditory Verbal Learning Test (Rey, 1941; Helmstaedter et al., 2001); DST, Digit Span Test (Tewes, 1991; Wechsler, 1981); MWT-B, verbal IQ test (Lehrl, 1995); FEEST, Facial Expressions of Emotion: Stimuli and Tests (Young et al., 2002).

^a Maximum possible score 75.

^b Maximum possible score 15.

^c Maximum possible score of sum 28.

^d Maximum possible score 37; raw score 30 is IQ 107.

^e Maximum possible score 9.

domized placebo-controlled parallel-group experimental design. In view of the pharmacokinetics of propranolol (time to peak plasma concentration, 1–2 h; elimination half-life, 3–4 h), subjects received one pill containing either verum or a lactose placebo 90 min prior to testing. We administered a 40-mg single oral dose of propranolol in line with previous studies where this dose was found to alter amygdala responses to facial expressions (Hurlemann et al., 2010b). Blood pressure (BP) was measured at the time of verum/placebo administration, and plasma samples and BP were taken immediately before testing. Consistent with our previous studies, propranolol produced trend-to-significant decreases in systolic and diastolic BP (Hurlemann et al., 2005, 2010b). Interindividual variation in the degree of first-pass metabolism contributes to the differences in propranolol plasma levels after oral administration of equivalent doses (Wood et al., 1978). Consequently, we determined individual propranolol plasma levels in each subject by high-performance liquid chromatography (HPLC) (for a detailed synopsis of analytical procedures see Hurlemann et al., 2005), and mean \pm SEM plasma concentrations were 44.9 ± 9.29 μ g/L.

2.3. Feedback-guided learning task

We used the same feedback-guided learning task as previously described (Hurlemann et al., 2010a). This task required subjects to make push-button responses to judge the category membership 'A' or 'B' of 3-digit numerical items repeatedly presented on a computer screen, with visual feedback immediately following each item-category judgment (Fig. 1A). The letters 'A' and 'B' flanked either a female or a male face in social trials and a black circle in nonsocial trials. Depending on whether a particular item-category judgment was right or wrong, facial displays changed from neutral to happy for correct responses or from neutral to angry for incorrect responses, whereas black circles changed to green or to red color, respectively. In the first trial, subjects had no knowledge of the category membership and responded by guessing, while social-emotional or nonsocial feedback served to enhance performance over subsequent trials. In total, subjects completed 4 blocks, with 8 trials (including 4 items of each category) presented over 6 cycles during each of these blocks, resulting in 192 trials over the entire paradigm. Within each cycle, trials were presented in random order. The order of blocks was alternated, with the first being social in half of the subjects and nonsocial in the other half. Social and nonsocial trials were identical in all aspects of spatial configuration and timing, with a trial duration of 3 s (stimulus-response duration, 2 s; feedback duration, 1 s) and a jittered intertrial interval of 5.5 s (3–8 s). To avoid simple visuomotor learning, 'A' and 'B' changed position on the screen. Subjects were informed that there was no underlying rule defining which item belonged to category 'A' or 'B'. Once assigned, category membership remained constant. This paradigm thus incorporates a condition in which facilitative effects through social-emotional feedback have been observed: reinforcing (encouraging vs. discouraging) feedback from others (Dashiell, 1930; Gates & Rissland, 1923) using changes in the observer's facial expression towards either rewarding (smiling) or punishing (angry) to guide judgments in subsequent trials. This design is consistent with current concepts that positive facial emotion increases the probability of a particular behavior, whereas negative facial emotion decreases it on future occasions (Blair, 2003). Nonsocial trials lacked this specific social-emotional input and thus served as a control. Stimulus delivery and response recording were carried out using Presentation version 14.3 (Neurobehavioral Systems Inc., Albany, CA, USA).

