

Inferior Frontal Gyrus Activity Triggers Anterior Insula Response to Emotional Facial Expressions

Mbemba Jabbi

University of Groningen and National Institutes of Mental Health, Bethesda, Maryland

Christian Keysers

University of Groningen

The observation of movies of facial expressions of others has been shown to recruit similar areas involved in experiencing one's own emotions: the inferior frontal gyrus (IFG), the anterior insula and adjacent frontal operculum (IFO). The causal link between activity in these 2 regions, associated with motor and emotional simulation, respectively, has remained unknown. Here using psychophysiological interaction and Granger Causality Modeling, we show that activity in the IFO is causally triggered by activity in the IFG, and that this effective connectivity is specific to the IFG. These findings shed new light on the intricate relationship between motor and affective components of emotional empathy.

Keywords: emotional contagion, facial mimicry, mirror neuron system, insula, inferior frontal gyrus

Emotions play a key role in our lives and understanding the emotions of other people is essential for adequate social functioning. However, how our brain associates feelings to the facial expressions of other people's emotions remains poorly understood.

Mirror neurons were shown to respond while a monkey performs a goal directed action as well as when the monkey sees or hears another individual perform a similar action (e.g., breaking the shell of a peanut apart; Fogassi, Ferrari, Gesierich, Rozzi, Chersi, & Rizzolatti, 2005; Gallese et al., 1996; Keysers et al., 2003; Kohler et al., 2002). When these neurons were first discovered, the concept of motor simulation gained great popularity. This concept demonstrated that although we witness the actions of others, our brain simulates their behavior by activating part of the neurons involved in executing the same action—"as if" the observer was doing the same. Although in the monkey, evidence for mirror neurons is mainly restricted to goal directed actions (but see Ferrari, Gallese, Rizzolatti, & Fogassi, 2003), the concept of simulation has been extended to sensations in the somatosensory cortex (Blakemore, Bristow, Bird, Frith, & Ward, 2005; Keysers et al., 2004) and emotions in the anterior insula and adjacent frontal operculum (IFO; Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi,

2003; Jabbi, Swart, & Keysers, 2007; Jackson, Meltzoff, & Decety, 2005; Singer et al., 2004, 2006; van der Gaag, Minderaa, & Keysers, 2007; Wicker et al., 2003) in humans (Gallese, Keysers, & Rizzolatti, 2004; Goldman & Sripada, 2005; Keysers & Gazzola, 2006; Singer, 2007a, 2007b). Neuroscientific support for extending the concept of simulation to emotions primarily stems from two lines of research that examine whether observing the emotional facial expressions of other individuals activates regions involved in (a) performing similar facial expressions and (b) experiencing similar emotions and sensations.

Carr et al. (2003) and Leslie, Johnson-Frey, and Grafton (2004) asked participants to observe and imitate facial expressions and found extensive sectors of the ventro-lateral frontal cortex including BA45 in the inferior frontal gyrus (IFG) to be involved in both the observation and the imitation of facial expressions. Hennenlotter et al. (2005) asked participants to view and execute smiles, and found a network including the right IFG to be involved in both. Van der Gaag et al. (2007) instructed participants to observe moving patterns, neutral facial movements (blowing up the cheeks), and emotional facial expressions (disgust, fear, and happy) in an event related fashion, and asked them to subsequently produce all four observed facial movements. Contrasting the observation of facial expressions against the movies of pattern motion that do not match the observer's motor vocabulary, they found that, of the brain regions involved in the execution of facial expressions, only a relatively circumscribed network involving the right BA45 and bilateral MTG responded more to all the facial expressions (neutral or emotional) compared to pattern motion (van der Gaag et al., 2007).

In the monkey, the most ventral sector of F5 contains mirror neurons that respond both during the production and observation of facial movements (Ferrari et al., 2003). This area is considered to be the homologue of human Broca's area in the IFG (Petrides, Cadoret, & Mackey, 2005). Taken together, the existence of facial mirror neurons in region F5 of the monkey and voxels shared between the observation and execution of facial expressions in the human IFG suggest that in humans, mirror neurons within these voxels could transform observed facial expressions into a pattern

Mbemba Jabbi, Social Brain Lab, BCN Neuroimaging Center, Department of Neuroscience, University Medical Center Groningen and Section on Integrative Neuroimaging, Clinical Brain Disorders Branch, Genes Cognition and Psychos's Program, National Institutes of Mental Health, Bethesda, Maryland; Christian Keysers, Social Brain Lab, BCN Neuroimaging Center, Department of Neuroscience, University Medical Center Groningen, University of Groningen.

This study was supported by a Marie Curie Excellence Grant of the European Commission and a VIDDI grant of the Dutch Science Foundation (N.W.O.) to Christian Keysers. We thank Remco Renken and Luca Nanetti for implementing and calculating the Granger Causality Values, Marte Swart for data collection, and Aarthi Padmanabhan for comments.

