

Persistence and brain circuitry

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Contributed by Marcus E. Raichle, December 31, 2002

The orbitofrontal and adjacent medial prefrontal cortex may play an important role in normal social functioning and affect modulation. Recent anatomical studies of this area of the prefrontal cortex have demonstrated a striking correspondence of fine-grained architectonic partitioning schemes in humans and nonhuman primates. This finding allows neurophysiological recording and anatomical connectivity data in animals to be considered together with functional imaging data and lesion studies in humans. In a functional MRI study, we show that individual differences in Persistence, a dimensional trait assessed with a seven-factor personality model, may be linked to specific areas in the lateral orbital and medial prefrontal cortex and the ventral striatum. These areas are part of an anatomical circuit that has been defined in nonhuman primates and has been implicated in functions related to behavioral persistence. These findings represent a fresh approach to linking normal individual differences in personality and behavior to specific neuronal structures and subsystems.

Clinical evidence suggests that the orbital and adjacent medial prefrontal cortex (OMPFC) is significantly involved in modulation of social behavior and in control of mood and motivational drive, function(s) that are important components of the personality of an individual. Since the published description of the paradigmatic patient Phineas Gage (1–3), there have been numerous reports of striking personality changes and deviant social behavior appearing in premorbidly normal individuals after damage to the OMPFC (4–9). The personality changes have been deemed such because they are manifest to others as enduring (i.e., state) changes in the individuals' characteristic behavior, moods, and attitudes. Lack of persistence is among the specific impairments in social conduct and aspects of decision-making that have been described as arising relatively frequently in these patients (e.g., ref. 9).

Persistence as a behavioral phenomenon has been extensively studied in both animals and humans. Depending on the perspective of the investigator, research on persistence has tended to emphasize common mechanisms across individuals that generally relate patterns of reinforcement to resistance to extinction, or differences between individuals on the basis of their dispositions or cognitive processing. There has, however, been little work to date that has tried to integrate these research approaches to the study of behavioral persistence (10, 11). Except for the aforementioned lesion studies of humans, almost no work has been done that has attempted to relate this behavioral phenomenon to the brain. Work that has been done has been confined to experimental animals (e.g., refs. 12 and 13).

An understanding of common mechanisms and individual differences will ultimately be necessary for a complete understanding of brain–behavior relationships. An understanding of both is likely to be particularly important for more complex behavioral phenomena, such as social behavior and decision-making, as well as emotional and motivational processing. For historical reasons, modern functional neuroimaging has tended to emphasize the exploration of common mechanisms in brain–behavior relationships by means of group-average data (14). Recently, however, an awareness of the importance and feasibility of studying individual differences with this technique has begun to emerge (e.g., refs. 15–18).

In this report, we describe our results in relating data on a specific personality trait, Persistence, to subjects' task performance and regional changes in brain activity viewed with functional MRI (fMRI). We also show how these functional imaging results in humans may be transformed to architectonic mappings of prefrontal cortex derived in monkeys and extended by us to humans, which provides a means of directly comparing experimental neuroscientific work between species.

Methods

This study employs a data set for which the group-average data have already been reported (19). Twenty-four subjects (12 females) without significant psychiatric or neurologic history between the ages of 20 and 35 (mean age 24 ± 3 yr) were recruited from the local Washington University community and underwent fMRI. Behavioral data were also obtained on an additional 11 normal subjects (7 females) between the ages of 20 and 27 (mean age 23 ± 2 yr). All subjects were right-handed as judged by the Edinburgh Handedness Inventory (20) and were normal or corrected-to-normal in visual acuity. Subjects were paid \$25/h and gave their informed consent in accordance with guidelines set by the Human Studies Committee of Washington University Medical Center.

Self-report inventories based on a seven-factor model (21) and a five-factor model (22) were used to characterize their personalities.

Imaging was performed on a 1.5 tesla MAGNETOM Vision system (Siemens, Erlangen, Germany). For details concerning image data acquisition for this study, see ref. 19.

