Individual Variation in Neural Correlates of Sadness in Children: A Twin fMRI Study

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Abstract: Functional neuroimaging studies show substantial individual variation in brain activation accompanying the experience of emotion, including sadness. Here we used functional magnetic resonance imaging (fMRI) in 104 pairs of 8-year-old twins (47 MZ, 57 DZ) to assess genetic-environmental contributions to individual differences in neural activation in two prefrontal cortex (PFC) areas previously shown to be involved in sadness. No genetic effects were found for any area, individual environmental factors entirely accounting for individual variation in brain activation related to sadness. Sadness being the prevailing mood in depression, these findings may be of relevance to the etiology of childhood depressive disorders. *Hum Brain Mapp 28:482–487, 2007.* © 2007 Wiley-Liss, Inc.

Key words: twin study; heritability; fMRI; emotion; sadness; genetics; environment; etiology; prefrontal cortex; interindividual variability

INTRODUCTION

The subjective experience of emotion is a conscious process [Lane, 2000] by which the emotional "tone" is given to a particular arousing situation. Heteromodal associative brain areas that integrate signals coming from different sensory modalities mediate this process. The assessment of an emotionally charged situation involves the interpretation of external stimuli (e.g., visual, auditory, somatosensory) as well as of internal sensations (changes in the viscera) caused by the situation. The signals associated with these stimuli and sensations converge in PFC areas

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Received for publication 10 January 2007; Revised 1 March 2007; Accepted 5 March 2007

DOI: 10.1002/hbm.20400

Published online 16 April 2007 in Wiley InterScience (www.interscience.wiley.com).

[Mesulam, 2000] where significance is attributed to the situation. The subjective experience of emotion follows [Damasio et al., 2000; Lane, 2000].

Several functional neuroimaging studies using group analysis [Beauregard et al., 2003; Damasio et al., 2000; Eugene et al., 2003; Phan et al., 2002; Reiman et al., 1997] have shown that two heteromodal associative brain areas, namely the medial prefrontal cortex (MPFC) (Brodmann area [BA] 10) and the ventrolateral prefrontal cortex (VLPFC) (BA 47), are implicated in the subjective experience of sadness. With respect to this issue, a positive correlation has been demonstrated between BOLD signal increases in the VLPFC (BA 47) and the self-rated intensity of the subjective experience of sadness [Beauregard et al., 2003]. As for the MPFC (BA 10), various lines of evidence indicate that this prefrontal cortical area is involved in the metacognitive representation of one's own emotional state [Lane, 2000].

Other functional neuroimaging studies have shown, however, that there are major individual differences in activation patterns in the VLPFC and the MPFC when sadness is experienced [Eugene et al., 2003; Phan et al., 2002]. Phenotypic variation in a population can be caused by genetic differences between individuals or by differential exposure to environmental factors, or a combination of both. Environmental effects can be divided into those that are shared by family members and those that are unique to individuals. The twin design that we are using does not purport to assess whether a particular phenotype, such as brain activation, is "genetic" or "environmental". By definition, all phenotypes develop through the joint action of genotype and environment. However, phenotypic *variation*, i.e., differences between individuals in the expression of a particular phenotype, can be caused by genetic and/or environmental differences between individuals. The twin design makes it possible to tease apart and quantify these respective contributions of genes, shared environment, and nonshared environment to phenotypic variance [Neale and Cardon, 1992], a necessary first step in understanding the etiology of mental and physical disorders.

METHODS

Subjects

Two hundred and nineteen pairs of twins aged 8 years 4 months from the Quebec Newborn Twin Study [Brendgen et al., 2005; Forget-Dubois and Pérusse, 1997; Pérusse, 1995] participated in the present experiment. Since we were interested in naturally occurring variation in a population-based sample, all subjects were included in the study regardless of gender and history of neurological or psychiatric disorder. There were two inclusion criteria: (1) both twins of a pair had to have successfully completed the fMRI acquisition protocol and (2) head movement had to be less than three voxels in one of the x, y, or z axis when realigning the images. Based on these criteria, 104 twin pairs were included (MZ = 47, DZ = 57). Zygosity was determined by genotyping of 8–10 highly polymorphic DNA markers [Forget-Dubois et al., 2003]. The study was approved by the ethics review boards of Ste. Justine Hospital and CHUM-Notre-Dame Hospital. Written informed consent was obtained from parents of all subjects as well as written assent from all subjects.