Correspondence concerning this article should be addressed to Christian Keysers, BCN Neuroimaging Center, University Medical Center Groningen, Antonius Deusinglaan 2, 9713 AW Groningen, the Netherlands. E-mail: c.m.keysers@rug.nl

of neural activity that would be suitable for producing similar facial expressions and provide the basis for a motor simulation of facial expressions (Keysers & Gazzola, 2006; van der Gaag et al., 2007). However, these putative mechanisms would not be limited to emotional facial expressions. van der Gaag and collaborators did not find significant differences between the observation (and production) of neutral versus emotional facial movements in the lateral aspects of the IFG. In line with this finding, this form of motor simulation has sometimes been referred to as “cold” simulation because it is not specific to the “heat” of affect (Gallese et al., 2004). In contrast to the active IFG during both the observation and the execution of facial expressions, in human functional MRI (fMRI) studies, the primary motor cortex has been found to be typically active only during the execution of goal directed actions and facial expressions, but not during their observation (e.g., Carr et al., 2003; Gazzola, Aziz-Zadeh, & Keysers, 2006; Gazzola et al., 2007; Hennenloter et al., 2004; Leslie et al., 2004; van der Gaag et al., 2007). This suggests that the observation of facial expressions triggers a motor simulation in regions involved in higher motor functions (i.e., BA6, 44, 45, and SMA/pre-SMA), but that this simulation does not automatically lead to the activation of the primary motor cortex region that would produce overt facial movements.

Wicker et al. (2003) and Jabbi et al. (2007) examined whether brain regions involved in experiencing emotions (instead of expressing them as discussed earlier) are activated while people view emotional facial expressions. In these studies, participants were shown movies of faces expressing disgust and subsequently exposed them to unpleasant odors (Wicker et al., 2003) or tastes (Jabbi et al., 2007). They found that a transition zone between insula and frontal operculum, a region they label IFO (because their reported activation regions consistently encompassed both the anterior insula and frontal operculum), was active both during the experience of disgust and while viewing the disgust of other individuals. The IFO is also shown to activate while participants view (Botvinick et al., 2005; Jackson et al., 2005; Jackson, Rainville, & Decety, 2006; Lamm, Batson, & Decety, 2007; Moriguchi et al., 2007; Morrison, Lloyd, di Pellegrino, & Roberts, 2004; Saarela et al., 2007) or are aware (Singer et al., 2004, 2006) that another individual is in pain and when they experience pain themselves. To underline that this region is not specifically involved in mapping aversive experiences of one's self and while being aware of others' similar aversive experiences, the same region is also shown to be involved in the experience of gustatory pleasure and while viewing pleased facial expressions (Jabbi et al., 2007).

More important, the overlapping regions of the IFO are more strongly activated during the observation of another individual's emotions if the participant reports being more prone to sharing the distress of others (Jabbi et al., 2007) as well as during the awareness of another individual's pain, in more empathically concerned individuals (Singer et al., 2004). Together, these data suggest that the brain may not only perform a cold motor simulation of what the emotionally expressive face of the other individual is doing (in the IFG), but also a hot (i.e., affect laden) simulation of what the other individual is feeling (in the IFO). Lesions in the IFO have been shown to lead (among other complex deficits of emotional awareness) to an impairment of the experience and recognition of disgust in particular (Adolphs, Tranel, & Damasio, 2003; Calder, Keane, Manes, Antoun, & Young, 2000).

In summary, there is evidence that the right BA45 within the IFG is involved during both the observation and execution of facial move-

ments and that the IFO is involved during both the observation of facial expression and the experience of similar emotions. However, a notable difference between activations in BA45 and the IFO is that the former is similarly strong for emotional and neutral facial movements whereas the latter is stronger for emotional facial expressions. This supports the idea that activity in BA45 may reflect a form of cold motor simulation whereas that of the IFO may underlie a hot simulation of emotional feeling states (Damasio, 1999, 2003; Gallese & Goldman, 1998; Gallese et al., 2004).

The critical question that remains unanswered is whether activations during the observation of facial expressions in BA45 and the IFO reflect two independent processes or are causally related with activity in BA45 triggering activity in IFO or vice versa.

To examine this question, we performed a multilevel functional connectivity analyses on data previously acquired using fMRI from 18 participants while they viewed movies of emotional and neutral facial expressions. In the movies, actors sipped a liquid from a cup and reacted by displaying a disgusted or neutral facial expression. As reported elsewhere (Jabbi et al., 2007), the same participants also experienced unpleasant and neutral tastes in a separate session of fMRI scanning to determine the location of the (right) IFO region common to the observation and experience of gustatory emotions and its empathic related activation patterns.

Facial movements of the actors are the main source of information about their emotions, and BA45 in particular, has been shown in a separate experiment to respond similarly during the observation of emotional and neutral facial expressions, whereas the IFO responded more during the observation of emotional compared to neutral facial expressions (van der Gaag et al., 2007). With this in mind, and in accord with the proposals of Carr et al. (2003) and Dapretto et al. (2006), we hypothesized that activity in BA45 may causally determine activity in the IFO of our participants during the observation of facial expressions and that this functional connectivity should be effectively stronger while viewing emotional compared to neutral facial expressions.

