The Location of Feedback-Related Activity in the Midcingulate Cortex Is Predicted by Local Morphology

Céline Amiez,^{1,2} Rémi Neveu,³ Delphine Warrot,^{1,2} Michael Petrides,⁴ Kenneth Knoblauch,^{1,2} and Emmanuel Procyk^{1,2}

¹Institut National de la Santé et de la Recherche Médicale U846, Stem Cell and Brain Research Institute, 69675 Bron, France, ²Université de Lyon, Lyon 1, Unité Mixte de Recherche S-846, 69003 Lyon, France, ³Neuroscience Research Center, Centre National de la Recherche Scientifique, Unité Mixte de Recherche 5292, Institut National de la Santé et de la Recherche Médicale, Université de Lyon, 69366 Lyon, France, and ⁴Montreal Neurological Institute, McGill University, Montreal, Quebec H3A2B4, Canada

Information processing in the medial frontal cortex is often said to be modulated in pathological conditions or by individual traits. This has been observed in neuroimaging and event-related potential studies centered in particular on midcingulate cortex (MCC) functions. This region of the brain is characterized by considerable intersubject morphological variability. Whereas in a subset of hemispheres only a single cingulate sulcus (cgs) is present, a majority of hemispheres exhibit an additional sulcus referred to as the paracingulate sulcus (pcgs). The present functional magnetic resonance imaging study defined the relationship between the local morphology of the cingulate/paracingulate sulcal complex and feedback-related activity. Human subjects performed a trial-and-error learning task in which they had to discover which one of a set of abstract stimuli was the best option. Feedback was provided by means of fruit juice, as in studies with monkeys. A subject-by-subject analysis revealed that the feedback-related activity during exploration was systematically located in the cgs when no pcgs was observed, but in the pcgs when the latter sulcus was present. The activations had the same functional signature when located in either the cgs or in the pcgs, confirming that both regions were homologues. Together, the results show that the location of feedback-related MCC activity can be predicted from morphological features of the cingulate/paracingulate complex.

Introduction

Understanding the functional organization of the human cingulate cortex has significantly advanced in the last 15 years (Rushworth et al., 2007; Shackman et al., 2011; Vogt, 2009a). A clearer description of the different regions of the cingulate gyrus, such as anterior, mid (MCC), posterior, and retrosplenial regions, has contributed to a resolution of the confusion created in the past by the use of earlier nomenclatures (Vogt, 2009a,b). With regard to the MCC region, convergent data suggest that it is involved in performance monitoring, although its precise role remains to be clarified (Botvinick et al., 2004; Rushworth et al., 2012).

We here propose, as have others (Bush, 2009; Shackman et al., 2011), that problems in determining the exact function of the MCC arise in part from the considerable intersubject morphological variability in the cingulate regions. The cingulate sulcus (cgs) can be continuous or divided into segments. In addition, a

supplementary sulcus referred to as the paracingulate sulcus (pcgs) is observed in >75% of subjects in at least one of the cerebral hemispheres (Paus et al., 1996a,b; Fornito et al., 2008; Buda et al., 2011). The location of cytoarchitectonic areas in MCC, and in particular area 32', depends on the presence or absence of the pcgs (Vogt et al., 1995). Intersubject variability can thus be an important confounding factor in anatomo-functional studies in normal and pathological populations, especially when using group-averaged data.

Subject-by-subject assessment of potential links between function and the local cingulate/paracingulate morphology might help disambiguate the role of subregions of the MCC in specific processes (Bush, 2009). In the lateral frontal cortex, single-subject studies have enabled precise morphology–function relationships to be established within the dorsal premotor cortex (Amiez et al., 2006), the supplementary eye field (Grosbras et al., 1999), and the inferior frontal junction (Derrfuss et al., 2012).

Studies in both the monkey and human subjects suggest that the MCC is critically involved in behavioral error analysis (Holroyd and Coles, 2002), and more generally in processing any feedback relevant for behavioral adaptation (Rushworth et al., 2007; Quilodran et al., 2008; Amiez and Petrides, 2009). Does this functional contribution map onto particular parts of the extensive and morphologically variable MCC region? Alternative interpretations of MCC activity during behavioral adaptation (e.g., conflict monitoring) also lack conclusive evidence for specific anatomo-functional relations (Rushworth et al., 2007). Furthermore, although results from monkey and human studies are

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Correspondence should be addressed to Dr. Céline Amiez, Stem Cell and Brain Research Institute, Institut National de la Santé et de la Recherche Médicale U846, 18, Avenue du Doyen Lépine, 69675 Bron, France. E-mail: celine.amiez@inserm.fr.

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Figure 1. Protocol and behavioral results. **A**, The subjects had to find by trial and error which one of the three stimuli led to the highest juice feedback value (stimulus A) by selecting one stimulus through a press on the corresponding mouse button. Note that the same stimuli appeared on successive trials until the problem was completed (i.e., after discovery and repetition of the correct response). Stimuli B and C refer to incorrect stimuli. There were four conditions, presented pseudo-randomly, and indicated by the color of the fixation cross throughout the entire trial (table inset). **B**, The percentage of correctly solved problems (i.e., with no repetition of erroneous choice in exploratory periods and without erroneous choice in the exploitative periods) for each condition. **C**, Response times (RTs) for the 4 conditions and for each trial type (NEGexplore, incorrect during exploration; POSexplore, first correct trial; POSexploit, correct during exploitation) between the 4 conditions and the 3 trial types. Error bars represent SEM. * $p < 0.05$, *post hoc* Fisher test.

often discussed (Botvinick et al., 2004; Cole et al., 2009), discrepancies in task designs used with the two species contribute to interpretational difficulties.

In the present functional magnetic resonance imaging (fMRI) study, we investigate how feedback processing foci may relate to individual morphological variability in the sulci of the MCC region. For comparison with previous monkey studies, we used a trial-and-error task with fruit juice as feedback. Results clearly demonstrated that MCC feedback-related activity occurring only during exploration relates to specific morphological features of the cingulate/paracingulate sulcal complex.

Materials and Methods

Subjects. Fifteen healthy volunteers (7 females and 8 males, mean age = 26.3 years $\pm$ 4.5 SD) participated in this fMRI study. Informed, written consent was obtained from all the participants according to the institutional guidelines established by the local ethics committee (Comité de Protection des Personnes Sud-Est IV).