Behavioral Protocol

BOLD signal changes were measured while subjects first viewed five blocks of emotionally neutral excerpts showing adults performing a TV news interview (reference task), followed by five blocks of sad film excerpts (activation task) depicting the death of a father. These excerpts had been previously validated [Gross and Levenson, 1995] and used in several studies of sadness induction [Eugene et al., 2003; Lévesque et al., 2003]. This block design was used to avoid the contamination of the neutral stimuli by the sad stimuli [Garrette and Maddock, 2001]. Each block lasted 39 s and was separated by resting periods of 15 s, during which subjects were instructed to fixate a white cross on a black screen. To assess the subject's subjective response to the stimuli (neutral and sad), children were instructed to identify the emotion (happiness, surprise, anger, sadness, fear, disgust, or none) that they felt using a visual analog scale presented immediately after the run.

Image Acquisition

Echoplanar images (EPI) were acquired on a 1.5-Tesla system (Magnetom Vision, Siemens Electric, Erlangen, Germany). Twenty-eight slices (5 mm thick) were acquired every 2.65 s in an inclined axial plane, aligned with the anterior commissure-posterior commissure axis. These T2*-weighted functional images were acquired using an EPI pulse sequence (time repetition [TR] = 0.8 ms, time-echo [TE] = 54 ms, flip = 90°, field of view [FOV] = 215 mm, matrix = 64 × 64, voxel size = 3.36 mm × 3.36 mm × 5 mm). Following functional scanning, high-resolution data were acquired via a T1-weighted three-dimensional volume acquisition obtained using a gradient echo pulse sequence (TR = 9.7 ms, TE = 4 ms, flip = 12°, FOV = 250 mm, matrix = 256 × 256, voxel size = 0.94 mm^3).

Image Analysis

Data were analyzed using Statistical Parametric Mapping software (SPM2, Wellcome department of Cognitive Neurology, London, UK). Images for all subjects were realigned to correct for artifacts due to small head movements. To obtain standardized data, the images for all subjects were then spatially normalized into an EPI stereotaxic space (Montreal Neurological Institute [MNI] template). The MNI adult template was used to derive Talairach and Tournoux [1988] coordinates defining the ROIs. Burgund et al. [2002] have shown that there are no significant differences in the use of an adult or child template in fMRI

TABLE I. Genetic modeling of intensity of sadness-related activation in PFC areas

Brain areas	Mean ($n = 208$)	SD ($n = 208$)	Intraclass correlations (n MZ = 94, n DZ = 114)	A, C, and E% of variance from best-fitting model (E in all cases)
rMPFC BA10				
SR	41.96	43.498	MZ = −0.19 (CI = −0.46; 0.14), DZ = −0.16 (CI = −0.41; 0.13)	$A = 0$, $C = 0$, $E = 100$
ZS	2.858	2.858	MZ = −0.04 (CI = −0.24; 0.15), DZ = −0.26 (CI = −0.37; 0.12)	$A = 0$, $C = 0$, $E = 100$
lMPFC BA10				
SR	32.65	40.454	MZ = −0.03 (CI = −0.32; 0.26), DZ = −0.19 (CI = −0.45; 0.05)	$A = 0$, $C = 0$, $E = 100$
ZS	2.654	2.654	MZ = 0.10 (CI = −0.18; 0.39) DZ = −0.11 (CI = −0.37; 0.15)	$A = 0$, $C = 0$, $E = 100$
rVLPFC BA47				
SR	32.08	36.634	MZ = 0.03 (CI = −0.26; 0.31), DZ = −0.13 (CI = −0.39; 0.13)	$A = 0$, $C = 0$, $E = 100$
ZS	2.692	0.982	MZ = 0.008 (CI = −0.28; 0.29), DZ = −0.12 (CI = −0.38; 0.14)	$A = 0$, $C = 0$, $E = 100$
lVLPFC BA47				
SR	29.18	35.355	MZ = −0.15 (CI = −0.43; 0.13), DZ = −0.05 (CI = −0.31; 0.21)	$A = 0$, $C = 0$, $E = 100$
ZS	2.611	0.968	MZ = −0.11 (CI = −0.4; 0.18), DZ = 0.04 (CI = −0.23; 0.3)	$A = 0$, $C = 0$, $E = 100$