To test this hypothesis, we applied a novel combination of two methods for the analysis of functional connectivity. First, using psychophysiological interaction (PPI) analysis of brain activity (Friston et al., 1997), we tested whether the IFO is effectively more connected with BA45 during the observation of emotional compared to neutral facial expressions, and whether such a pattern of effective connectivity is restricted to BA45. Second, to determine if the changes of effective connectivity reflect a causal influence from BA45 \rightarrow IFO, we applied Granger Causality modeling (Geweke, 1982, 1984; Goebel, Roebroeck, Kim, & Formisano, 2003; Roebroeck, Formisano, & Goebel, 2005; see Method), which is based on the rationale that if BA45 causally influences the IFO more than vice versa, the state of BA45 at time t should predict the state of the IFO at time $t + 1$ better than the state of the IFO at time t that of BA45 at time $t + 1$.

Method

Participants and Procedure

We used the fMRI data of 18 participants who viewed an actor sip a liquid from a cup and look either disgusted or neutral, and later experienced unpleasant tastes (Jabbi et al., 2007).

Image Acquisition

Images were acquired using a Philips 3T whole-body scanner (Best, The Netherlands) using a circular sense head coil. T2*-weighted echo-planar sequencing was performed with 39 interleaved 3.5 mm thick axial slices with 0 mm gap (TR = 2,000 ms, TE = 30 ms, flip angle = 80°, FOV = 224 mm, 64 × 64 matrix of 3.5 × 3.5 × 3.5 mm voxels). At the end of each functional scan, a T1-weighted anatomical image (1 × 1 × 1 mm) parallel to the bicommissural plane, covering the whole brain was acquired.

Statistical Parametric Mapping (SPM2; Wellcome Department of Cognitive Neurology, London; <http://www.fil.ion.ucl.ac.uk>) was used for the preprocessing and data analysis. All functional volumes were realigned to the first acquired volume and images were then coregistered to each individual's anatomical space and subsequently spatially normalized to obtain images with a voxel size of 2 × 2 × 2 mm (Friston et al., 1995). All volumes were then smoothed with an 8 mm full-width half-maximum isotropic Gaussian kernel. For the time series on all 18 participants, high-pass filters with cut-off points at 106 s for the observation conditions were included in the filtering matrix to remove low-frequency noise and slow-drifts in the signal.

Condition-specific effects at each voxel were estimated using the general linear model. Participant's contrast maps were then compared against a null hypothesis using a *t* test across participants to implement a random effect analysis.

PPI Analysis

The analysis was conducted according to the methods suggested by Friston et al. (1997). First, for each participant, we extracted the time course of activity in the IFO. To achieve this, we used the peak of the activation cluster derived from the random effect group analysis (overlap between the observation of disgust-neutral inclusively masked with the experience of disgust-neutral, see Jabbi et al., 2007) as a starting point (MNI [Montreal Neurological Institute]: $x = 52$ $y = 18$ $z = -6$). For each individual participant, we used the results of the observation runs at a statistical threshold of $p < .05$ uncorrected, placed the cursor at the group peak (MNI: $x = 52$ $y = 18$ $z = -6$) and pressed the VOI button. In many cases, there was a slight jump of the cursor to the nearest suprathreshold voxel (see Table 1). The eigenvalue of a sphere of 5 mm around these coordinates were then extracted. The PPI analysis function in SPM2 was then used to build a design matrix suitable to estimate the PPI, including three columns per run reflecting the time course of the IFO, the psychological variable (1s while participants viewed disgusted facial expressions, -1 while they viewed neutral facial expressions and 0s elsewhere), and the product of the IFO and the psychological variable. The GLM was then used to determine parameter estimates for all three components, and the 18 parameter estimates of the interaction were entered into a one sample *t* test to assess whether it differed from zero on average across the population.

To examine if the a priori expectation that the right BA45 shows the hypothesized effective connectivity pattern, we first restricted our analysis to the ipsilateral BA45 and applied a small volume correction using a region of interest encompassing the cytoarchitectonic maximum probability maps for the right BA45 (Eickhoff et al., 2006). We then extended the analysis to the entire brain to examine if effects are regionally specific to the right BA45.

Granger Causality Modeling

In addition to the time course of the IFO, we extracted the time course in the right BA45 that was found to be effectively more connected to the IFO during the emotional compared to the neutral facial expressions from the peak of the Group PPI analysis defined above (MNI $x = 56$ $y = 36$ $z = -12$). For each participant, within the GLM of the observation condition ($p < .05$ uncorrected), we navigated to these coordinates and pressed the VOI button, often leading to a slight shift to the nearest suprathreshold voxel (see Table 1). We then extracted the eigenvalue of a 5 mm sphere for both ROIs and subsequently included the extracted IFG/BA45 versus IFO time courses derived from these two 5 mm sphere ROIs in the Granger Causality modeling using a Matlab (www.mathworks.com)-based script.