Protocol. Subjects performed a problem-solving task in which they had to discover by trial and error in successive trials which one of three simultaneously presented abstract stimuli was associated with positive feedback (i.e., the largest juice reward, the others being considered as negative feedback). In each successive “problem”, subjects

searched for and then exploited the correct response; hence, two periods were distinguished in this task: an exploration and an exploitation period. In each problem, the correct stimulus was randomly selected by the computer. In each trial, three abstract unknown stimuli appeared simultaneously at the three possible locations on the screen for 2 s (Fig. 1A). During these 2 s, the subjects had to select one of these stimuli by pressing the corresponding mouse button. Note that the spatial position of each stimulus varied randomly from trial to trial throughout a problem, thus rendering the spatial information irrelevant to task performance (Fig. 1A). After a delay varying 0.5–6 s (average = 2 s), a feedback was delivered. If the choice was incorrect, a negative feedback stimulus was presented (i.e., trials called NEGexplore) and, after an intertrial interval pseudo-randomly varying 0.5–8 s (average = 3.5 s), the same 3 stimuli were presented again at different spatial positions and the subject would make another selection. Testing proceeded in this manner until the subject found the correct stimulus, the correct choice being indicated by the delivery of the positive feedback. After the first correct choice (associated with the delivery of the first positive feedback, labeled POSexplore trials), the exploration period terminated and the exploitation period started. The exploration period lasted 1–3 trials and the exploitation period consisted of 2 trials (POSexploit trials) during which the subject could keep selecting the correct stimulus. When a problem was

solved, three new novel abstract stimuli were presented and the subject attempted to solve the new problem.

Importantly, and to reduce discrepancies with monkey experiments using similar tasks, various volumes of fruit juice were used to provide the feedback. To control for motivational state, subjects were asked not to drink for 12 h before the experiment, the experiment being always planned at 8 to 10 am. During the entire experiment, each subject drank on average 200 ml over ~75 min so he/she was not fully satiated by the end of the experiment. This is an important point as it has been shown that liquids in the mouth are considered as pleasant only when thirsty and that this feeling disappears when satiated (Rolls et al., 1980).

To equalize as much as possible sensory information provided for negative versus positive feedback, we designed 4 conditions in which negative feedback could be juice delivery. In every condition, the positive feedback corresponded to the largest reward delivery. In conditions 1 (c1), 2 (c2), 3 (c3), and 4 (c4), the positive and negative feedback values were 1.2 and 0 ml, 1.2 and 0.4 ml, 0.8 and 0 ml, and 0.8 and 0.4 ml, respectively, of fruit juice (Fig. 1). The condition was indicated by the cross placed in the center of the screen throughout the trials. A blue, yellow, green, or pink cross indicated that the subject was performing condition 1, 2, 3, or 4, respectively. These four conditions were pseudo-randomly selected for each problem (i.e., randomly selected but with the constraint that the same condition never appeared in two successive problems).

The presentation of the stimuli was controlled with Presentation 14.8 (Neurobehavioral Systems). The juice was delivered using a reward system comprising a dispenser unit that was pressure controlled and a controller unit (5-RPD-D1/D1B, Crist Instrument). This reward system permitted the delivery of precise small volumes of juice and was controlled by Presentation software. The subject received liquid volumes through a tube placed in his/her mouth delivered by the reward system. Note that a nonreturn valve at the end of the tube ensured that the volume received was exactly what the reward system delivered.

Subjects were trained on the task in a 1-h session before the fMRI session, until they reached a level of 90% correct performance on all problem types. Problems were labeled as correct when no repetition of incorrect choices occurred in the exploration period and no incorrect choices occurred in the exploitation period. Only data obtained from problems solved correctly were used for fMRI analysis.

MRI acquisition. Each volunteer was scanned using a 1.5T Siemens Sonata MRI Scanner (Siemens). Brain imaging acquisitions were performed at the imaging facility (CERMEP-imagerie du vivant, Bron, France). After a high-resolution T1 anatomical scan (whole head, 1 mm³ isotropic resolution), five functional runs of 260 images each (37 oblique T2* gradient echoplanar images, voxel size = 3.4 × 3.4 × 3.4 mm, TR = 3.5 s, TE = 50 ms, flip angle = 90°) sensitive to the blood oxygenation level-dependent (BOLD) signal were acquired. The field of view covered the whole brain. We used a tilted acquisition sequence at 30° to the anterior commissure–posterior commissure line to recover signal loss in the orbitofrontal cortex for subsequent analysis (Deichmann et al., 2003). The first trial onset in each run was synchronized with the scanner acquisition via a trigger signal generated by the scanner. Behavioral and imaging data were acquired in all trials. In each functional run, the subjects performed 24 problems (i.e., 6 problems of each condition).

Data analysis. Performance in the four task conditions was compared using an ANOVA. In addition, performance in the four task conditions was compared between the subjects exhibiting different patterns of cingulate/paracingulate complex morphology using a factorial ANOVA (with morphology patterns and conditions as factors). Finally, in the four conditions, reaction times in NEGexplore, POSexplore, and POSexploit trials in problems solved correctly were also compared using a factorial ANOVA (with trial type and conditions as factors). ANOVAs and Fisher *post hoc* tests were performed using Statistica.

Preprocessing and data analysis were performed with Statistical Parametric Mapping software (SPM8B; Wellcome Department of Cognitive Neurology, University of College London, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>) and Matlab 7.11 (www.mathworks.com). First, the first five volumes of each run were removed to allow for T1 equilibrium effects. We applied a slice-timing correction using the time center of the

volume as reference. The subject-mean functional MR images were coregistered with the corresponding structural MR images using mutual information optimization. Then, head motion correction was applied using rigid-body realignment. Realignment parameters were used as covariates during the statistical analysis to model out potential nonlinear head motion artifacts. Functional and morphological images were spatially normalized into standard MNI space using SPM's default templates. Finally, functional images were smoothed using a 6-mm full-width half-maximum Gaussian kernel (Friston et al., 1995a; b; c). A 128-s temporal “high-pass filter” regressor set was included in the design matrix to exclude low-frequency confounds.