Random effect multilevel modeling of twin data allows for a full likelihood estimation and testing strategy. The full model estimates six parameters: mean, within-pair variance, and between-pair variance for both MZ and DZ twin groups separately. Etiologic submodels (*ACE*, *AE*, *CE*, *E*) account for the data using fewer parameters. For example, the *ACE* model explains the data using only four parameters: one global mean for all subjects (i.e., the phenotypic mean is not expected to differ according to zygosity), additive genetic effects (*A*), environmental effects common to twins of a pair (*C*), and environmental effects unique to individuals (*E*). The best-fitting model is the one with the best-goodness-of-fit and greatest parsimony compared with the full model, based on the χ^2 statistics and the Akaike Information Criterion. The estimates for each model yield the percentages of explained variance for each parameter. For all measures, the only parameter contributing to the phenotypic variance was *E*.
SR, Spatial range, in term of number of voxels activated in each area; ZS, *Z*-score associated with the local maximum for each area; CI = 95% confidence interval.

studies of children. Images were then convolved in space with a three-dimensional isotropic Gaussian kernel (6 mm FWHM) to improve the signal-to-noise ratio.

Statistical Analysis

For all subjects, individual statistical parametric maps were generated on a voxel-by-voxel basis (height threshold: $P = 0.05$ uncorrected) by contrasting the brain activity associated with the viewing of the sad film excerpts and that associated with the viewing of the emotionally neutral excerpts (i.e., Sad minus Neutral). Voxel values for this contrast yielded a statistical parametric map of the *t* statistic (SPM *t*), subsequently transformed to the unit normal distribution (SPM Z). We then used the number of voxels and the *Z*-score associated with the local maxima for each of the two brain regions of interest (ROIs), i.e., MPFC (BA 10) and VLPFC (BA 47), bilaterally, yielding eight phenotypic measures of brain activation related to sadness (Table I). The standard deviation was equal to or greater than the mean for six out of the eight variables, which shows the large amount of individual variation for these phenotypes.

Quantitative Genetic Modeling

According to quantitative genetic theory, phenotypic variation can result from genetic and/or environmental variation occurring naturally within populations. Additive genetic effects (*A*) cause genetically related individuals to resemble each other. Common (*C*) environmental factors shared between members of a family also contribute to familial aggregation, whereas environmental factors uniquely experienced by individuals (*E*) cause differences within families. In a twin design, *A* factors thus contribute only to the between-pair phenotypic variance in MZ twins who share all their genes, whereas they generate between-pair and within-pair variance equally in DZ twins who share half their genes on average. *C* factors contribute to between-pair variance only whereas *E* factors generate between-individual (within-pair) variance only, irrespective of zygosity.