Granger causality is a linear autoregressive model of time series that is based on the concept that each data point X_t (the measured value at time t) can be modeled as a linear combination of k previous data points, starting from a lag $l \geq 1$. The number k is called the order of the model. According to previous studies, for fMRI, both k and l are best set to 1 (Goebel et al., 2003; Roebroeck et al., 2005). This means that the time series of a voxel or ROI X can be modeled using an autoregressive model including the immediate past of the same voxel ($X_t = \alpha X_{t-1} + \epsilon_t$). If one suspects that another voxel Y may have a causal influence on X , one can expand the auto regression to incorporate the past of Y as well $X_t = \alpha X_{t-1} + \beta Y_{t-1} + \epsilon'_t$. Granger (1969) then proposed that if the amount of variance explained by this new model is significantly higher than that of the purely autoregressive model, it is said then that Y "Granger causes" X . In other words, a directional influence in time from Y to X is detected when the combined past of X and Y are characterized by a significantly in-

Table 1
Center of 5 mm Radius Sphere Used for the PPI Analysis in MNI Coordinates

| Participant | IFO | | | IFG | | |
|-------------|----------|----------|----------|----------|----------|----------|
| | <i>x</i> | <i>y</i> | <i>z</i> | <i>x</i> | <i>y</i> | <i>z</i> |
| 1 | 52 | 18 | -6 | 52 | 32 | 10 |
| 2 | 52 | 18 | -6 | 56 | 30 | 12 |
| 3 | 52 | 18 | 0 | 56 | 28 | 12 |
| 4 | 50 | 20 | -10 | 56 | 30 | 12 |
| 5 | 52 | 18 | -6 | 56 | 30 | 12 |
| 6 | 54 | 18 | -2 | 56 | 26 | 16 |
| 7 | 52 | 16 | -2 | 56 | 30 | 12 |
| 8 | 50 | 18 | -14 | 56 | 24 | 12 |
| 9 | 48 | 14 | -6 | 56 | 34 | 6 |
| 10 | 56 | 22 | -2 | 60 | 26 | 14 |
| 11 | 52 | 18 | -8 | 56 | 30 | 12 |
| 12 | 52 | 18 | -6 | 56 | 30 | 12 |
| 13 | 52 | 18 | -6 | 54 | 28 | 10 |
| 14 | 52 | 18 | -6 | 56 | 30 | 12 |
| 15 | 54 | 18 | -8 | 52 | 32 | 12 |
| 16 | 50 | 18 | -6 | 56 | 30 | 12 |
| 17 | 48 | 16 | -12 | 54 | 26 | 12 |
| 18 | 52 | 18 | -6 | 60 | 26 | 8 |
| Average | 51.6 | 17.8 | -6.22 | 55.7 | 29 | 11.5 |
| SEM | 0.46 | 0.38 | 0.82 | 0.48 | 0.61 | 0.49 |

Note. PPI = psychophysiological interaction; MNI = Montreal Neurological Institute; IFO = anterior insula and adjacent frontal operculum; IFG = inferior frontal gyrus.

creased explanatory power over the past of X alone. The mathematic framework for assessing Granger Causality was laid out by Geweke (1982), who demonstrated how the total amount of linear dependence, or feedback, between two time series can be decomposed into three components: the amount of linear influence exerted over time, respectively by X on Y and by Y on X , and the amount of information that cannot be assigned neither to XY nor to YX because a lack of temporal resolution in data acquisition: the so-called “instantaneous causality.” Granger Causality was first applied to fMRI data by Goebel et al., 2003 and Roebroeck et al., 2005, who have emphasized the fact that although the absolute values of Granger Causality suffer from the relatively slow sampling frequency of fMRI, the difference between the Granger Causality values from $X \rightarrow Y$ and $Y \rightarrow X$ remain reliable. Accordingly, we calculated the Granger Causality between IFG and IFO in both direction, and test whether they differ at the group level.

Results

A traditional general linear model analysis published elsewhere (Jabbi et al., 2007) showed that a sector of the right IFO was involved both during the viewing of disgust and the experience of disgust. This region serves as the reference region for the present analysis (Figure 1a). The fact that the vision of disgusted facial expressions produces stronger activations in this region in more empathic individuals, as assessed by self-report questionnaires, links such activity to empathic emotional sharing (Jabbi et al., 2007).

By applying the PPI method to identify functional connectivity pathways using the right IFO (see Figure 1) as the seed region during the observation of disgusted facial expressions relative to neutral ones, we found that voxels in right BA45 are indeed significantly more strongly correlated with the IFO during the vision of disgusted compared to neutral facial expressions (Figure 1b; $p_{unc} < .005$, $p_{fdr} < .05$ within right BA45, extent threshold of 10 voxels). Given that the participants in this study did not