At the first level, each trial was modeled with impulse regressors at the time of the presentation of the different types of feedback (i.e., NEGexplore, POSexplore, and POSexploit). These regressors were then convolved with the canonical hemodynamic response function and entered into a general linear model of each subject's fMRI data. The six scan-to-scan motion parameters produced during realignment were included as additional regressors in the general linear model to account for residual effects of subject movement. At the second level, we first generated single-subject contrast images and compiled the corresponding group (from 15 subjects) contrast images. In both the group and individual subject analyses, the brain regions exhibiting increased activity in relation to the occurrence of feedback during the exploration period were assessed by comparing the BOLD signal at the occurrence of explorative negative feedback with the exploitative positive feedback (i.e., NEGexplore minus POSexploit), and by comparing the BOLD signal at the occurrence of explorative first positive feedback with the exploitative positive feedback (i.e., POSexplore minus POSexploit). In the group analysis (Fig. 2), we performed a spatial conjunction between these two comparisons. Because the group analysis revealed that the same brain regions showed increased activity in both the comparisons “NEGexplore minus POSexploit” and “POSexplore minus POSexploit” (see Results, Group analysis: both incorrect and first correct explorative feedback recruit common MCC regions, below), in the individual subject analysis (Fig. 3), the brain regions exhibiting increased activity in relation to the feedback occurrence during the exploration period were assessed by comparing the BOLD signal at the occurrence of both explorative negative feedback and first positive feedback with the exploitative positive feedback: (NEGexplore + POSexplore) – POSexploit.

For both the group and the individual subject analyses, the resulting *t* statistic images were thresholded using the minimum given by a Bonferroni correction and random field theory to account for multiple comparisons. Significance was assessed on the basis of the spatial extent of consecutive voxels. For the group analysis, a cluster volume extent >191.31 mm³ with a *t* value >3 was significant (*p* < 0.05), corrected for multiple comparisons using the method of Friston et al. (2005). In addition, for a single voxel in an exploratory search involving all peaks within an estimated gray matter of 600 cm³ covered by the slices, the threshold for reporting a peak as significant (*p* < 0.05) was *t* = 5.54 if the peaks were predicted (Worsley et al., 1996). Concerning the individual subject analysis, we conducted a region of interest (ROI) analysis. It has been shown that the cortex within the cingulate sulcus and the paracingulate sulcus in the right hemisphere has a total volume of 1273.67 mm³ and 97.49 mm³, respectively (total = 1371.16 mm³) (Rametti et al., 2010). In the left hemisphere, the cortex within the cingulate sulcus and the paracingulate sulcus has a volume of 1405.5 mm³ and 113.66 mm³, respectively (total = 1522.16 mm³). In this ROI analysis, a predicted cluster of voxels with a *t* value >2.5 and with a volume extent >98.97 mm³ in the right anterior cingulate/paracingulate complex and a predicted cluster of voxels with a *t* value >2.5 and with a volume extent >101.82 mm³ in the left anterior cingulate/paracingulate complex was significant (*p* < 0.05), corrected for multiple comparisons using the method of Friston et al. (1995c).

Percentage of BOLD signal change was extracted at the occurrence of incorrect and first correct explorative feedback, as well as of correct exploitative feedback in the four conditions of the task using marsbar release 0.43 (Brett et al., 2002). The variation of the percentage of BOLD signal change through task conditions was assessed with ANOVA and *post hoc* Fisher tests.

Results

Morphological features of the cingulate/paracingulate region in the participants

In the midcingulate region of the human brain, there may be a double cingulate sulcus. In such cases, the dorsal one is referred to as the paracingulate sulcus and the ventral one as the cingulate sulcus, the latter being located close to the corpus callosum (Petrides, 2012). In the present study, a pcgs was observed in at least one hemisphere in 73% of subjects, in agreement with the literature (Paus et al., 1996a, b; Fornito et al., 2008; Buda et al., 2011). The morphology of the cingulate/paracingulate complex could be classified in three patterns. The first pattern was observed in 8 subjects and corresponds to brains where both a *cgs* and a *pcgs* could be observed in one hemisphere and only a *cgs* in the other hemisphere. Specifically, 5 subjects (S1, S8, S9, S10, and S12) displayed a *cgs* and a *pcgs* in the left hemisphere and only a *cgs* in the right hemisphere, and 3 subjects (S2, S5, and S15) exhibited both a *cgs* and a *pcgs* in the right hemisphere and only a *cgs* in the left hemisphere. The second pattern was observed in 3 subjects (S4, S11, and S14) and refers to brains where both a *cgs* and a *pcgs* could be observed in both hemispheres. The third pattern was observed in 4 subjects (S3, S6, S7, and S13) and refers to brains where only a *cgs* could be observed in both hemispheres. These patterns are summarized in Table 1.

In addition, three vertical paracingulate sulci joining either the *cgs* or the *pcgs* can be distinguished in all subjects as already observed (Amiez and Petrides, 2012). The most posterior of these sulci is the paracentral sulcus (*pacs*) (Petrides, 2012), followed by the precentral sulcus (*prpacs*), and then the vertical paracingulate sulcus (*vpcgs*), which is the most anterior (Fig. 3). Note that the name “*vpcgs*” was selected to describe a sulcus located next to the *cgs* and vertically oriented.

Behavior

Performance was modulated by the conditions of the task ($F_{(3,17)} = 9.45$, $p < 10^{-6}$, one-way ANOVA), decreasing from c1 to c4 (Fig. 1B). This result was expected given that the difference between the positive and the negative feedback decreased from c1 to c4, and thus increasing the task difficulty (Fig. 1B). No difference in reaction times was observed between the four conditions and the three trial types in problems solved correctly ($F_{(6,63)} = 1.94$, $p < 0.07$, conditions (c1–c4) $\times$ trial types; i.e., NEGexplo, POSexplo, and POSexploit; factorial ANOVA) (Fig. 1C).