2.4. Statistical analysis

Descriptive data are presented as means \pm SEM. For statistical analysis, all data were initially examined using the Shapiro–Wilk procedure for possible deviations from normality of distribution, and Mauchly's test for the assumption of sphericity. To test the effects of repetition, feedback, and drug treatment on task performance, parametric analyses of variance (ANOVAs) for repeated measures, with Greenhouse–Geisser correction for deviations from sphericity, were applied. Since several deviations from normality were present, nonparametric analyses were also calculated (Brunner & Puri, 2001). For the interpretation of statistical results, we applied Fisher's p -value as a continuous measure for the strength of evidence against the Null hypothesis, supplemented by reports on the partial η^2 size of an effect-estimator. Thus, we avoided using the procedure of null hypothesis significance testing (NHST), which has been criticized for its theoretical inconsistency and incompatibility with concepts of crucial importance such as effect size or test power (Gigerenzer, 2004). Statistical analyses were performed with the software packages PASW 18.0 (SPSS Inc., Chicago, IL, USA) and R 2.9.2 (R Development Core Team, Vienna, Austria).

3. Results

3.1. Drug effects on learning from social-emotional feedback

A condition (social-emotional vs. nonsocial feedback) \times cycles (trials 1–6) repeated measures ANOVA (Table 2 and Fig. 1B) restricted to the placebo group yielded main effects of condition

