

The Link between Facial Feedback and Neural Activity within Central Circuitries of Emotion—New Insights from Botulinum Toxin–Induced Denervation of Frown Muscles

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Afferent feedback from muscles and skin has been suggested to influence our emotions during the control of facial expressions. Recent imaging studies have shown that imitation of facial expressions is associated with activation in limbic regions such as the amygdala. Yet, the physiological interaction between this limbic activation and facial feedback remains unclear. To study if facial feedback effects on limbic brain responses during intentional imitation of facial expressions, we applied botulinum toxin (BTX)–induced denervation of frown muscles in combination with functional magnetic resonance imaging as a reversible lesion model to minimize the occurrence of afferent muscular and cutaneous input. We show that, during imitation of angry facial expressions, reduced feedback due to BTX treatment attenuates activation of the left amygdala and its functional coupling with brain stem regions implicated in autonomic manifestations of emotional states. These findings demonstrate that facial feedback modulates neural activity within central circuitries of emotion during intentional imitation of facial expressions. Given that people tend to mimic the emotional expressions of others, this could provide a potential physiological basis for the social transfer of emotion.

Keywords: amygdala, botulinum toxin, emotion, facial feedback, fMRI, imitation

Introduction

The “facial feedback hypothesis” suggests that the control of facial expression produces parallel effects on subjective feelings. This idea dates back to Darwin’s (1896, p. 365) contention that expression intensifies emotion, whereas suppression softens it. It is also explicit in the influential emotion theory of William James (1890) who did not only attribute an essential role to visceral and cardiovascular feedback as determinants of emotion but also to cutaneous and muscular afferents. The facial feedback hypothesis has received support by findings showing that amplification of facial expressiveness is correlated with an increase, inhibition with a decrease in autonomic arousal, and self-reported emotional experience (Adelmann and Zajonc 1989).

This notion is in line with recent studies showing that volitional imitation of facial expressions is associated with neural activation in limbic regions such as the amygdala (Carr et al. 2003; Wild et al. 2003; Dapretto et al. 2006; Lee et al. 2006) which has strong reciprocal connections to the hypothalamus and brain stem regions involved in autonomic control (LeDoux 2000). However, the physiological interaction between this limbic brain activation and facial feedback remains unclear. As yet, it can only be speculated that it is the feedback from facial muscles and skin during imitation which modulates activation of the amygdala and its coupling with neural networks implicated in autonomic manifestations of emotional states.

We tested this hypothesis by investigating the neural correlates of intentional facial mimicry after peripheral denervation of emotionally expressive face muscles. To this purpose, we studied with functional magnetic resonance imaging (fMRI) the brain responses of healthy volunteers during imitation and observation of angry and sad facial expressions either before (control group) or 2 weeks after localized botulinum toxin (BTX) injections of the corrugator supercilii (frown) muscle (BTX group). The corrugator supercilii pulls the medial parts of the eyebrows together and down which is a prototypical action during negative facial expressions such as anger (Jancke 1996) and sadness (Brown and Schwartz 1980). The BTX treatment induces a temporary muscle denervation by blocking the release of acetylcholine at the neuromuscular junction (Hambleton 1992) and consequently reduces afferent muscular and cutaneous input from the injected area. This provides an ideal reversible lesion model to investigate the effects of facial feedback on brain activation. Based on our hypotheses, we focused our analyses on the modulation of amygdala activation and its functional coupling with brain stem areas involved in the regulation of autonomic responses.

Materials and Methods

A more detailed description of experimental design and methods is provided as Supplementary Information.

Subjects and BTX Treatment

Participants (38 females) gave written informed consent, and the study protocol was approved by the ethics board of the 'Klinikum rechts der Isar, Technische Universität München'. BTX treatment of the corrugator muscles was applied for treatment of facial skin furrows (frown lines). Each corrugator muscle was injected with 0.2 mL (3 injection points, 200 U/mL) of BTX type-A (Dysport, Ipsen Pharma, Ettlingen, Germany) producing complete corrugator paralysis. Participants were randomly assigned to either the control group ($N = 19$), studied before BTX treatment and scheduled for BTX treatment after the functional imaging session, or the BTX group ($N = 19$), studied 2 weeks after treatment when the effects of BTX are usually greatest.