The stimuli were pictures from the International Affective Picture System (IAPS) (23). Subjects viewed a total of 360 pictures during the course of the experiment. No picture was seen more than once. The pictures chosen for the experiment were apportioned according to the norms of the IAPS in the following manner: 180 neutral, 90 pleasant, and 90 unpleasant. For each of the two tasks performed, the apportionment was 90 neutral, 45 pleasant, and 45 unpleasant. However, across the six runs performed for each task, the percentage of neutral pictures varied from 10% to 90% (i.e., 10%, 26%, 42%, 58%, 74%, and 90%). The remainder of the pictures in each run was equally divided between pleasant and unpleasant. Two versions of each set were created. One version of each set was used once for each task and each set constituted the pictures in a run. The order in which the sets were used varied systematically across subjects.

The fMRI paradigm was a block design with picture blocks alternating with visual fixation blocks of equal length (36 sec). Ten pictures varying along the dimensions of valence and arousal were presented within each block, with a total of 30 pictures being presented during each run. Each picture was displayed for 500 msec with an interstimulus interval (ISI) of 3,600 msec, during which period subjects made their key-press responses. A fixation crosshair was displayed between picture blocks.

Abbreviations: fMRI, functional MRI; OMPFC, orbital and adjacent medial prefrontal cortex; IAPS, International Affective Picture System; TCI, Temperament and Character Inventory; BOLD, blood-oxygen-level-dependent.

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The subjects were instructed to perform one of two tasks for any particular run. For one task, they were asked to decide how the picture made them feel and note whether the feeling evoked was pleasant, unpleasant, or neutral, and to press an appropriate key. For the other task, they were asked to judge whether the picture depicted a scene that was indoors, outdoors, or they could not tell, and to press an appropriate key. The two tasks were performed on alternate runs and the order was counter-balanced across subjects. Subjects were informed immediately before each run which task they were to perform. For both tasks, subjects' key-press responses were recorded and reaction times were measured.

The fMRI data were analyzed by using the general linear model [refs. 24–27; for further details, see ref. 19]. The results of voxel-based *t* tests were used as the basis for correlation with personality variables.

Correlations were performed between subjects' scores on the personality dimensions of both personality inventories and the response magnitudes of their image data for four contrasts: (i) both tasks together, compared with fixation control; (ii) tasks separately compared with fixation control; (iii) the interaction between both tasks taken together, and the percentage of neutral pictures; and (iv) the interaction of task and the percentage of neutral pictures. Correlation results were then corrected for multiple comparisons: those associated with the voxel-based correlation analysis itself, and those associated with all seven personality dimensions of the Temperament and Character Inventory (TCI; see ref. 21) and the five dimensions of the five-factor model (22).

The resulting correlation data were then mapped to fiducial (3D) surface reconstructions from the Human.colin atlas (28, 29), which is registered to Talairach space (30). These mappings were then carried onto flat maps (29). Areal boundaries of the medial and orbital systems of the OMPFC defined by Price and coworkers (31) were identified on individual hemispheres studied postmortem (two left hemispheres and three right hemispheres) and were registered to the atlas by using a surface-based registration algorithm (29).

Results

Imaging Results. We focus on the imaging results associated with only one of the personality dimensions of the seven-factor model (21, 32), Persistence, in this report because of its specific association with the OMPFC. Imaging results with regard to other personality dimensions of the seven-factor model will be reported separately. Results related to Conscientiousness, the dimension of the five-factor model most closely related to Persistence, are also reported.

In the correlations performed between the subjects' Persistence scores¹ and the response magnitudes of their image data for the four contrasts, a robust finding ($P < 0.05$) arose from analysis (contrast *iii*). This analysis revealed a complex relationship between Persistence and activity changes within areas of the OMPFC and ventral striatum (Figs. 1–3).

Within these areas, the subjects highest in Persistence exhibited increases in activity, whereas those lowest in Persistence exhibited decreases (Fig. 1 *Middle*). Subjects between these extremes varied systematically from increases to decreases according to their individual Persistence scores. We note with regard to the near-symmetrical distribution of responses (slopes) about 0 that the group mean for Persistence scores in our subjects (73 ± 8.5 SD, a median of 75, a skewness of -0.04 , and a kurtosis of 2.5) was almost identical with estimates of the

population mean (69 ± 11.3 , a median of 70, a skewness of -0.06 , and a kurtosis of 0.2) obtained on a large community-based sample of subjects by Cloninger *et al.*, ref. 21, and C.R.C., unpublished data. Thus, our image data may be viewed as reflecting responses on both sides of the population mean.