Because twins are clustered within pairs, forming a natural two-level hierarchy, we used random effect multilevel modeling [Dubois et al., in press; Guo and Wang, 2002; Pérusse, 1999]. A multilevel model has two parts: a fixed component, which represents the average relation for all individuals regardless of grouping, and a random compo-

nent, which accounts for the variation at each level. We first built a model that completely specifies the means, between-pair and within-pair variances separately for MZ and DZ twins. Thus, the predicted means, variances, and covariances of this saturated model are equal to their observed values in both twin groups. This can be written as a random effect model with six parameters:

$$P_{ij} = \mu_{MZ}MZ_i + \mu_{DZ}DZ_i + \lambda_{MZ(B)}\eta_i^{MZ(B)}MZ_i + \lambda_{DZ(B)}\eta_i^{DZ(B)}DZ_i + \lambda_{MZ(W)}\eta_{ij}^{MZ(W)}MZ_i + \lambda_{DZ(W)}\eta_{ij}^{DZ(W)}DZ_i$$

where P_{ij} is the phenotype of individual j (level 1) in the i^{th} pair (level 2), and MZ_i and DZ_i are observed indicator variables denoting zygosity. Thus, μ_{MZ} is a fixed parameter that represents the mean phenotypic value across MZ twins, whereas μ_{DZ} models the mean across DZ twins. The random (latent) variables $\eta_i^{MZ(B)}$ and $\eta_i^{DZ(B)}$ vary only between twin pairs with unit variance and represent the between-pair variation for MZ and DZ twins, respectively. In the same way, the random (latent) variables $\eta_{ij}^{MZ(W)}$ and $\eta_{ij}^{DZ(W)}$ vary between individuals with unit variance, and represent the within-pair variation for MZ and DZ twins, respectively. Finally, the parameters, $\lambda_{MZ(B)}$, $\lambda_{DZ(B)}$, $\lambda_{MZ(W)}$, and $\lambda_{DZ(W)}$ are factor loadings for $\eta_i^{MZ(B)}$, $\eta_i^{DZ(B)}$, $\eta_{ij}^{MZ(W)}$, and $\eta_{ij}^{DZ(W)}$, respectively. Random effect models are commonly used in genetics, and allow for a full likelihood estimation of all parameters.

In a twin design, the random part of the model can be specified to reflect the additive genetic (A), common environmental (C), and individual environmental (E) components of phenotypic variance described above. The specification for the ACE model can be written as:

$$P_{ij} = \mu + \alpha A_i^{MZ(B)}MZ_i + \alpha A_i^{DZ(B)}DZ_i + \alpha A_{ij}^{DZ(W)}DZ_i + cC_i + eE_{ij}$$

where P_{ij} is the measured phenotype of the j^{th} individual in the i^{th} twin pair, and μ is a constant representing the mean phenotypic value for both MZ and DZ twins. The random variables C_i and E_{ij} are pair-level and individual-level effects of common and individual environmental influences, respectively, for all twins. Both have unit variance. The observed variables MZ_i and DZ_i are indicator variables denoting zygosity of the i^{th} pair, and are thus indices of genetic similarity. Therefore, the random variables $A_i^{MZ(B)}$ and $A_i^{DZ(B)}$ represent the effects of genetic similarity on the phenotype, and $A_{ij}^{DZ(W)}$ represents the effects of genetic dissimilarity on the phenotype in DZ twins. Since MZ twins are identical genetically, there are only common genetic effects in these twins. However, there are two genetic components contributing equally to phenotypic variance in DZ twins, one common and one unique, corresponding to the shared and unshared genetic effects, respectively. Thus, we have the following constraints on the genetic variances:

$$\mathrm{Var}\left(A_i^{MZ(B)}\right) = 1$$

and

$$\mathrm{Var}\left(A_i^{DZ(B)}\right) = \mathrm{Var}\left(A_{ij}^{DZ(W)}\right) = \frac{1}{2}.$$

The resulting ACE model estimates four parameters (phenotypic mean, additive genetic variance, common environ-