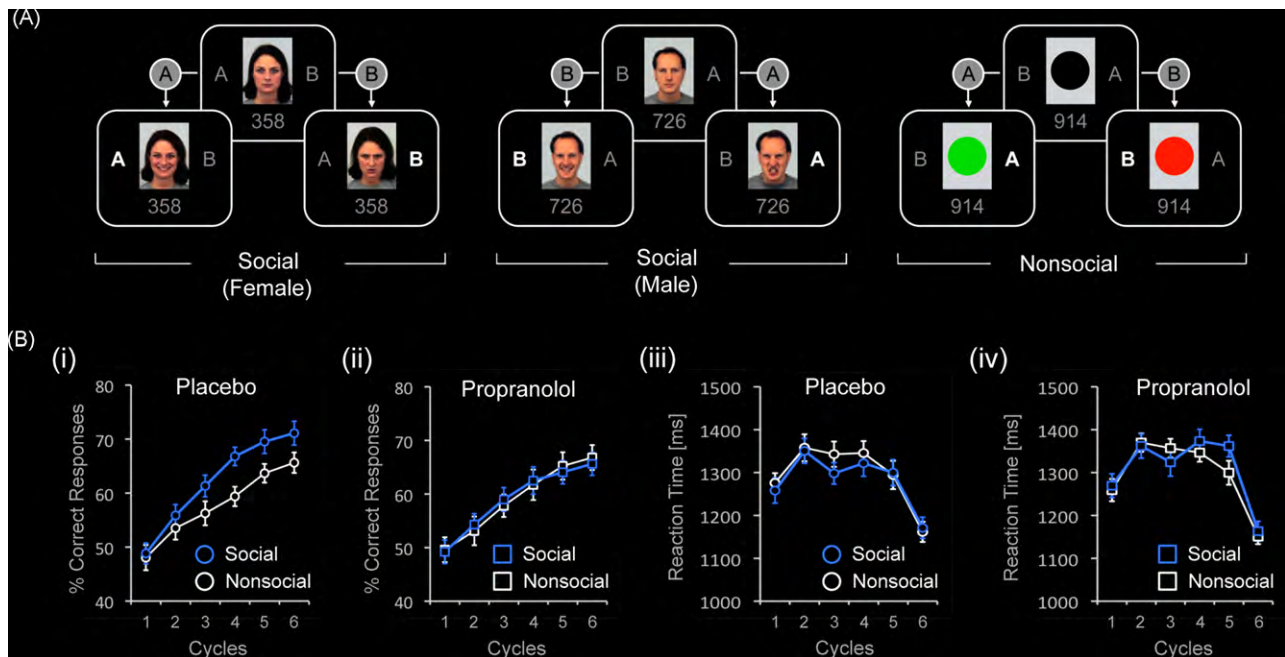


Fig. 1. Feedback-guided learning task. (A) Letters 'A' and 'B' flanked either a female or a male facial display in social trials and a black circle in nonsocial trials. Subjects judged whether 3-digit numerical items presented repeatedly on a computer screen belonged to either category 'A' or 'B', with visual feedback immediately following each judgment. Neutral faces changed to happy for correct responses or to angry for incorrect responses in the social-emotional feedback condition, whereas black circles changed to green for correct responses or to red for incorrect responses in the nonsocial feedback condition. (B) Task performance. (i) Placebo-treated subjects learned better under conditions of social-emotional reinforcement than nonsocial reinforcement. (ii) This social-emotional reinforcement advantage was absent in the propranolol group. (iii) There was no reaction time difference between the social-emotional and the nonsocial feedback condition in the placebo group. (iv) No such difference occurred in the propranolol group either.

($F_{(1,15)} = 5.597$; $p = 0.032$; $\eta^2 = 0.272$) and cycles ($F_{(5,75)} = 32.583$; $p < 0.001$; $\eta^2 = 0.685$), i.e. placebo-treated subjects learned better under conditions of social-emotional reinforcement than nonsocial reinforcement. In contrast, a condition \times cycles repeated measures ANOVA restricted to the propranolol group revealed a main effect of cycles ($F_{(5,75)} = 17.871$; $p < 0.001$; $\eta^2 = 0.544$) but no effect of condition ($F_{(1,15)} = .002$; $p = 0.964$; $\eta^2 < 0.001$), indicating that there was no social-emotional reinforcement advantage on learning following propranolol treatment.

The same analyses performed with the reaction time data (Table 2 and Fig. 1B) yielded a main effect of cycle for both placebo and propranolol treatment (placebo: $F_{(5,75)} = 32.583$; $p < 0.001$; $\eta^2 = 0.685$; propranolol: $F_{(5,75)} = 30.809$; $p < 0.001$; $\eta^2 = 0.673$). After an initial increase from the first to the second cycle (i.e. from guessing to the first retrieval trial), reaction time progressively decreased. Statistical analyses revealed no interaction between social-emotional feedback and cycle and no main effect of social-emotional feedback on reaction times (all p -values > 0.1 ; all

$\eta^2 < 0.15$), indicating that social-emotional reinforcement had no effect on reaction times in both placebo- and propranolol-treated groups. The results of nonparametric and parametric tests closely resembled each other, indicating that the results of the parametric analyses were not biased by deviations from normality.

3.2. Drug effects on learning from nonsocial feedback

To exclude a potential influence of propranolol on learning from nonsocial feedback, we calculated two separate repeated measures ANOVAs with the between-subjects factor group (propranolol vs. placebo) and the within-subjects factor cycles. The analyses yielded a main effect of cycle for both performance accuracy ($F_{(5,150)} = 19.659$; $p < 0.001$; $\eta^2 = 0.396$) and reaction time ($F_{(5,150)} = 30.473$; $p < 0.001$; $\eta^2 = 0.504$), but no effect of treatment and no cycle \times treatment interaction effect (all p -values > 0.1 ; all $\eta^2 < 0.15$), confirming that both learning performance and reaction times were not altered after propranolol treatment. These

Table 2
Results of the parametric statistical analyses. Condition (social-emotional vs. nonsocial feedback) \times cycles (trials 1–6) repeated measures ANOVAs were calculated separately for the placebo- and propranolol-treated groups to determine drug effects on task accuracy and reaction times. Reported values are Greenhouse–Geisser corrected.

Treatment	Variable	Effect	F	Significance (p -value)	Effect size (η^2)
Placebo	Accuracy	Cycle	32.58	<0.001	0.685
		Feedback	5.597	0.032	0.272
		Feedback \times cycle	1.186	0.326	0.073
	Reaction time	Cycle	32.656	<0.001	0.685
		Feedback	0.323	0.578	0.021
		Feedback \times cycle	0.561	0.670	0.036
Propranolol	Accuracy	Cycle	17.871	<0.001	0.54
		Feedback	0.002	0.964	<0.001
		Feedback \times cycle	0.115	0.989	0.008
	Reaction time	Cycle	30.809	<0.001	0.673
		Feedback	0.387	0.543	0.025
		Feedback \times cycle	2.120	0.102	0.124

results argue against a potential impact of drug treatment on vigilance, attention or learning capacity per se. Thus, propranolol treatment specifically abolished an augmentation of learning by social-emotional feedback, while leaving intact the ability to learn from nonsocial feedback.