Activation Paradigm

Stimuli were 8 different gray scale pictures of female faces displaying angry or sad expressions (Young et al. 2002). Within each of 2 consecutive fMRI scans, pictures were presented for 4 s within twelve 32-s picture blocks, alternated with twelve 32-s baseline blocks (blank screen with fixation cross). Picture blocks (6 per condition) consisted of either 8 angry or sad expressions presented in randomized order. Motion artifacts induced by task-correlated facial movements were carefully controlled by using a "compressed image acquisition" protocol (Amaro et al. 2002), whereby facial movement was timed to coincide with the beginning of a 5-s scan-free interval between the acquisition of 2 consecutive brain volumes. Subjects were required to either imitate or observe the expressions, depending on whether the picture was preceded by an upright (for imitation) or inverted triangle (for observation) presented just before the appearance of each picture.

Analysis of Behavioral Data

Immediately after fMRI scanning, all subjects performed the tasks during a videotaped session in front of a computer monitor. The intensity of brow-lowering actions was scored by 2 blinded scorers trained in Facial Action Coding System (FACS) and using the 5-point intensity scale provided by the FACS system. Because inspection of the videotapes revealed no signs of brow-lowering actions during the observation task, the scoring procedure was confined to the imitation condition. Scores were based on image frames of maximum expression intensity of each of the 8 different facial expressions (4 angry and 4 sad expressions) that were extracted from the digitized videotapes of 35 subjects. Videotapes of 3 subjects (2 subjects from the control group and 1 from the BTX group) were excluded due to poor visibility of the glabellar region of the faces. Based on our research interest, only the intensity of action unit (AU) 4, that is, lowering of medial eyebrows, was evaluated. Interscorer reliability was sufficiently high (intraclass correlation = 0.96), and mean values were calculated across scorers. Finally, mean intensity scores were calculated for each subject across images portraying the same emotion, yielding 2 scores per subject: Mean intensity of AU 4 in 1) angry and 2) sad expressions.

Image Acquisition and Data Analysis

We used a 1.5-T Siemens Symphony MRI scanner (Erlangen, Germany) to acquire gradient-echo, T_2^* -weighted echo-planar images with blood oxygenation level-dependent contrast. T_1 -weighted structural images were also acquired for each subject.

Preprocessing and statistical analysis were performed using SPM2 (Wellcome Department of Imaging Neuroscience, London). Images were realigned to correct for head motion in time, normalized, and spatially smoothed. The study was based on a $2 \times 2 \times 2$ factorial design with the between-subject factor "BTX treatment" (control vs. BTX) and the 2 within-subject factors "task" (imitation vs. observation) and "expression type" (anger vs. sadness).

To create regressors of interest, each condition was modeled using a finite impulse response basis function with a bin width of 3 s at each interstimulus interval onset. To capture residual motion-related artifacts, movement parameters estimated during realignment preprocessing were included in the model. Contrast images were calculated by applying appropriate linear contrasts to the parameter estimates for the regressors and entered into second level 1-sample and 2-sample t -tests to allow for inferences to be made at the population level. These second-level t -tests at the between-subject level represent a summary

statistic approach to a random-effects analysis. Statistical parametric maps were estimated for task (imitation and observation) versus baseline and for imitation versus observation (only region of interest [ROI] analysis), separately for each group (control and BTX) and expression type (anger and sadness), as well as for group comparisons. For our a priori ROI, the amygdala, correction for multiple comparisons was based on an anatomical ROI for the bilateral amygdala derived from Talairach definitions of the WFU PickAtlas software (Maldjian et al. 2003) ($P < 0.05$ familywise error (FWE) correction, extent threshold (k) = 5 voxels). Activations in other regions are reported for clusters of at least 5 contiguous voxels at $P < 0.05$ FWE corrected across the whole brain. For descriptive purpose, we also report uncorrected results for group comparisons ($P < 0.001$, $k = 10$ voxels).