Group analysis: both incorrect and first correct explorative feedback recruit common MCC regions

We first assessed whether the processing of negative and first positive juice feedback recruited the same region within the

Figure 2. fMRI group results in the MCC. **A**, Difference in the feedback-related BOLD signal change observed in the MCC between the negative exploratory and the positive exploitative trials (NEGexplo minus POSexploit). **B**, Difference in the feedback-related BOLD signal change observed in the MCC between the first correct exploratory and the positive exploitative trials (POSexplo minus POSexploit). **C**, Results of conjunction between these two comparisons. Functional maps are represented on sagittal sections in the left (L) and right (R) hemispheres of the average anatomical brain from 15 subjects, at the mediolateral levels described by the *x*-values. The color scale represents the range of *t* values.

MCC, as previously shown using visual feedback (Amiez et al., 2012). Toward that goal, we performed a group analysis in which we contrasted, in our 15 subjects, negative explorative feedback and positive exploitative feedback (i.e., NEGexplo minus POSexploit) as well as first positive explorative feedback and positive exploitative feedback (i.e., POSexplo minus POSexploit) from all conditions. The comparison “NEGexplo minus POSexploit” revealed increased activity in two subregions of the MCC (MNI coordinates *x*, *y*, and *z*: 6, 30, and 34, $t = 4.37$ and -4 , 24, and 42, $t = 4.37$ [anterior MCC (aMCC) subregion in the right and left hemisphere, respectively], 8, 16, and 48, $t = 8.23$ and -8 , 16, and 46, $t = 4.98$ [posterior MCC (pMCC) subregion in the right and left hemisphere, respectively] (Fig. 2A). The comparison “POSexplo minus POSexploit” revealed increased activity in two subregions of the MCC (MNI coordinates *x*, *y*, and *z*: 6, 28, and 34, $t = 6.66$ and -6 , 16, and 46, $t = 5.53$ (aMCC subregion in the right and left hemisphere, respectively), 6, 18, and 46, $t = 5.53$ and -10 , 14, and 50, $t = 5.35$ (pMCC subregion in the right and left hemisphere, respectively) (Fig. 2B). A conjunction analysis (Friston et al., 2005) revealed that both contrasts recruited the two subregions of the MCC in both hemispheres (MNI coordinates *x*, *y*, and *z*: 6, 30, and 34, $t = 4.34$ and

Figure 3. Example patterns of anatomo-functional organization of the MCC observed in typical individual subjects. The feedback-related activity is always located in the *cgs* when no *pcgs* is observed, or in *pcgs* otherwise. The examples illustrate subjects of Type 1 in which a *pcgs* is observed in the left hemisphere but not in the right hemisphere (**A**, S1) or in which a *pcgs* is observed in the right hemisphere but not in the left hemisphere (**B**, S2), a subject of Type 2 in which a *pcgs* is observed in both hemispheres (**C**, S4), and a subject of Type 3 where no *pcgs* is observed (**D**, S6). The activation foci are presented on sagittal sections on the left and right hemispheres (at the mediolateral levels $x = -4$ (**A**), -8 (**B**), -8 (**C**), -10 (**D**) for the left hemisphere and $x = 12$ (**A**), 6 (**B**), 10 (**C**), 8 (**D**) for the right hemisphere), as well as on coronal section [at anteroposterior levels $y = 26$ (**A**), 28 (**B**), 22 (**C**), 28 (**D**)]. The *cgs* and *pcgs* are color-coded in yellow and blue, respectively. L, Left hemisphere; right, right hemisphere; cs, central sulcus. The color scale represents the range of t values.

Table 1. Morphology of the cingulate sulcus in individual subjects

	Left hemisphere		Right hemisphere	
	cgs	pcgs	cgs	pcgs
Pattern type 1				
S1	Not segmented	Not segmented	3 segments	—
S8	Not segmented	Not segmented	Not segmented	—
S9	Not segmented	Not segmented	Not segmented	—
S10	Not segmented	Not segmented	Not segmented	—
S12	Not segmented	Not segmented	Not segmented	—
S2	2 segments	—	2 segments	2 segments
S5	Not segmented	—	Not segmented	2 segments
S15	2 segments	—	2 segments	2 segments
Pattern type 2				
S4	Not segmented	Not segmented	Not segmented	Not segmented
S11	Not segmented	Not segmented	Not segmented	2 segments
S14	Not segmented	Not segmented	2 segments	2 segments
Pattern type 3				
S3	Not segmented	—	Not segmented	—
S6	2 segments	—	Not segmented	—
S7	3 segments	—	Not segmented	—
S13	3 segments	—	Not segmented	—

The presence or not of a *pcgs* “was classified as present when there was a clear identifiable sulcus running dorsal and parallel to the *cgs* for 3 consecutive sagittal slices and that was at least 20 mm in length,” as described by Fornito et al. (2008).

−4, 24, and 42, $t = 4.43$ in aMCC in the right and left hemisphere, respectively; 8, 18, and 46, $t = 7.69$ and −8, 16, and 46, $t = 5.06$ in pMCC in the right and left hemisphere, respectively) (Fig. 2C).

Note that the conjunction analysis revealed also bilateral activity in the mid-dorsolateral prefrontal area 46 (MNI coordinates x, y , and z : 30, 46, and 18, $t = 3.25$; −40, 42, and 4, $t = 3.88$), mid-dorsolateral prefrontal area 9 of 46 bilaterally (MNI coordinates x, y , and z : 44, 32, and 32, $t = 5.15$; −44, 32, and 20, $t = 4.25$), VLPFC (MNI coordinates x, y , and z : 30, 22, and 4, $t = 7.78$; −28, 22, and 6, 8.05), inferior frontal junction (MNI coordinates x, y , and z : 36, 8, and 32, $t = 4.52$; −46, 2, and 30, 5.97), area 6 of 8 (MNI coordinates x, y , and z : 32, 0, and 54, $t = 5.97$; −26, 0, and 50, $t = 5.79$), intraparietal cortex (MNI coordinates x, y , and z : 38, −42, and 42, $t = 7.87$; −44, −42, and 44, $t = 6.42$), and posterior parietal cortex (MNI coordinates x, y , and z : 34, −52, and 50, $t = 6.15$; −36, −54, and 52, $t = 6.87$).