Fig. 2 shows Persistence-related correlation maps displayed on medial, lateral, and ventral views of the inflated left and right hemisphere atlas surfaces (*A–C* and *E–G*), and on cortical flat maps that include the architectonic partitioning scheme determined on individual postmortem brains and registered to the atlas (see *Methods*). Foci (a, c, and d) lie mainly in areas identified as part of the medial system in the macaque (33). Fig. 3 shows coronal views of correlation maps for regions b and e in the ventromedial striatum (*A*), expanded views of the frontal lobe flat maps (*B*), and the pattern of labeling in macaque striatum after a tracer injection in the medial network. These patterns and relationships are considered further in the figure legends and in *Discussion*.

The dimension most closely related to Persistence within the five-factor model, Conscientiousness, also exhibited a significant correlation with the percentage of neutral pictures (contrast *iii*) but this correlation was restricted to the left area [pregenual 24 (24pg)] and the right ventral striatum (see Fig. 4, which is published as supporting information on the PNAS web site).

The other three contrasts (*i*, *ii*, and *iv*) did not reveal any association between any of the other personality dimensions and the blood-oxygen-level-dependent (BOLD) contrast in the OMPFC.

Behavioral Results. We assessed the behavior of our subjects on the affective rating task by comparing the distribution of their picture ratings (i.e., pleasant, unpleasant, and neutral) to the IAPS norms. The pictures were distributed according to the IAPS norms as 50% neutral, 25% pleasant, and 25% unpleasant, whereas our subjects' ratings were 23% neutral, 37% pleasant, and 39% unpleasant. These differences from the IAPS norms were highly significant ($P < 0.001$) in all instances.

To determine whether there was any effect of the measured personality differences that could contribute to the above observation, we examined the relationship between the number of pictures assigned to each category by our subjects and each of the dimensions of the TCI and the five-factor model. This analysis, which included the 24 subjects from our imaging experiment and the additional 11 subjects on whom we had behavioral results for the same tasks (see *Methods*), revealed a complex interaction among three personality variables, Persistence, Self-Directedness, and Harm Avoidance, three dimensions of the seven-factor model (32).

The results of this analysis ($n = 35$) indicated that there was a positive correlation with Persistence ($r = 0.34$; $P < 0.05$) and Self-Directedness ($r = 0.50$; $P < 0.01$) such that individuals higher on these dimensions made significantly more pleasant judgments. For Harm Avoidance, there was an opposite effect ($r = -0.44$; $P < 0.05$). (Further details related to Self-Directedness and Harm Avoidance will be reported elsewhere.) A trend in the same direction as the correlation observed for Persistence was also noted for Conscientiousness of the five-factor model ($r = 0.21$; $P < 0.2$). These behavioral results were independent of the percentage of neutral pictures within a run.

Discussion

The individual differences we observed in the brain with regard to Persistence were most prominent when our subjects were exposed to higher percentages of neutral pictures and were much less when they were exposed to fewer neutral pictures. Why might this be? One possibility may be that individuals high in Persistence may represent less arousing situations (e.g., 90% neutral pictures) as more intrinsically motivating, arousing, and

¹The subjects' Persistence scores were determined by responses, measured with five-point Likert scales, to 20 questions. These 20 questions can be found in *Supporting Text*, which is published as supporting information on the PNAS web site, www.pnas.org.