To examine whether attenuation of the amygdala response is associated with a decrease in functional coupling between the amygdala and hypothalamus/brain stem regions, we used a functional connectivity analysis similar to a psychophysiological interaction (PPI) (Friston et al. 1997). In a first step, individual time series for the left amygdala were obtained by extracting the first principal component from the time series of all voxels within a functionally defined amygdala ROI. This ROI was defined by creating a binary mask from the cluster of voxels in the left amygdala showing significantly reduced activation in BTX-treated subjects during imitation versus observation of angry expressions. Two subjects (one BTX-treated and one BTX-naïve) showed no amygdala activations and were therefore excluded from the functional connectivity analysis. Time series were then used as regressors in subsequent single-subject regression analyses. Again, movement parameters estimated during realignment preprocessing were included in the model to capture residual motion-related artifacts. For the coupling-by-group interaction analysis, the resulting parameter estimates were then compared between groups (control vs. BTX) at the second or between-subject level in exactly the same way as the contrast testing for activations. In this case, the parameter estimates reflect coupling (i.e., the regression coefficient or slope of a plot of regional responses against amygdala activity). A PPI analysis of this sort can be regarded as a simple analysis of directed or effective connectivity under a linear coupling between the amygdala and all other parts of the brain. Statistical correction ($P < 0.05$ FWE correction, $k = 5$) was based on spheres with 8 mm radius centered at hypothalamus and brain stem coordinates specifically associated with anger arousal in a previous study (Damasio et al. 2000). For descriptive purpose, activations in other regions are reported at $P < 0.001$, $k = 10$ voxels.

Correlation analysis was used to assess whether individual differences in the intensity of brow-lowering actions covary with amygdala activation elicited during imitation versus observation of angry and sad expressions. To implement this analysis, individual parameter estimates from the appropriate first-level contrast images which reflect specific activation effects when comparing imitation versus observation of angry and of sad expressions respectively were derived for activation peaks within left and right amygdala determined in the second-level ROI analysis (Table 1). These parameter estimates were subsequently correlated with mean intensity scores of brow-lowering actions (see Analysis of Behavioral Data) for both angry and sad expressions across subjects. Correlations are reported at $P < 0.05$.

Results

Effect of BTX-Induced Frown Muscle Denervation on Behavioral Parameters

Postscan behavioral ratings confirmed that BTX treatment significantly impaired brow lowering during imitation of angry as well as sad facial expressions ($P < 0.001$), as assessed using the FACS (Ekman and Friesen 1978) (Fig. 1 and Supplementary Fig. 1 online). Brow-lowering actions were significantly stronger during imitation of angry than of sad expressions ($P < 0.01$). No signs of involuntary brow lowering were detected when subjects simply observed the facial displays, although this does not exclude the possibility that subtle movements occurred on a more fine-grained level.

Amygdala Activation during Imitation of Emotional Expressions

First, we tested whether the amygdala exhibits a neural response during intentional imitation of angry or sad facial expressions. BTX-naïve and BTX-treated subjects showed bilateral activation of the amygdala during imitation of both angry and sad expressions versus baseline (i.e., blank screen

with fixation cross) as well as versus the observation condition (Table 1). In contrast to imitation and in line with some of the previous studies on facial perception (Hennenlotter and Schroeder 2006) and imitation (Wild et al. 2003; Lee et al. 2006), we found no amygdala activation during observation of angry and sad expressions (vs. baseline) in BTX-naïve and BTX-treated subjects (for whole-brain activations, see Supplementary Tables 1–4 and Fig. 2 online).