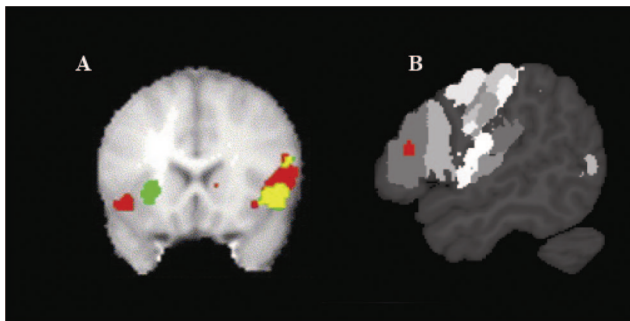


Figure 1. (A) Overlapping activations (yellow) between the observation of other people's (green) and own experience (red) of disgusting taste relative to neutral taste (Jabbi, Swart, & Keyers, 2007). Activations are shown on the mean anatomical images of the 18 participants normalized on the MNI template. The overlaps are shown at $p < .01$, uncorrected with a cut-off point at 10 voxels ($x = 52$; $y = 18$; $z = -6$ MNI coordinates), that is, with the likelihood of a false positive in the resulting logical AND function being equal to $p^2 = .0001$. (B) Functional connectivity map between the right IFG (BA45) at ($x = 54$; $y = 24$; $z = 17$ MNI coordinates) and the seed region of the right IFO (lower yellow activation cluster in A) as shown on the anatomy toolbox template (Eickhoff, Heim, Zilles, & Amunts, 2006).

perform an explicit facial expression execution task while in the scanner, we could not ensure that the region of BA45 was indeed involved in the control of facial expressions. We extracted the parameter estimates of the peak voxel in BA45 ($x = 56$, $y = 36$, $z = -12$) from data obtained from different participants during the observation and execution of facial expressions of van der Gaag et al. (2007) and found significant activations both during the observation (H_0 :neutral + fear + disgust + happy ≤ 0 , $p < .0003$) and execution (H_0 :neutral + fear + disgust + happy ≤ 0 , $p < .002$) of facial expressions (one-tailed t test, $n = 17$ participants). However, these voxels did not differentiate emotional from neutral facial expressions (execution: fear + disgust + happy-3neutral ≤ 0 , $p > .4$; observation: fear + disgust + happy-3neutral ≤ 0 , $p > .2$). Together, these findings provide the first evidence that a functional link may exist between BA45 and the IFO that is modulated by the emotional content of a social stimulus.

In a second step, we examined if this pattern of effective connectivity was restricted to BA45. We conducted a whole brain analysis and used a threshold of $p_{unc} < .005$ for the PPI analysis at the random-effects level in SPM2. This analysis revealed that no other brain areas showed a detectable stimulus dependent augmentation of their correlation with the IFO during emotional compared to neutral facial expressions at $p < .005$. In particular, the primary motor cortex or the primary somatosensory cortex did not show such a change of correlation.

To obtain further insights into the link between the IFO and BA45, we performed a Granger Causality analysis (Geweke, 1982, 1984; Goebel et al., 2003; Granger, 1969; Roebroeck et al., 2005; see Method). Granger Causality from BA45 to IFO (4.16 ± 0.95 SEM) was significantly larger than that from IFO to BA45 (1.22 ± 0.21 SEM) both according to a two-tailed t test (matched pair, $p < .0123$) or a permutation test ($p < .0106$; Nichols & Holmes, 2001). The finding is indicative of a causal relationship between IFG activity and IFO activity according to the definition of Granger Causality, and shows that this causality was predominantly from the IFG to the IFO.

Discussion

Here we examine the functional link between the IFO and BA45 during the observation of facial movements. The literature suggests that activity in right BA45 during the observation of facial expressions may reflect a cold motor simulation of the observed facial movements—motor because the same voxels were active while participants produced facial expression and cold because the degree of activity is similar for emotional and neutral facial movements (van der Gaag et al., 2007). Activity in the IFO on the other hand has been suggested to reflect the hot empathic sharing of other individual's emotional feeling because it is more strongly activated in more empathic individuals and for the observation of emotional compared to neutral facial expressions (Jabbi et al., 2007; Pfeifer, Iacoboni, Maxxiotta, & Dabretto, 2008; Singer et al., 2004; van der Gaag et al., 2007; Keyers & Gazzola, 2007). This interpretation is also supported by studies showing that the IFO is involved in experiencing the participant's own feeling states (Craig, 2004; Critchley, 2005; Damasio, 1999, 2003; Gray et al., 2007). However, the question regarding the functional link between BA45 and IFO activity still remains unanswered. It has been suggested that for emotional facial expressions, the putative cold motor simulation in BA45 could be the trigger for the putative hot

emotional simulation in the IFO (Carr et al., 2003; Dapretto et al., 2006), but this proposal has never been experimentally tested.

Using psychophysiological interaction analyses, we show for the first time that the right IFO, common to observing and experiencing emotions, is indeed more functionally connected to the ipsilateral, right BA45 during the observation of emotional compared to neutral facial expressions. In addition, using Granger Causality, we show that this functional connectivity is not only correlational but causal in nature (Granger, 1969). Finally, we showed that the influence of BA45 on the IFO is stronger than the influence of the IFO on BA45. To our knowledge, this represents the first empirical evidence in support of the idea that motor simulation is causally linked to emotional simulation (It should be noted that finding significantly higher Granger Causality values from IFG → IFO compared with IFO → IFG does not exclude the possibility that significant information does flow from IFO → IFG, nor that the IFG is the only input to IFO).