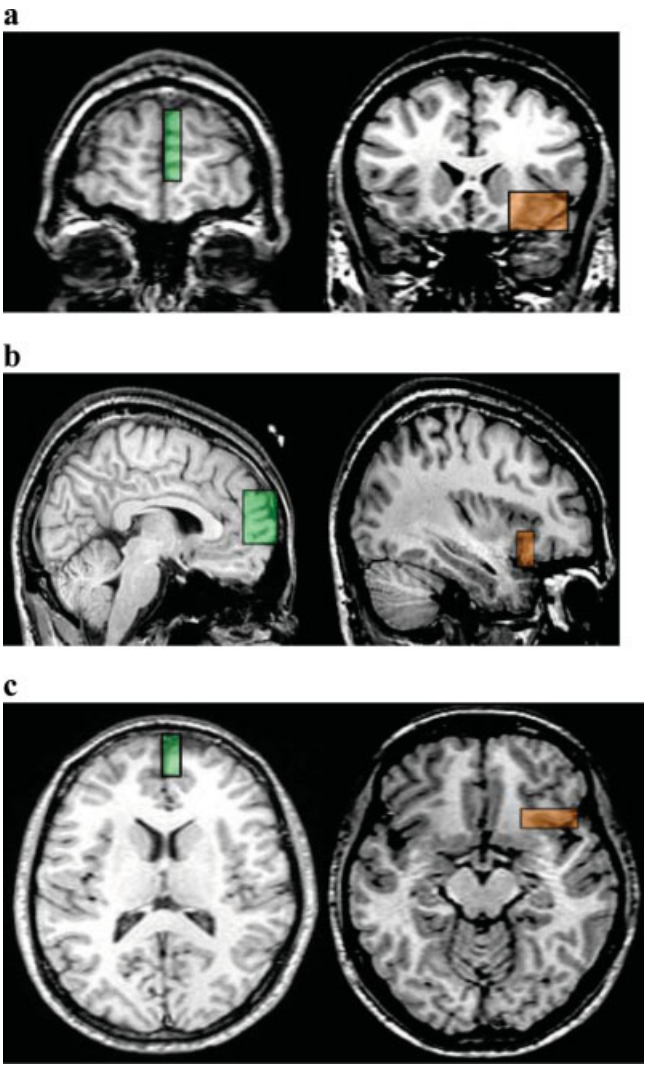

Figure 1.
Anatomical sections showing coronal (**a**), sagittal (**b**), and axial (**c**) views of the VLPFC (BA 47) (in orange, on the right) and the MPFC (BA 10) (in green, on the left). Talairach coordinates are $x = 36/-36$, $y = 20$, $z = -11$ for the VLPFC and $x = 5/-5$, $y = 61$, $z = 10$ for the MPFC.

mental variance, and unique environmental variance), and thus has two degrees of freedom. Specifications are similarly formulated for all nested submodels. For example, the *E* model (no genetic and no shared environmental effects) is specified from the *ACE* model by removing all genetic components at both levels and the environmental component at the between-pair level, thus leaving two parameters (phenotypic mean and unique environmental variance) to estimate and four degrees of freedom. All modeling was performed with house-scripts using Mplus V.4 (Muthen & Muthen).

RESULTS

The intensity of the BOLD signal changes was measured in two a priori defined ROIs: MPFC (BA10) (right hemisphere: rMPFC; left hemisphere: lMPFC) and VLPFC (BA47) (right hemisphere: rVLPFC; left hemisphere: lVLPFC) (Fig. 1). For each of the ROIs and each subject, we reasoned that BOLD signal changes could be conceptualized in terms of spatial range of the activation (i.e., the number of voxels activated) and *Z*-score associated with the local maximum (i.e., the voxel activated more intensely in a region). To obtain a continuum of phenotypic measures for all subjects, we used a probability threshold uncorrected for multiple comparisons of $P \leq 0.05$ for individual analysis. The use of such an uncorrected threshold was motivated by the fact that we are not in the discovery phase of the neural correlates of sadness, but rather in the evaluation of individual differences in activation patterns within brain areas that have previously been identified as correlated to sadness [Beauregard et al., 2003; Damasio et al., 2000; Eugene et al., 2003; Phan et al., 2002; Reiman et al., 1997].