Table 1

Results of the ROI analysis for imitation of facial expressions

Emotion	Analysis	Talairach coordinates			t-score
		x	y	z	
Anger	Control				
	Left amygdala	−28 (−26)	−4 (−3)	−12 (−12)	11.93 (7.77)
	Right amygdala	26 (28)	−3 (−5)	−12 (−13)	10.78 (6.44)
	BTX				
	Left amygdala	−26 (−24)	−3 (−3)	−12 (−12)	7.56 (7.30)
	Right amygdala	22 (22)	−3 (−3)	−12 (−12)	9.52 (8.97)
	Control–BTX				
	Left amygdala	−16 (−16)	−8 (−8)	−13 (−13)	4.07 (4.16)
Sadness	Control				
	Left amygdala	−24 (−28)	−3 (−5)	−12 (−13)	6.19 (5.32)
	Right amygdala	26 (26)	−3 (−3)	−12 (−12)	6.87 (6.10)
	BTX				
	Left amygdala	−26 (−26)	−3 (−3)	−12 (−12)	9.77 (6.36)
	Right amygdala	28 (28)	−3 (−3)	−12 (−12)	9.62 (5.64)
	Control–BTX				
	BTX–Control				

Note: Results are given for imitation versus baseline and imitation versus observation (values in brackets). No amygdala activations were found for observation of facial expressions (relative to baseline) in both within- and between-group comparisons. Coordinates (in mm) refer to peak activation in Talairach space. All activations are significant at $P < 0.05$ corrected for multiple comparisons within the amygdala ROI.

BTX-Induced Attenuation of Amygdala Activation

In a next step, we explored whether BTX treatment had a modulatory effect on amygdala responses associated with facial imitation. Direct between-group comparisons (control vs. BTX group) revealed that during imitation of angry expressions (vs. baseline), activation of the left amygdala was significantly reduced in BTX-treated subjects (Table 1). Attenuation of the left amygdala response was also significant after the effects of visual input had been canceled out as apparent in the between-group comparison of the “imitation versus observation” contrast for anger, further supporting the robustness of this finding (Fig. 2*a/b*). This result is unlikely to be attributed to between-group differences in perceptual processing of facial expressions during the observation condition because 1) the within-group analyses of both groups revealed no significant amygdala activation during observation of angry expressions (vs. baseline) as mentioned above and 2) in contrast to anger imitation, we found no between-group differences in amygdala activation during anger observation (vs. baseline).

Both, imitation and observation of sad expressions yielded no between-group differences with respect to amygdala activation. During imitation of sad expressions (vs. baseline), however, attenuation of neural activity was present at an uncorrected statistical threshold of $P < 0.005$ in several other

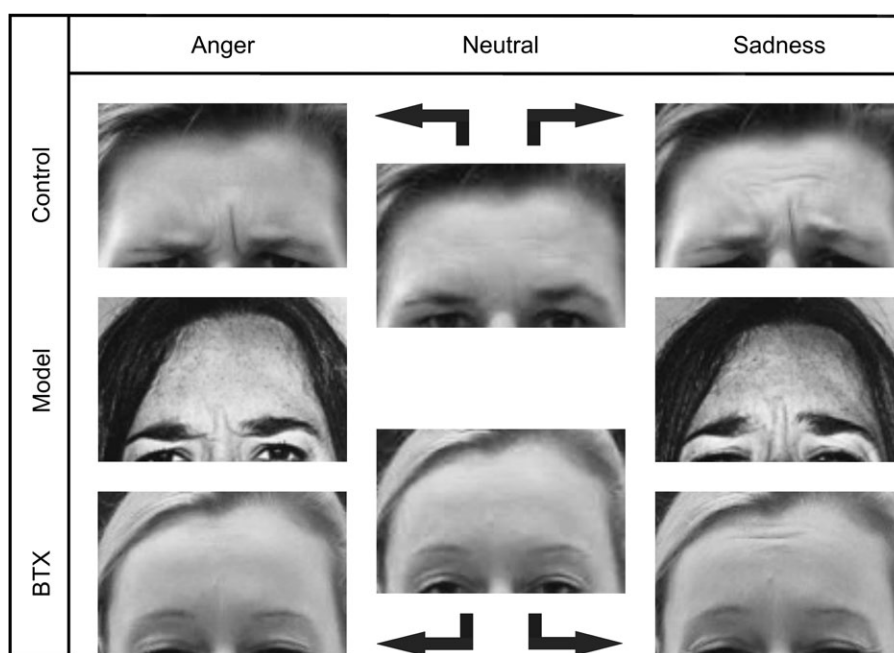


Figure 1. Effects of BTX treatment on frown muscle actions. Example of a BTX-naïve (upper row) and BTX-treated subject (bottom row) mimicking an angry (left column) and a sad expression (right column) of a face model (middle row, left and right column). The middle column shows both subjects with neutral expression. Note that unlike the BTX-naïve subject, the BTX-treated subject is unable to lower her eyebrows during imitation of both angry and sad expressions. Although whole-face expressions were mimicked, only the upper part of the faces is depicted where BTX treatment of the corrugator muscle was applied.