Importantly, this conjunction analysis revealed no activity in the primary motor tongue area (i.e., located in the ventral part of the precentral gyrus) (Meier et al., 2008). This result suggests that the simple sensorimotor perception of a small versus large feedback in the mouth is not responsible for the increased activity described in the network revealed by this conjunction analysis. To verify the involvement of the primary motor tongue area in the perception of a liquid in the mouth versus no liquid, we compared the BOLD signal at the occurrence of correct feedback during the exploitation period (POSexploit) to the signal obtained at the occurrence of negative feedback during the exploration period (NEGexploire) in conditions 1 and 3 (i.e., in conditions where the incorrect feedback value was 0 ml). Results revealed increased activity in the primary motor tongue area in both hemispheres (MNI coordinates x, y , and z : −54, −12, and 32, $t = 12.33$ (left hemisphere); 52, −8, and 30, $t = 12.96$ (right hemisphere)).

Individual subject analysis

The group analysis does not allow the assessment of the relationships between the locations of the two feedback-related MCC foci and specific morphological features of the cingulate cortex. Given

the strong intersubject variability within the region (Table 1), only a subject-by-subject analysis can permit the determination of anatomo-functional relationships.

Feedback-related activity relates to specific morphological features of individual brains

Because the group conjunction analysis revealed that both negative and first positive feedback recruited two common regions within the MCC, we grouped these trials and compared all explorative feedback (i.e., negative and first positive explorative feedback) to exploitative feedback in each individual subject for subsequent analyses (i.e., contrast [NEGexploire + POSexploire] minus POSexploit). We then assessed the location of the two subregions in each individual subjects. Results revealed that activation in the aMCC subregion was consistently observed in all subjects in both hemispheres. By contrast, the posterior pMCC subregion showed activity in only 2 subjects in the left hemisphere and in 6 subjects in the right hemisphere (Table 2).

Importantly, feedback-related activity during exploration was located in the *cgs* in subjects exhibiting no *pcgs*, and in the *pcgs* (not in the *cgs*) in subjects exhibiting a *pcgs*. Indeed, in subjects showing the first pattern of anatomical organization of the cingulate/paracingulate complex (i.e., *pcgs* observed only in the left hemisphere, Table 1), the explorative feedback-related activity was located in the *cgs* in the hemisphere exhibiting only a *cgs* and in the *pcgs* in the hemisphere displaying both a *cgs* and a the *pcgs* (Table 2; Fig. 3A,B). In subjects showing the second pattern of anatomical organization (*pcgs* observed in both hemispheres, Table 1), the explorative feedback-related activity was located in the *pcgs* in both hemispheres (Table 2; Fig. 3C). In subjects showing the third pattern of anatomical organization of this region (only a *cgs* observed in both hemispheres, Table 1), the explorative feedback-related activity was located in the *cgs* in both hemispheres (Table 2; Fig. 3D). Figure 4 shows peaks of activation for all subjects in each hemisphere grouped by types depending on whether or not a paracingulate sulcus was present.

In addition, the increased activity observed in the aMCC was systematically located at the intersection between the *cgs* or the *pcgs* with the *vpacs* (Table 2). In subjects exhibiting a *pcgs*, the feedback-related activity was, on average, more dorsal by 11.1 mm in the left hemisphere and 5.1 mm in the right hemisphere than in subjects exhibiting only a *cgs*. The increased activity observed in the pMCC was located at the intersection between the *cgs* (in S6 and S7 bilaterally and in the right hemisphere of S9, S10, and S12) or the *pcgs* (in the right hemisphere of S15) with the *prpacs* (Table 2). Given that the pMCC in both hemispheres was observed in a minority of subjects, we focused our following analysis on the aMCC in both hemispheres.

To confirm that, in subjects exhibiting a *pcgs*, the activity within the *cgs* was negligible, we looked at, in individual subjects showing a *pcgs*, the t value at the average coordinates at which the aMCC increased activity was observed in subjects showing only a *cgs* [i.e., at average MNI coordinates x, y , and z : −7, 26, and 31 (left hemisphere) and 8, 28, and 34 (right hemisphere)] (Table 2). Results revealed an average ($\pm$ SD) t value of 0.45 ± 1.77 and 1.47 ± 0.53 in the *cgs* in the left and right hemisphere, respectively. This result confirms that, in subjects exhibiting a *pcgs*, the feedback-related activity during exploration is located in the *pcgs*, and not in the *cgs*.

Table 2. Results from individual subject analysis in the comparison between explorative and exploitative feedback

	Anterior/posterior ACC	MNI coordinates			<i>t</i> value	Location
		<i>x</i>	<i>y</i>	<i>z</i>		
Left hemisphere						
S1	Anterior	−4	22	44	2.96	pcgs/vpcgs
S2	Anterior	−10	28	30	5.17	cgs/vpcgs
S3	Anterior	−2	30	44	5.50	cgs/vpcgs
S4	Anterior	−8	16	46	3.50	pcgs/vpcgs
S5	Anterior	−10	26	26	3.48	cgs/vpcgs
S6	Posterior	−8	12	44	6.69	cgs/prpacs
S7	Anterior	−10	26	32	5.08	cgs/vpcgs
	Posterior	−8	6	48	4.15	cgs/prpacs
	Anterior	−6	18	28	2.98	cgs/vpcgs
S8	Anterior	−2	38	42	3.48	pcgs/vpcgs
S9	Anterior	−2	18	48	3.65	pcgs/vpcgs
S10	Anterior	−4	22	40	6.97	pcgs/vpcgs
S11	Anterior	0	24	44	3.25	pcgs/vpcgs
S12	Anterior	−6	24	38	3.82	pcgs/vpcgs
S13	Anterior	−8	22	34	4.25	cgs/vpcgs
S14	Anterior	−4	26	38	5.22	pcgs/vpcgs
S15	Anterior	−6	30	26	3.43	cgs/vpcgs
Posterior increased activity in the cgs, mean ± SD		−8.0 ± 0	9.0 ± 4.2	46.0 ± 2.8		
Anterior increased activity in the cgs, mean ± SD		−7.4 ± 3.0	25.7 ± 4.4	31.4 ± 6.3		
Anterior increased activity in the pcgs, mean ± SD		−3.8 ± 2.5	23.8 ± 6.6	42.5 ± 3.7		
Right hemisphere						
S1	Anterior	12	26	26	6.63	cgs/vpcgs
S2	Anterior	6	26	44	5.28	pcgs/vpcgs
S3	Anterior	8	40	42	6.23	cgs/vpcgs
S4	Anterior	10	26	44	4.12	pcgs/vpcgs
S5	Anterior	10	36	30	3.43	pcgs/vpcgs
S6	Posterior	8	16	44	7.76	cgs/prpacs
S7	Anterior	8	28	28	6.00	cgs/vpcgs
	Posterior	8	8	48	3.74	cgs/prpacs
	Anterior	6	16	38	4.30	cgs/vpcgs
S8	Anterior	6	26	42	6.03	pcgs/vpcgs
S9	Posterior	6	16	46	3.53	cgs/prpacs
S10	Anterior	8	32	38	2.58	cgs/vpcgs
	Posterior	2	16	42	8.61	cgs/prpacs
	Anterior	8	28	36	6.23	cgs/vpcgs
S11	Anterior	6	36	36	4.40	pcgs/vpcgs
S12	Posterior	4	14	48	5.68	cgs/prpacs
S13	Anterior	12	28	22	4.98	cgs/vpcgs
	Anterior	4	28	42	10.18	cgs/vpcgs
	Anterior	4	40	36	4.73	pcgs/vpcgs
S14	Anterior	4	20	52	6.74	pcgs/prpacs
S15	Posterior	4	30	42	4.23	pcgs/vpcgs
Posterior increased activity in the cgs, mean ± SD		5.3 ± 2.4	15.0 ± 3.9	46.7 ± 3.5		
Anterior increased activity in the cgs, mean ± SD		8.3 ± 2.7	28.3 ± 6.6	34.0 ± 7.6		
Anterior increased activity in the pcgs, mean ± SD		6.6 ± 2.5	31.4 ± 5.9	39.1 ± 5.3		