This finding may have important implications for our understanding of emotion perception. Lipps (1907) suggested that seeing someone else's emotional facial expression triggers the observer to adopt a similar facial expression (facial mimicry). The observer then senses the state of his face, and this process in turn triggers internal emotional feeling states in the observer that correspond to those now displayed by the observer's face (facial feedback). As a result, the observer shares both facial expression and emotional feeling state with the person he observes (emotional contagion), and this sharing allows the observer to feel what is going on in the other individual (emotional understanding) and eventually empathize. This account is similar to that proposed by James (1884).

Our current finding is compatible with the gist of this proposal: Activity in BA45 may indeed reflect a certain sharing of motor components of the observed facial expression, and our Granger Causality analysis suggests that this activity in BA45 triggers activity in the IFO, which may reflect a sharing of the emotional feeling state. However, our findings constrain the idea of Lipps (1907) in that the IFO appears causally linked with BA45, but not with somatosensory or primary motor areas—at least at the statistical threshold we used and in an experimental setting in which overt facial mimicry was not explicitly instructed. If facial feedback in the classical sense of Lipps were to be the only trigger for sharing the affect of the people, somatosensory areas (needed to sense the observer's facial mimicry) would be the most robust source of modulation of the IFO. This was not the case in our study. Instead, BA45 was the strongest source of modulation, suggesting that instead of a long facial feedback loop as suggested by Lipps (involving the overt production of a similar facial expression and its somatosensation), a covert, shorter direct connection between areas putatively involved in high-level motor simulation (BA45) with areas putatively involved in emotion sharing (IFO) may exist, bypassing the need for overt facial mimicry. The idea that a covert motor simulation may be sufficient to trigger emotion sharing may also help explain why the amount of overt facial mimicry does not reliably correlate with the amount of emotional sharing in a number of experiments (Blairy, Herrera, & Hess, 1999; Gump & Kulik, 1997; Hess, Blairy, & Philippot, 1999).

Given that the degree of overt facial mimicry is known to vary depending on a number of factors (Bourgeois & Hess, 1999; McHugo, Lanzetta, & Bush, 1991) including whether one is in a collaborative or competitive context with an observed individual

(Lanzetta & Englis, 1989), repeating our analyses in an experiment that systematically manipulates such variables will be critical to determine how functional connectivity and overt facial mimicry covary. Measuring electromyography during scanning, although methodologically challenging, may help address these issues in the future. Applying a similar causal connectivity analysis to experiments examining the perception of the sound of emotions will be important to understand the generality of the findings presented here.

In sum, although the current experiment used viewing of facial expressions as the source of emotional information, a similar system may apply to other channels: the sound of mouth actions for instance triggers activity in sectors of the IFG involved in producing similar sounds (Gazzola et al., 2006), and emotional vocalizations (e.g., baby cries or retching) trigger emotional sharing (Martin & Clark, 1987; Schneider, Gur, Gur, & Muenz, 1994). Together, these findings and our demonstration of a functional influence of the motor IFG on the more affect related IFO during the observation of vivid disgusted facial expressions, underscores the important role of motor simulation in social emotional perception. This dovetails with the fact that motor behavior (including vocalization, weeping, etc.) is the only observable cue to other people's emotions.

References

- Adolphs, R., Tranel, D., & Damasio, A. R. (2003). Dissociable neural systems for recognizing emotions. *Brain and Cognition*, 52, 61–69.
- Blairy, S., Herrera, P., & Hess, U. (1999). Mimicry and the judgement of emotional facial expressions. *Journal of Nonverbal Behavior*, 23, 5–41.
- Blakemore, S. J., Bristow, D., Bird, G., Frith, C., & Ward, J. (2005). Somatosensory activations during the observation of touch and a case of vision-touch synaesthesia. *Brain*, 128(Pt. 7), 1571–1583.
- Botvinick, M., Jha, A. P., Bylsma, L. M., Fabian, S. A., Solomon, P. E., & Prkachin, K. M. (2005). Viewing facial expressions of pain engages cortical areas involved in the direct experience of pain. *NeuroImage*, 25, 312–319.
- Bourgeois, P., & Hess, U. (1999). Emotional reactions to political leaders' facial displays: A replication. *Psychophysiology*, 36, S36.
- Calder, A. J., Keane, J., Manes, F., Antoun, N., & Young, A. W. (2000). Impaired recognition and experience of disgust following brain injury. *Nature Neurosci*, 3, 1077–1078.
- Carr, L., Iacoboni, M., Dubeau, M. C., Mazziotta, J. C., & Lenzi, G. L. (2003). Neural mechanisms of empathy in humans: A relay from neural systems for imitation to limbic areas. *Proceedings of the National Academy of Sciences, USA*, 100, 5497–5502.
- Craig, A. D. (2004). Human feelings: Why are some more aware than others? *Trends in Cognitive Science* 8, 239–241.
- Critchley, H. D. (2005). Neural mechanisms of autonomic, affective, and cognitive integration. *Journal of Comparative Neurology*, 493, 154–166.
- Damasio, A. R. (1999). *The feeling of what happens*. London: Random House.
- Damasio, A. R. (2003). *Looking for Spinoza: Joy, sorrow and the feeling brain*. New York: Hartcourt.
- Dapretto, M., Davies, M. S., Pfeifer, J. H., Scott, A. A., Sigman, M., Bookheimer, S. Y., et al. (2006). Understanding emotions in others: Mirror neuron dysfunction in children with autism spectrum disorders. *Nature Neurosci*, 9, 28–30.
- Eickhoff, S. B., Heim, S., Zilles, K., & Amunts, K. (2006). Testing anatomically specified hypotheses in functional imaging using cytoarchitectonic maps. *NeuroImage*, 32, 570–582.
- Ferrari, P. F., Gallese, V., Rizzolatti, G., & Fogassi, L. (2003). Mirror neurons responding to the observation of ingestive and communicative mouth actions in the monkey ventral premotor cortex. *European Journal of Neuroscience*, 17, 1703–1714.