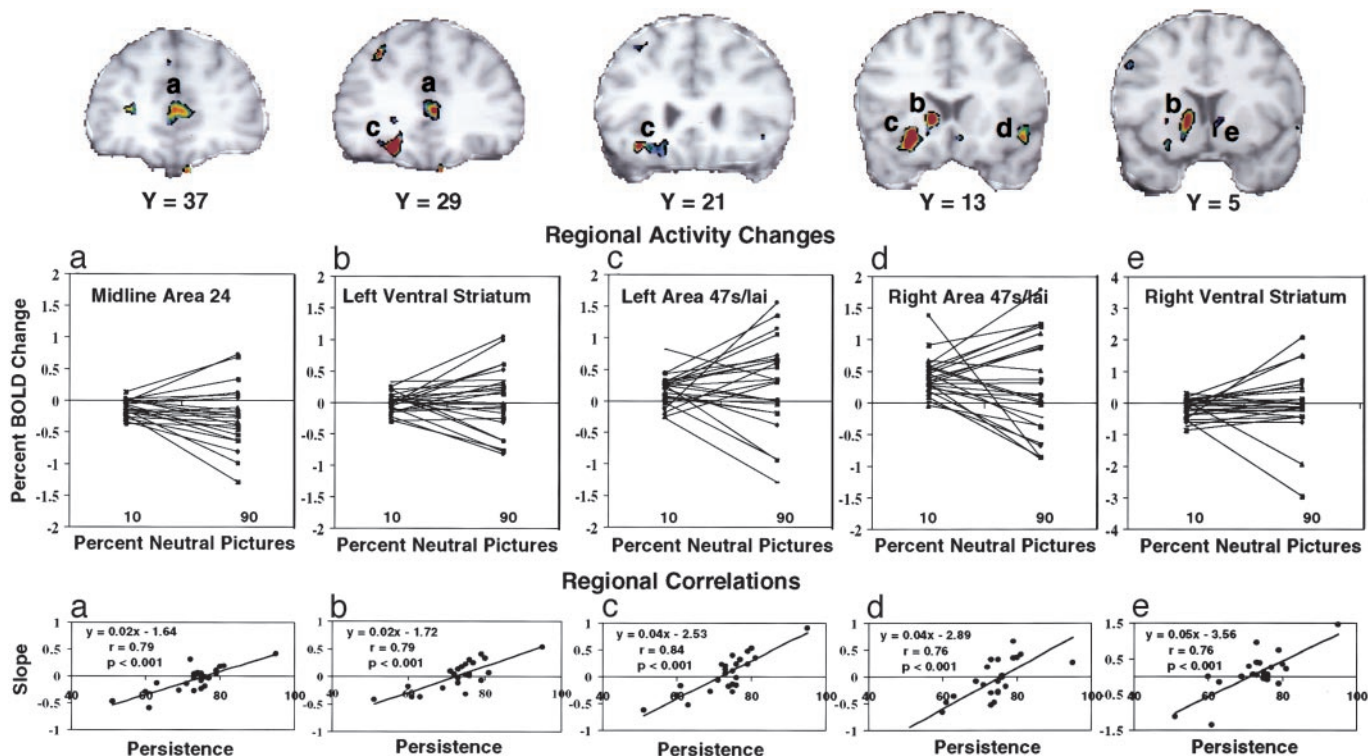


Fig. 1. The location and analysis of Persistence-related correlations. The loci (a–e) of the correlations are displayed on coronal sections of the Colin brain (see *Methods*), which has been transformed into atlas space (*Top*). These correlations arise from the slope of a linear relationship between the percentage of neutral pictures viewed by the subjects and the percent BOLD change as shown in the graphs in *Middle*, where each of the lines represents the data from an individual subject. The individual lines are the best fit to the data across all percentages of neutral pictures (i.e., 10–90% in increments of 16%). The slopes of the lines characterizing the relationship between the percentage of neutral pictures and the percent BOLD change varied from positive to negative across subjects for each region. We note that the differences among our subjects became greater as the percentage of neutral pictures increased, which may be related to individual differences in the ability to persist as external stimulation or immediate incentive is reduced. The correlations between the slopes of the lines shown in the graphs in *Middle* and the Persistence scores for each subject are shown in *Bottom*, where data from individual subjects are plotted for each region. As an aside, we note that on group-activation images it would be the *average* change across all percentages of neutral pictures relative to baseline (visual fixation in this case) that would determine the percent BOLD change. Thus, in such an image, activity (percent BOLD change) would appear as an increase in regions c and d, as a decrease in regions a and e, and no change in region b. In *Top*, the position of each slice within the coronal, or y plane, relative to the anterior commissure, is shown below the images. The left sides of the images are on the reader's left. Coordinates (x, y, z) for regions a–e are, respectively: 3, 35, 10; –13, 9, 2; –27, 13, –10; 45, 15, –4; and 7, 5, 0.