All increased activities were statistically significant at $p < 0.05$ corrected for multiple comparison. The stereotaxic coordinates are expressed in mm within the MNI stereotaxic space.

Pattern of feedback-related activity in the aMCC at the occurrence of explorative and exploitative feedback

Given the fact that all subjects exhibited feedback-related activity but that this activity was located within the *pcgs* or the *cgs* depending on the occurrence of a *pcgs* or not, we hypothesized that both these *cgs* and *pcgs* foci of feedback-related activity displayed the same functional signature. Specifically, from our previous study (Amiez et al., 2012), we know that, in such tasks, the MCC feedback-related activity is increased at the occurrence of both negative and first positive explorative feedback, but not at the occurrence of exploitative feedback. We therefore expected to observe this functional signature in the *cgs* and in the *pcgs*, even after the two subject populations were separated. We thus extracted the percentage of BOLD signal change in individual subjects at the feedback occurrence of NEGexplore, POSexplore, and POSexploit trials in the four task conditions. First, for each individual subject, we used the coordinates of the increased activity

observed in the aMCC bilaterally in the comparison: (NEGexplore + POSexplore) minus POSexploit (Table 2 for the coordinates of individual subjects). Then, in each subject, we extracted the percentage of BOLD signal change, with a radius of 5 mm centered on these coordinates, at feedback for NEGexplore, POSexplore, and POSexploit trials in the four task conditions (c1, c2, c3, and c4; Fig. 1). Finally, the percentage of BOLD signal change was averaged across subjects exhibiting a *cgs* and across subjects exhibiting a *pcgs* in both hemispheres, and across conditions sharing the same feedback values. Specifically, incorrect explorative trials in which negative feedback was 0 or 0.4 ml were pooled separately (c1 + c3 and c2 + c4, respectively), as well as first correct explorative and correct exploitative trials in which positive feedback was 0.8 or 1.2 ml (c3 + c4 and c1 + c2, respectively). Results are presented in Figure 5. They revealed that the percentage of BOLD signal change in the aMCC in both the *cgs* and *pcgs* and in both hemispheres was significantly higher at the

occurrence of both negative and first positive feedback compared with correct explorative trials. Importantly, this result was observed when the increased activity was located in the *cgs* in subjects exhibiting no *pcgs* (Fig. 5A, right hemisphere; $F_{(5,90)} = 14.24$, $p < 10^{-5}$; left hemisphere: $F_{(5,78)} = 3.33$, $p < 0.01$, ANOVA), and in the *pcgs* when present (Fig. 5B, right hemisphere; $F_{(5,78)} = 3.16$, $p < 0.01$; left hemisphere: $F_{(5,90)} = 7.90$, $p < 10^{-5}$, ANOVA). The percentage of BOLD signal change in the aMCC in both the *cgs* and *pcgs* in both hemispheres was similar at the occurrence of negative and first positive explorative feedback ($p > 0.05$, *post hoc* Fisher test). These results show that both the *cgs* and *pcgs* foci have the same functional signature.

To verify that the pattern of feedback-related activations were absent in *cgs* when present in the *pcgs*, we compared activation in both regions in subjects with a *pcgs*. Because no activity was observed in the *cgs* in subjects exhibiting a *pcgs* in the comparison “(NEGexploit + POSexploit) minus POSexploit,” we used the same *x* and *y* MNI coordinates as the increased activity observed in the *pcgs* but we adjusted the *z*-coordinate value to fall into the *cgs* in individual brains (see example in Fig. 5C). We then extracted the percentage of BOLD signal change in this *cgs* region within a radius of 5 mm. Results revealed no modulation of the percentage of BOLD signal change by the task period (exploration vs exploitation) or the feedback value in either the left ($F_{(5,90)} = 0.92$, $p > 0.47$, ANOVA) or the right hemisphere ($F_{(5,66)} = 0.69$, $p > 0.63$, ANOVA). This result confirms that, in subjects exhibiting a *pcgs*, the feedback-related activity during exploration is located in the *pcgs*, and not in the *cgs*.

Results also revealed that the feedback value was somewhat modulating the activity in the aMCC at the occurrence of negative feedback, but not for first positive feedback. Mainly, aMCC activity was higher when the negative feedback was a juice delivery compared with no juice (Fig. 5). Specifically, this result was significant for the aMCC focus located in the *cgs* in the right hemisphere and for the aMCC focus located in the *pcgs* in the left hemisphere. This result should be taken with caution as it was not observed in the aMCC focus located in the *pcgs* in the right hemisphere and in the focus located in the *cgs* in the left hemisphere.