4. Discussion

These results confirm our previous findings that receipt of social-emotional feedback during a declarative learning task augments performance compared with nonsocial feedback (Hurlemann et al., 2010a) and show for the first time that this social-emotional feedback facilitation is β -noradrenergic-dependent. Previous experimental approaches have demonstrated the β -noradrenergic dependency of emotional declarative learning (Cahill et al., 1994; Strange & Dolan, 2004; Strange et al., 2003; van Stegeren et al., 2005) where it is the emotional value of items that enhances their subsequent remembering. Here we have extended this to include the social-emotional value of feedback in enhancing memory for items with no intrinsic social-emotional value per se. Importantly, we have shown that this β -noradrenergic effect is specific for the learning component that is sensitive to social-emotional feedback, since learning under conditions of nonsocial feedback is unaltered.

Although propranolol treatment can produce both peripheral and central effects which might affect declarative learning through nonspecific impairments in attention or vigilance, there was no evidence for altered reaction times or response misses following propranolol treatment. Our findings indicate a functional dissociation in the role of noradrenaline (norepinephrine) via β -noradrenergic receptors, in that it enables a specific augmentation of declarative learning by social-emotional feedback, but appears less critical for mediating the modulatory effects of performance feedback on declarative learning in general.

We have previously shown that nonsocial feedback-guided declarative learning robustly engages the hippocampus, and that both behavioral performance and related hippocampal activity are facilitated by a 250-mg single oral dose of D-cylcoserine, a co-agonist of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors (Onur et al., in press). NMDA receptor-dependent long-term potentiation (LTP) is the leading synaptic model of associative learning in the hippocampus. It is possible therefore that social-emotional feedback effects on declarative learning are promoted via a neural pathway which similarly facilitates the induction of hippocampal LTP, most likely by involving a β -noradrenergic- and BLA-dependent mechanism (Akirav & Richter-Levin, 2002; Buffalari & Grace, 2007; Frey, Bergado-Rosado, Seidenbecher, Pape, & Frey, 2001; Ikegaya, Nakanishi, Saito, & Abe, 1997; Ikegaya, Saito, & Abe, 1994). In support of this we have previously demonstrated that two monozygotic twin patients with congenital Urbach–Wiethe disease and selective bilateral amygdala calcification damage show no enhancement of learning by social-emotional feedback on the same task (Hurlemann et al., 2010a), and that propranolol significantly attenuates the BLA response to both neutral and emotional faces (Hurlemann et al., 2010b). Given this empirical background, we suggest that without a sufficient β -noradrenergic activation in response to facial feedback a BLA-induced facilitation of hippocampal synaptic plasticity is absent. It thus appears likely that the same amygdala- and β -noradrenergic-dependent mechanism involved in a declarative memory enhancement for emotional stimuli (Cahill et al., 1994, 1995; Strange & Dolan, 2004; Strange et al., 2003; van Stegeren et al., 2005) also mediates the influence of social-emotional feedback on encoding of neutral stimuli.

The mechanism discussed above might be particularly impaired in Alzheimer's disease (AD), which is characterized by a profound degeneration of cholinergic and noradrenergic projections (Lyness,

Zarow, & Chui, 2003). While current perspectives on the underlying pathophysiology of AD emphasize cholinergic deficits as central to the pathognomonic decline of declarative learning and memory, noradrenergic deficits and a putative lack of social-emotional enhancement of declarative learning and memory may also be relevant for the clinical presentation of AD, and patients with AD may therefore benefit if placed on a combination of cholinergic and noradrenergic therapy. It remains to future clinical studies to prove these hypotheses.

Conflicts of interest

The authors report no biomedical financial interests or potential conflicts of interest.

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