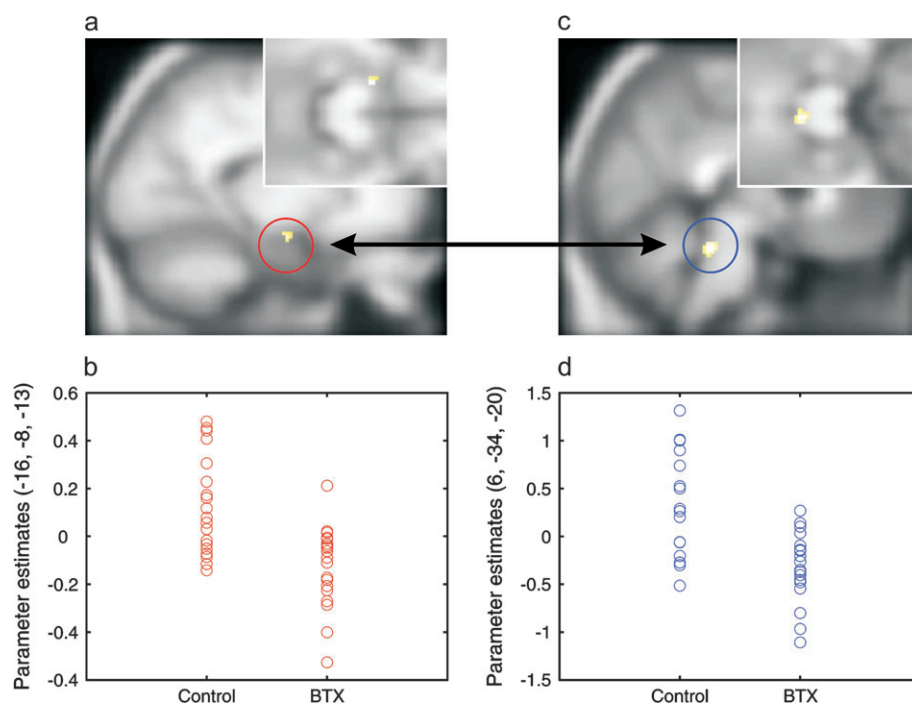


Figure 2. Effects of BTX treatment on amygdala activation and coupling with the dorsal brain stem. (a) Reduction of left amygdala activation ($-16, -8, -13$; $t = 4.16$, $P < 0.05$ SVC corrected) in BTX-treated subjects during imitation versus observation of angry expressions, plotted on parasagittal and coronal (upper right corner) sections of the averaged T_1 anatomical image of the 38 participants. (b) Individual parameter estimates (arbitrary units) of left amygdala response as a function of BTX treatment. (c) Decrease in functional coupling between the left amygdala and dorsal brain stem ($6, -34, -20$; $t = 4.40$, $P < 0.05$ SVC corrected) in BTX-treated subjects. (d) Individual parameter estimates (arbitrary units) of amygdala-brain stem coupling as a function of BTX treatment. Here, the parameter estimates denote the “strength” of the connection between the left amygdala and dorsal brain stem. Note that paralysis-related effects were not influenced by structural alterations following BTX treatment as revealed by an additional structural imaging study using voxel-based morphometry (see Supplementary Methods and Results online).

regions including the left lateral orbitofrontal cortex (Supplementary Table 5).