Together, these results suggest that feedback-related activity located in the *cgs* and in the *pcgs* displays similar functional

Figure 4. A–D, Anatomical organization of the MCC in all subjects displaying a morphology of Type 1 (A, B), Type 2 (C), and Type 3 (D). Each dot corresponds to the location of the feedback-related activity observed during exploration periods of each subject. Each number corresponds to the subject's name referred to in Tables 1 and 2. The light and dark gray dots indicate the feedback-related activity observed in the aMCC and pMCC, respectively. As it can be observed, all subjects displayed feedback-related activity in the aMCC at the intersection between *cgs* or *pcgs* and *vpcgs*. In 6 subjects, an additional activation focus was detected in the pMCC at the intersection between *cgs* and *pracs*. Abbreviations as in Figure 3. LH, Left hemisphere; RH, right hemisphere.

A cgs activity in hemispheres displaying no pcgs **B** pcgs activity in hemispheres displaying a pcgs **C** cgs activity in hemispheres displaying a pcgs

Figure 5. Functional signature of feedback-related activation. Left, For a typical subject (S1), example ROIs in the MCC in the cgs (**A**), the pcgs (**B**), and the cgs for subjects, as S1, exhibiting a pcgs (**C**), from which the percentage of BOLD signal change was extracted. Middle and right columns, Average percentage of BOLD signal change at feedback within the aMCC focus in the right (middle) and left (right) hemisphere. The volumes of juice obtained in NEGexplore, POSexplore, and POSexploit trials are indicated below the abscissa. Error bars represent SEM.

properties. Note, however, that the modulation of aMCC activity in relation to the feedback value would need further investigation before providing clear conclusions.

Figure 6 summarizes the data; Figure 6A (left) displays the dispersion of the feedback-related activation foci in aMCC for all hemispheres. Results clearly show that the individual aMCC foci form two groups depending on whether a pcgs is present or not. To assess whether this result could be appreciated at the group level, we assessed the location of the average feedback-related activity in three subgroups of hemispheres: (1) pooled left and right hemispheres with a pcgs; (2) pooled left and right hemispheres without a pcgs; and (3) pooled left and right hemispheres with and without a pcgs. Results show again that the increased activity observed in the aMCC is located in the cgs when there is no pcgs (at MNI coordinates $x = 10$, $y = 22$, $z = 36$, t value = 5.16) and in pcgs when present (at MNI coordinates $x = 4$, $y = 22$, $z = 44$, t value = 9.91). Therefore, when a pcgs is present, the increased activity observed in the aMCC is shifted 8 mm dorsally. In addition, data reveal an additional increased activity within the pMCC in hemispheres exhibiting no pcgs. The individual subject analysis indeed revealed that activity in pMCC was observed in 8

hemispheres from which 7 had no pcgs (Table 2), suggesting that the increased activity within the pMCC is more specifically observed in hemispheres without a pcgs. Importantly, when pooling all hemispheres with and without a pcgs, both specificities were lost (Fig. 6A, right).

Together, these results show a gradient in the degree of precision that one can obtain in the location of feedback-related activity depending on the method used for analysis. Whereas a full group analysis revealed a feedback-related activity focus located in the MCC, a subgroup analysis separating hemispheres with and without a pcgs revealed that this feedback-related activity was located in the pcgs when present and in the cgs when no pcgs was observed, and a subject-by-subject analysis revealed that this feedback-related activity was systematically located at the intersection between the cgs or pcgs and the vpcgs.

Discussion

During exploratory behavior, the processing of both juice feedback indicating incorrect selections and juice feedback indicating the first correct selection reliably engage the aMCC in individual subjects. Importantly, the present study demonstrated that the

location of aMCC activity is strongly related to particular morphological features of the region. When the *pcgs* is present, the feedback-related activity is in the *pcgs* and not in the *cgs*, but when the *pcgs* is absent, feedback-related activity appears in the *cgs* (Tables 1, 2; Figs. 4, 6A). In addition, the aMCC focus of feedback-related activity was consistently located at the intersection with *vpcgs* in all subjects, and a posterior locus within pMCC could be observed in 8 hemispheres at the intersection with *prpacs*, almost exclusively in hemispheres without a *pcgs* (Table 2; Fig. 6A, right).

The aMCC locus of feedback-related activity displayed the same functional signature whether located in the *cgs* in hemispheres with no *pcgs*, or in the *pcgs* (Fig. 5), strongly suggesting that these regions indeed refer to the same unique functional region that is displaced depending on the local folding patterns. Importantly, two cytoarchitectonic areas of the MCC region (i.e., areas 24c' and 32') relate in a predictable manner to the presence or absence of the *pcgs*. When there is no *pcgs*, the cortex lying in the dorsal bank of the *cgs* is area 32', with area 24c' lying below it (Vogt et al., 1995). When the *pcgs* is present, area 24c' lies in both banks of the *cgs* and area 32' lies in the *pcgs* and the gyrus between *cgs* and *pcgs*. Area 32' is a transitional cytoarchitectonic area that lies between cingulate area 24c' and the surrounding granular prefrontal areas of the medial frontal lobe (Vogt et al., 1995; Palomero-Gallagher et al., 2008). Our results showing that the feedback-related activity was systematically located in the *pcgs* when present, and in the *cgs* when no *pcgs* was present, strongly suggest that the locus for feedback-related activity is in area 32' (Fig. 6). Thus, the fact that subjects who do not have a *pcgs* display feedback-related activity, just as much as subjects who do have a *pcgs*, suggests that these *cgs* and *pcgs* feedback-related regions correspond actually to the same anatomical and functional area (i.e., area 32') that appears in two different folding patterns.