rewarding than individuals low in Persistence. Indeed, a relative increase in activation of the putative reward circuitry (ventral striatum, ventral prefrontal cortex) under conditions of low extrinsic arousal (90% neutral pictures) would seem to make sense if Persistence is related to the ability to generate and maintain arousal and motivation internally, in the absence of immediate external reward. This possibility would also be compatible with a suggested specialization of the OMPFC for holding incentive information in representational memory during delay periods in the guidance of behavior (e.g., ref. 34).

Not only were the individual differences greater as the percentage of neutral pictures was increased but also these differences occurred in opposite directions. Those highest in Persistence showed increases in activity, whereas those lowest in Persistence showed decreases (Fig. 1). These changes might reflect a property of the cellular elements of this circuit to exhibit individually unique reactivity in the context of our specific judgment tasks, which may be either an increase or a decrease. There are physiological precedents for the cellular elements within areas of the cerebral cortex and basal ganglia to exhibit directionally selective responses that depend on local membrane properties at the time of stimulation (e.g., see refs. 35 and 36) and local concentrations of neuromodulators such as dopamine (35). It seems reasonable to suggest that our understanding of the

neurobiological substrates of individual differences will eventually be found at this level of analysis within specific brain systems.

The individual differences in behavior (i.e., a tendency to rate pictures as pleasant) that we observed in our subjects, although consistent with conceptualizations of Persistence, nevertheless appeared to result from a complex interaction of several personality variables, namely Persistence, Self-Directedness, and Harm Avoidance. Such an interaction would not be surprising given the complexity of such decisions and the potential for individual aspects of one's personality to contribute to them. It remains a challenge for the future to design experiments that will progressively refine our understanding of the unique contributions of each of these personality variables.

Our study relates Persistence to specific anatomical circuitry. Anatomical studies of architectonics and connectivity in macaque monkeys (31, 37, 38) indicate that the areas that correlated with the Persistence scores of our subjects are part of an interactive neural circuit that involves the OMPFC and the ventromedial striatum, which includes the nucleus accumbens. In this study we have taken advantage of the fact that the cytoarchitecturally distinct elements of this neural circuit have now been identified in the human brain (31), and these elements have been registered within the anatomical space used for the analysis of our data. As a result, we have the potential to relate our