- Fogassi, L., Ferrari, P. F., Gesierich, B., Rozzi, S., Chersi, F., & Rizzolatti, G. (2005). Parietal lobe: From action organization to intention understanding. *Science*, *308*(5722), 662–667.
- Friston, K. J., Buechel, C., Fink, G. R., Morris, J., Rolls, E., & Dolan, R. J. (1997). Psychophysiological and modulatory interactions in neuroimaging. *NeuroImage*, *6*, 218–229.
- Friston, K. J., Holmes, A. P., Worsley, K. J., Poline, J. B., Frith, C. D., & Frackowiak, R. J. S. (1995). Statistical parametric maps in functional imaging: A general linear approach. *Human Brain Mapping*, *3*, 189–210b.
- Gallese, V., Fadiga, L., Fogassi, L., & Rizzolatti, G. (1996). Action recognition in the premotor cortex. *Brain*, *119*, 593–609.
- Gallese, V., & Goldman, A. (1998). Mirror neurons and the simulation theory of mind-reading. *Trends in Cognitive Sciences*, *2*(12), 493–501.
- Gallese, V., Keysers, C., & Rizzolatti, G. (2004). A unifying view of the basis of social cognition. *Trends in Cognitive Sciences* *8*(9), 396–403.
- Gazzola, V., Aziz-Zadeh, L., & Keysers, C. (2006). Empathy and the somatotopic auditory mirror system in humans. *Current Biology*, *16*, 1824–1829.
- Gazzola, V., van der Worp, H., Mulder, T., Wicker, B., Rizzolatti, G., & Keysers, C. (2007). Aphasics born without hands mirror the goal of hand actions with their feet. *Current Biology*, *17*, 1235–1240.
- Geweke, J. (1982). Measurement of linear dependence and feedback between multiple time series. *Journal of the American Statistical Association*, *77*(378), 304–313.
- Goebel, R., Roebroeck, A., Kim, D. S., & Formisano, E. (2003). Investigating directed cortical interactions in time-resolved fMRI data using vector autoregressive modeling and Granger causality mapping. *Magnetic Resonance Imaging*, *21*, 1251–1261.
- Goldman, A. I., & Sripada, C. S. (2005). Simulationist models of face-based emotion recognition. *Cognition*, *94*, 193–213.
- Granger, C. W. T. (1969). Investigating causal relations by econometric models and cross-spectral methods. *Econometrica*, *37*, 424–438.
- Gray, M. A., Harrison, N. A., Wiens, S., & Critchley, H. D. (2007). Modulation of emotional appraisal by false physiological feedback during fMRI. *PLoS ONE*, *2*, e546.
- Gump, B. B., & Kulik, J. A. (1997). Stress, affiliation and emotional contagion. *Journal of Personality and Social Psychology*, *72*, 305–319.
- Hennenlotter, A., Schroeder, U., Erhard, P., Castrop, F., Haslinger, B., Stoeker, D., et al. (2005). A common neural basis for receptive and expressive communication of pleasant facial affect. *NeuroImage*, *26*, 581–591.
- Hess, U., Blairy, S., & Philippot, P. (1999). Facial mimicry. In P. Philippot, R. Feldman, & E. Coats (Eds.), *The social context of nonverbal behavior* (pp. 213–241). New York: Cambridge University Press.
- Jabbi, M., Swart, M., & Keysers, C. (2007). Empathy for positive and negative emotions in the gustatory cortex. *NeuroImage*, *34*, 1744–1753.
- Jackson, P. L., Meltzoff, A. N., & Decety, J. (2005). How do we perceive the pain of others? A window into the neural processes involved in empathy. *NeuroImage*, *24*, 771–779.
- Jackson, P. L., Rainville, P., & Decety, J. (2006). To what extent do we share the pain of others? Insight from the neural bases of pain empathy. *Pain*, *125*(1–2), 5–9.
- James, W. (1884). What is an emotion. *Mind*, *9*, 188–205.
- Keysers, C., & Gazzola, V. (2006). Towards a unifying neural theory of social cognition. *Progress in Brain Research*, *156*, 379–401.
- Keysers, C., & Gazzola, V. (2007). Integrating simulation and theory of mind: From self to social cognition. *Trends in Cognitive Sciences*, *11*, 194–196.
- Keysers, C., Kohler, E., Umiltà, M. A., Nanetti, L., Fogassi, L., & Gallese, V. (2003). Audiovisual mirror neurons and action recognition. *Experimental Brain Research*, *153*, 628–636.
- Keysers, C., Wicker, B., Gazzola, V., Anton, J. L., Fogassi, L., & Gallese, V. (2004). A touching sight: SII/PV activation during the observation and experience of touch. *Neuron*, *42*, 335–346.