A recent study has suggested that subjects showing no *pcgs* had reduced reality monitoring performance and reduced metacognitive judgments on performance (Buda et al., 2011). The authors concluded that the structural variability impacts on the functional properties of this region. We assessed whether the presence of the absence of *pcgs* in one hemisphere or bilaterally affected subjects' performance in our task. The data revealed no difference in performance between subjects exhibiting a *pcgs* at least in one hemisphere (i.e., Types 1 and 2) and subjects exhibiting only a *cgs* (Type 3) (Table 1), indicating that the presence or not of the *pcgs* in one or both hemispheres did not impact performance in the different conditions in our task ($p > 0.45$, marginal logistic regression with performance as a function of subject types, conditions, and the interaction between subject types and conditions; proc genmod, SAS 9.2 Institute). Our functional data suggest that the presence or absence of a *pcgs* in some human brains should not be interpreted as indicating that subjects exhib-

Figure 6. *A*, Left, Dispersion of the feedback-related activation foci in the aMCC based on individual subject analysis in hemispheres with (in yellow) and without (in blue) a paracingulate sulcus. Each dot corresponds to the location of the highest t value observed in each subject during the analysis of feedback during exploratory behavior in aMCC in both hemispheres. Note that foci from both right and left are projected onto one hemisphere. Right, Subgroup analysis for pooled left and right hemispheres without a *pcgs*, with a *pcgs*, and for all hemispheres. Feedback-related activation foci of subgroups with and without a *pcgs* as well as with all hemispheres are presented on the anatomical averages of left and right hemispheres without a *pcgs*, with a *pcgs*, and with all hemispheres, respectively (Table 2). *B*, Summary of the organization of feedback-related activation foci in the aMCC of the human brain. The location of feedback-related activation depends on whether a *pcgs* is (case 2) or is not present (Case 1). Together with the cytoarchitectonic subdivisions described by Vogt et al., 1995 (see insets), this suggests that feedback related activity might be located in area 32'. Abbreviations as in Figure 3.

iting only a *cgs* lack a particular cortical area. It simply implies a difference in cortical folding. This finding adds to other observations that folding patterns can predict activity related to particular aspects of functional processing in the cingulate cortex (Crosson et al., 2009; Amiez and Petrides, 2012), the inferior frontal junction (Derrfuss et al., 2012), and the dorsal premotor cortex (Amiez et al., 2006).

Importantly, a recent human fMRI study (Amiez and Petrides, 2012) has provided direct evidence for the existence of three cingulate motor areas (CMAs) within the cingulate cortex, as in the monkey (Dum and Strick, 1991). The most anterior cingulate motor region contains hand, foot, and face (i.e., tongue and eye) motor representations. Remarkably, the face representation was displaced within the *pcgs* when present and remained in the *cgs* when no *pcgs* was observed. Finally, this anterior CMA was systematically located at the intersection between the *cgs* or *pcgs* with *vpcgs*. In other words, the anterior face motor representation and juice feedback-related activity during exploratory behavior may have similar locations. We can rule out the hypothesis that the feedback-related activity is only the result of swallowing the juice because the swallowing occurred both during exploration and exploitation periods of the task. Direct anatomofunctional relationships between CMAs and MCC feedback-related activity remain to be identified. It must be emphasized that such assessment will require, as in the present study, a careful single-subject examination of the location of activation sites relative to each other and in relation to the anatomical variability

observed in the MCC. Experiments are currently in progress to assess such relationships.

Compared with the focus in our previous study in which feedback was visual (i.e., a secondary reward) (Amiez et al., 2012), the aMCC region related to the juice feedback (primary reward) is located ~ 8 mm more posterior on average: $t = -6.8745$, $df = 39.2$, $p < 3.104 \times 10^{-8}$ when not assuming that the variances of both regions are equal (Welch two-sample t test) and $t = -7.0751$, $df = 48$, $p < 5.641 \times 10^{-9}$ when assuming that the variance of both regions are equal (two-sample t test). The secondary feedback-related activations might thus involve regions outside of CMAs. The existence of a network dissociating primary and secondary outcomes is of critical importance to analyze and adapt appropriately to the environment. Recently, Sescousse et al. (2010) have shown that, as opposed to the orbitofrontal cortex, the same MCC region encoded both reward types. The difference between our data and those of Sescousse and colleagues (2010) can be explained by the type of reward used. Whereas they used erotic stimuli as primary reward and money as secondary reward, we used juice and visual feedback, respectively. Also, these authors performed a group averaging analysis, possibly losing critical information concerning the link between local morphology and function. However, our comparison of the location of juice and visual feedback-related activity concerns data obtained in two different studies; thus, a direct single-subject comparison would be required to conclude on this issue.

The result showing that the same aMCC region encodes both negative feedback and the first positive juice feedback during exploratory behavior is in line with single-unit recording studies performed in the macaque monkey with juice feedback demonstrating prominent negative and first positive feedback-related activity in the dorsal bank of the cingulate sulcus during exploration (Procyk et al., 2000; Amiez et al., 2005; Quilodran et al., 2008). Interestingly, unit activity related to visual feedback (conditioned reinforcers) has also been observed in the dorsal bank of the cingulate sulcus in monkeys (Seo and Lee, 2009).

In conclusion, our study shows clear relationships between the local morphology of the cingulate/paracingulate complex and feedback-related activity in the human brain. Such a conclusion could only have been made on the basis of individual subject analyses that take into account individual morphological variation in the region of interest, and not on the basis of group average analyses. This conclusion has direct implications regarding brain imaging methods. We tested our dataset with one example of template ROIs (marsbar, <http://marsbar.sourceforge.net/>) that had been produced from one single individual (Tzourio-Mazoyer et al., 2002), and the feedback-related activity site fell outside (dorsal) of the midcingulate ROI for most subjects exhibiting a pcgs, falling into the superior medial frontal ROI. Thus, as discussed previously, it is necessary to consider seriously a single individual approach to define ROIs (Tzourio-Mazoyer et al., 2002). Most probably, the variability in peak locations in MCC globally decreases the statistical outcome in that region when averaging subjects, and the results should depend on the characteristic of the subject population. In addition, the morphological variability would have a significant impact on the outcome of correlations between activation and individual traits if morphological variation is not taken into account to isolate the activation sites. Finally, the establishment of clear structure–function links is of critical importance not only for our understanding of the functional organization of the cingulate cortex (Shackman et al., 2011), but also for clinical purposes, such as targeting precisely the site of manipulations in cases of pharmacological resistant

psychiatric conditions, and for providing clear guidance to surgeons for brain tumor removals (Amiez et al. 2008; Duffau, 2011).

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