Modulation of Functional Connectivity following BTX Denervation

We were also interested in whether attenuation of the left amygdala response in BTX-treated subjects would be associated with a decrease in functional coupling between the amygdala and hypothalamus/brain stem regions implicated in the control of autonomic arousal (LeDoux 2000). A coupling-by-group interaction analysis (Friston et al. 1997) revealed that the functional connectivity of the left amygdala with the dorsolateral pons was significantly reduced in BTX-treated subjects (Fig. 2c/d). The peak activation of this cluster was located in the right pons and extended into the left brain stem (for whole-brain results, see Supplementary Table 5).

Correlation between Frown Muscle Activity and Amygdala Activation

To further explore the link between brow-lowering actions and the amygdala response, we tested whether in BTX-naïve subjects, individual intensities of brow lowering covary with the amygdala response associated with imitation of angry expressions. This was indeed evident by a significant correlation between the magnitude of left amygdala activation and the individual postscan FACS ratings of brow lowering during imitation of angry expressions (Fig. 3). In contrast, covariation with the intensity of brow lowering was not found for activation of the right amygdala as well as for any amygdala activation associated with the imitation of sad expressions.

Discussion

Our data on intentional imitation of angry facial expressions demonstrate that a reduction of feedback from face muscles and skin due to BTX-induced frown muscle paralysis attenuates activation of the left amygdala and its functional coupling with autonomic brain stem centers. Attenuation of the neural response was found in the left amygdala which showed significant covariation with the individual intensity of brow lowering in BTX-naïve subjects.

These findings reveal a functional link between feedback from frown muscle movements during imitation of angry expressions and a modulation of neural activity in central circuitries of emotion. The absence of group differences with respect to regional activation and functional connectivity in motor and premotor areas involved in the execution of facial emotion patterns further supports this interpretation. This negative finding makes it unlikely that our results simply reflect a complex motor interaction between the task of mimicking emotional faces and a BTX-related inability to do so.

On the other hand, such an interpretation does not imply that the efferent copies which are associated with the production of facial expressions would have no impact on the amygdala response. In fact, the within-group analysis shows that facial imitation yielded a response of the amygdala even in BTX-treated subjects with a frown muscle paralysis. This finding suggests that efferent copies could be a relevant source of modulation of the amygdala response together with the peripheral feedback from the face. As it has been suggested previously that efferent copies are relayed to the amygdala via

the anterior insular cortex (Carr et al. 2003), our finding of significant insular activations during imitation of angry as well as sad expressions in the whole-brain analysis (Supplementary Fig. 2 and Tables 1 and 2 online) and the lack of a significant effect of BTX onto neural activation within this region further support this notion. In addition, feedback from other facial muscles, for example, from the lower face, may have contributed to amygdala activation during imitation in all including the BTX-treated subjects where BTX injections have only been applied to the corrugator muscle.

BTX-induced attenuation of the amygdala response was apparent only during imitation of anger where brow-lowering actions were found to be significantly stronger than during imitation of sadness. This finding indicates that the effect of frown muscle paralysis on amygdala activation is limited to the imitation of those emotion patterns where brow-lowering actions are sufficiently strong. Such a link between limbic brain activity and the strength of corrugator muscle contraction is underlined by the significant covariation between activation of the left amygdala and individual intensities of brow lowering during imitation of angry expressions in the BTX-naïve subjects.

During imitation of sadness, BTX treatment was associated with reduced activation, at a more liberal statistical threshold of $P < 0.005$ uncorrected, in several regions including the orbitofrontal cortex which is closely connected to the amygdala (Barbas and De Olmos 1990) and has been implicated in the representation of the affective value of somatosensory stimuli, for example, pleasant and painful touch (Rolls et al. 2003). Although we had no specific a priori hypothesis for activation of the orbitofrontal cortex, this finding indicates that some modulation of limbic brain activity also occurred during imitation of sadness. It suggests that the central effects of feedback from specific muscular movements might be partly dependent upon the facial action pattern during which they occur. Emotion-specific effects of facial feedback are in agreement with the finding that facial movement of the same facial muscles, that is, corrugator supercilii and depressor anguli oris, engages partly separable neural substrates depending on whether subjects mimic sad or angry expressions (Lee et al. 2006).