We found significant activations and substantial activation variation in all brain regions examined (Table I). To assess the internal and external validity of our measures, we computed correlations between *Z*-score values and the number of voxels activated for each ROI. We found that the greater the spatial range of the activation (number of voxels activated with a probability threshold of $P < 0.05$), the higher the *Z*-score value associated with the voxel more intensely activated in the area (the local maximum). Correlations were uniformly high for all areas: rMPFC (BA10) $r = 0.755$, $P < 0.0001$; lMPFC (BA10) $r = 0714$, $P < 0.0001$; rVLPFC (BA47) $r = 0.755$, $P < 0.0001$; lVLPFC (BA47) $r = 0.779$, $P < 0.0001$ (at α level $= 0.01$, two-tailed). Among the six emotions that could be subjectively reported after completion of the task, 89.65% of subjects reported having experienced sadness only. These results suggest that our measures of neural activation related to the external induction of sadness were highly valid.

Intraclass correlations were then calculated for MZ and DZ twins, respectively (Table I). All correlations were found to be nonsignificant and equal for both types of twins. This suggested a complete lack of familial aggregation, and thus of genetic effects and shared environmental influences on individual differences in sadness-related brain activation in all regions examined. We proceeded to formal quantitative genetic model-fitting to estimate the precise contributions of additive genetic effects (*A*), common (*C*) and unique (*E*) environmental influences on neural activation. For all regions examined, the best-fitting and most parsimonious model was an *E* model, indicating that individual variation in sadness-related brain activation was entirely accounted for by environmental factors uniquely experienced by children in a family (Table I).

DISCUSSION

The few structural MRI twin studies to date have shown that genetic contribution to individual differences in human brain anatomy are generally high but regionally variable, with heritability ranging from nil to nearly 100% [Baare et al., 2001; Thompson et al., 2001; Wright et al., 2002]. To our knowledge, however, the present study is the first to investigate brain activation using functional neuroimaging in twins. The interindividual variability in cerebral patterns in response to sadness observed in our study could not be attributed to any additive genetic effects or family environmental influences. Remarkably, we found that environmental effects that are not shared by members of the same family and are unique to individuals accounted entirely for the substantial individual differences observed in sadness-related brain activation. These unique environmental factors comprise all aspects of the physical and social environment experienced differentially by individuals in a family, such as birth complications, illness, physical and psychological trauma, relations with parents, siblings, peers, teachers, etc. Again, these findings should not be interpreted to mean that genes and family environment do not interact to produce the neurobiological substrate of emotion and sadness, but rather that they do not contribute to the widespread individual variation in the functional activation of this substrate.

In quantitative genetics, the *E* component of variance may include measurement error. However, it seems improbable that the present findings are attributable to measurement error, since test–retest reliability of fMRI has been demonstrated in several methodological studies involving sensory, motor, cognitive, and emotional tasks [for example, Brannen et al., 2001; Kurland et al., 2004; Manoach et al., 2001; Noll et al., 1997]. The strong correlations found between the two variables (SR and ZS) for each region also denote lawful relationships, which are not compatible with significant measurement error. Finally, this is the largest twin fMRI study to date, with ample power to disentangle reliable environmental effects from genetic influences if present.

Our results are congruent with developmental theories that envision emotional expression and experience as strongly linked to the development of the child's personal

social relationships and his understanding of others [Ekman and Davidson, 1994]. Our findings may also be of etiologic relevance for depressive disorders, in which sadness is the prevailing mood [APA, 1994], given that we found substantial correlations between sadness and depression scores: in the same sample [Mancini-Marïe et al., submitted]. It thus appears likely that environmentally induced neural plasticity in the human brain accounts for the development of individual emotional style linked to sadness in the normal, and perhaps abnormal, range.

ACKNOWLEDGMENTS

The authors thank Nancy Illick, Claude Kauffmann, and Jocelyn Malo for technical assistance. C.C. was supported by a Social Sciences and Humanities Research Council of Canada fellowship. This study was supported by grants from the Fonds de la recherche en santé du Québec and Hôpital Sainte-Justine (to D.P.).

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