- Kohler, E., Keysers, C., Umiltà, M. A., Fogassi, L., Gallese, V., & Rizzolatti, G. (2002). Hearing sounds, understanding actions: Action representation in mirror neurons. *Science*, *297*(5582), 846–848.
- Lamm, C., Batson, C. D., & Decety, J. (2007). The neural substrate of human empathy: Effects of perspective-taking and cognitive appraisal. *Journal of Cognitive Neuroscience*, *19*, 42–58.
- Lanzetta, J. T., & Englis, B. G. (1989). Expectations of cooperation and competition and their effects on observers' vicarious emotional responses. *Journal of Personality and Social Psychology*, *33*, 354–370.
- Leslie, K. R., Johnson-Frey, S. H., & Grafton, S. T. (2004). Functional imaging of face and hand imitation: Towards a motor theory of empathy. *NeuroImage*, *21*, 601–607.
- Lipps, T. (1907). Das wissen von fremden Ichen [The knowledge of foreign I]. In T. Lipps (Ed.), *Psychologische Untersuchungen [Psychological Research]* (Vol. 1). Leipzig, Germany: Engelmann.
- Martin, G. B., & Clark, R. D. (1987). Distress crying in neonates: Species and peer specificity. *Developmental Psychology*, *18*, 3–9.
- McHugo, G. J., Lanzetta, J. T., & Bush, L. K. (1991). The effect of attitudes on emotional reactions to expressive displays of political leaders. *Nonverbal Behavior*, *15*, 19–41.
- Moriguchi, Y., Decety, J., Ohnishi, T., Maeda, M., Mori, T., Nemoto, K., et al. (2007). Empathy and judging other's pain: An fMRI study of alexithymia. *Cerebral Cortex*, *17*, 2223–2234.
- Morrison, I., Lloyd, D., di Pellegrino, G., & Roberts, N. (2004). Vicarious responses to pain in anterior cingulate cortex: Is empathy a multisensory issue? *Cognitive, Affective and Behavioral Neuroscience*, *4*, 270–278.
- Nichols, T. E., & Holmes, A. P. (2001). Nonparametric permutation tests for functional neuroimaging: A primer with examples. *Human Brain Mapping*, *15*, 1–25.
- Petrides, M., Cadoret, G., & Mackey, S. (2005). Orofacial somatomotor responses in the macaque monkey homologue of Broca's area. *Nature*, *435*(7046), 1235–1238.
- feifer, J. H., Iacoboni, M., Mazziotta, J. C., & Dapretto, M. (2008). Mirroring others' emotions relates to empathy and interpersonal competence in children. *NeuroImage*, *39*, 2076–2085.
- Roebroeck, A., Formisano, E., & Goebel, R. (2005). Mapping directed influence over the brain using Granger causality and fMRI. *NeuroImage*, *25*, 230–242.
- Saarela, M. V., Hlushchuk, Y., Williams, A. C., Schurmann, M., Kalso, E., & Hari, R. (2007). The compassionate brain: Humans detect intensity of pain from another's face. *Cerebral Cortex*, *17*, 230–237.
- Schneider, F., Gur, R. C., Gur, R. E., & Muenz, L. R. (1994). Standardized mood induction with happy and sad facial expressions. *Psychiatry Research*, *51*, 19–31.
- Singer, T. (2007a). The neuronal basis of empathy and fairness. *Novartis Foundation Symposium*, *278*, 20–30.
- Singer, T. (2007b). The neuronal basis of empathy and fairness: Discussion. *Novartis Foundation Symposium*, *278*, 30–40, 89–96, 216–21.
- Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R. J., & Frith, C. D. (2004). Empathy for pain involves the affective but not sensory components of pain. *Science*, *303*(5661), 1157–1162.
- Singer, T., Seymour, B., O'Doherty, J. P., Stephan, K. E., Dolan, R. J., & Frith, C. D. (2006). Empathic neural responses are modulated by the perceived fairness of others. *Nature*, *439*(7075), 466–469.
- van der Gaag, C., Minderaa, R., & Keysers, C. (2007). Facial expressions: What the mirror neuron system can and cannot tell us. *Social Neuroscience*, *2*, 179–222.
- Wicker, B., Keysers, C., Plailly, J., Royet, J. P., Gallese, V., & Rizzolatti, G. (2003). Both of us disgusted in My insula: The common neural basis of seeing and feeling disgust. *Neuron*, *40*, 655–664.

Received January 31, 2008

Revision received August 6, 2008

Accepted August 15, 2008 ■