Attenuation of the amygdala response during imitation of anger in BTX-treated subjects was associated with a decrease in functional coupling between the amygdala and the dorsal pons. This pontine activation cluster encompasses nuclei involved in central autonomic regulation such as the periaqueductal gray, the reticular formation, and the parabrachial nucleus. All 3 receive prominent projections from the central nucleus of the amygdala (LeDoux 2000). A functional relevance of this connection between autonomic regulation and limbic brain centers can be hypothesized from previous findings showing that an amplification and inhibition of facial responses to others' emotional displays have parallel effects on measures of autonomic arousal such as heart rate and skin conductance (Kleck et al. 1976; Vaughan and Lanzetta 1981). In addition, there is evidence that the dorsal pons receives self-related afferent information from the body and is engaged in homeostatic regulation as revealed by differential neural activity of this area in patients suffering from "pure autonomic failure" (Critchley et al. 2001). Based on its involvement in homeostatic regulation, the dorsal pons was proposed to realize a first-order mapping of bodily state (Damasio 1999).

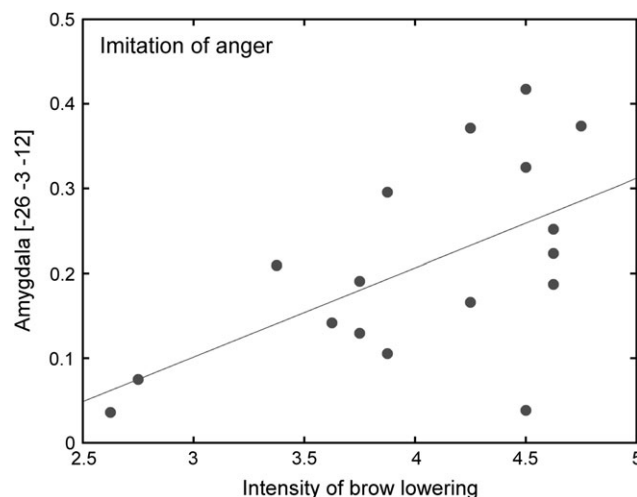


Figure 3. Correlation between amygdala activation and brow lowering in BTX-naïve subjects. Significant correlation ($r = 0.58$, $P < 0.05$) of left amygdala activation (parameter estimates), elicited during imitation versus observation of angry expressions, with individual differences in mean intensity of brow-lowering actions, as assessed after scanning using FACS (Ekman and Friesen 1978). The line represents the linear best fit.

Because afferent sensory information from the upper face enters the principal sensory nucleus of the trigeminal tract at the level of the dorsal pons, denervation of face muscles may consequently reduce the input from the brain stem nuclei to the amygdala (Bernard and Besson 1990). Because the amygdala projects back to and is modulated by regions of the brain stem (Bernard and Besson 1990; Aston-Jones et al. 1996; Berntson et al. 2003), disruption of facial feedback may alter functional coupling in both directions, that is, via efferent projections from the amygdala to the brain stem as well as afferent projections from brain stem areas to the amygdala. The hypothesis underlying our PPI analysis was that the influence of the amygdala on the brain stem would be reduced in the absence of enabling peripheral feedback. Our results confirm this hypothesis.

In summary, BTX-induced selective denervation of face muscles represents a conclusive model for investigating the physiological link between facial feedback and limbic brain activity during intentional imitation of facial expressions. Our findings provide evidence that peripheral feedback from face muscles and skin during imitation modulates neural activity within central circuitries that are known to be involved in the representation of emotional states. Although the present data do not allow immediate conclusions about the effect of reduced facial feedback onto "felt" emotions, our results disclose a potential physiological basis for the transfer of emotions during social interactions (Hatfield et al. 1994; Goldman and Sripada 2005). In the light of evidence that people tend to mimic emotional expressions of others (Dimberg 1982), afferent input from our facial expressions may influence and reinforce our felt emotion in response to somebody else's facial expression by appropriately modulating limbic brain activity.

Supplementary Material

Supplementary material can be found at: <http://www.cercor.oxfordjournals.org/>.

Notes

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