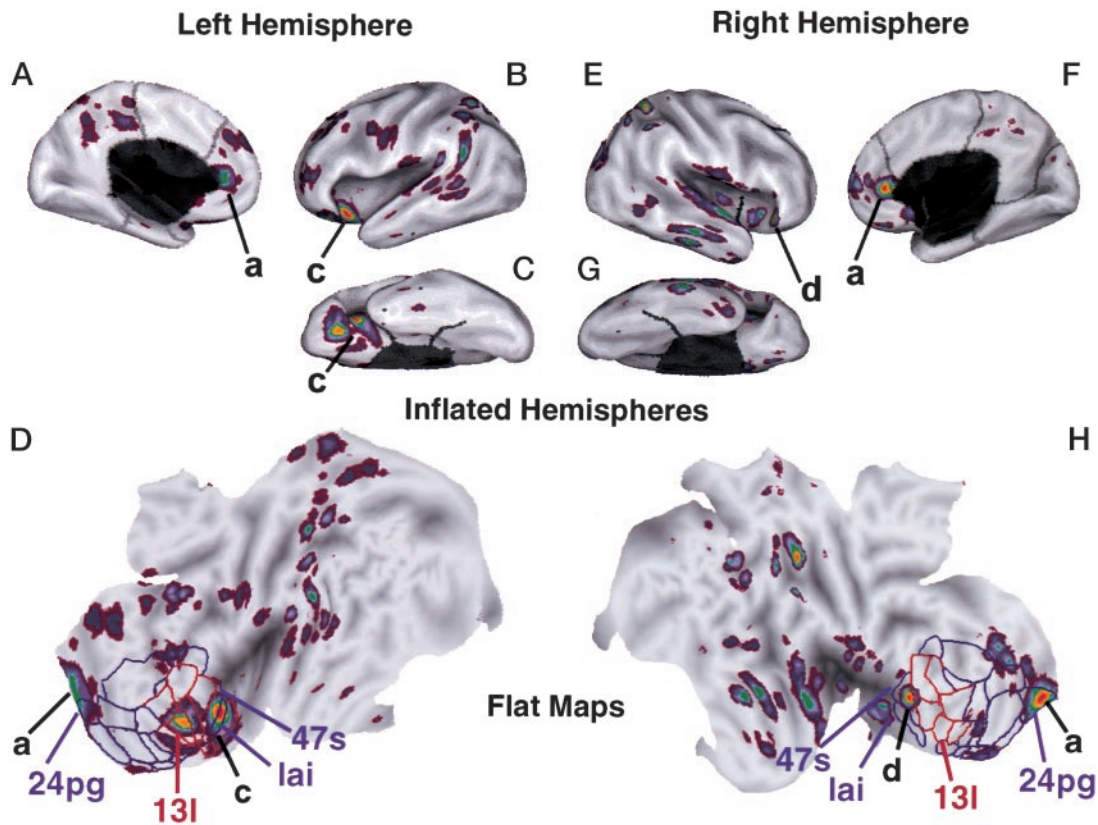


Fig. 2. Persistence-related correlation maps charted on a surface-based atlas (see *Methods*). Correlation data are mapped to surface reconstructions of the cerebral hemispheres from the Human.colin atlas. The fMRI data were mapped to fiducial (3D) surface reconstructions registered to Talairach space (30) and are displayed on inflated surfaces (A–C, left hemisphere; E–G, right hemisphere) and on flat maps (D and H, left and right hemispheres, respectively) where cuts were made outside the orbitofrontal region to reduce distortions. (D) Flat map of left hemisphere with the estimated boundaries of 20 architecturally identified orbitofrontal areas. Areal boundaries in blue denote the medial system and those in red denote the orbital system of Price and coworkers (31, 33). Focus a lies in or near area 24pg of the medial network; focus c lies in or near areas 47s and lai of the medial network (a portion of this focus appears to lie in or near area 13l of the orbital network, but may reflect spillover from the larger focus in area 47s, as noted in the text). (H) Flat map of right hemisphere with estimated architectonic boundaries in orbitofrontal cortex. Focus d, less prominent than focus c, lies in or near area 47s, and focus a lies in or near area 24. Additional activations on the correlation map are concentrated along a swath from the dorsal temporal cortex to the medial parietal cortex in both hemispheres. The individual foci in this strip are mostly of borderline statistical significance, but the overall pattern is unlikely to be purely coincidental. These data can be viewed online (See *Supporting Text*).

findings to the extensive literature on the anatomy and functionality of this circuit in animals and humans.

Three of our regions (Fig. 1, regions a, c, and d) are thought to constitute part of a medial network within the prefrontal cortex as illustrated in Fig. 2 (31). These three regions coincide with the pregenual part of area 24, medially, and area lai and part of area 47 (47s), laterally. These are comparable to areas 24b and 12o/lai in monkeys. It should be noted that area 24b is the most rostral part of the anterior cingulate cortex, which in humans wraps around the genu of the corpus callosum (31). On the basis of its connective anatomy, the medial network, including areas 24b and 12o/lai, has been suggested to be the site of the emotional motor output from the OMPFC, particularly to the hypothalamus and the periaqueductal gray, which exert coordinated control of aspects of visceral and autonomic function (39, 40). Part of region c (Figs. 1 and 2) extends across the white matter of the lateral orbital gyrus into area 13l, which is part of the more sensory input-related orbital network within the OMPFC. This area appears as a potentially separate focus of correlation on the unfolded cortical map (Fig. 2), but it is uncertain whether this is because of a genuine focus in area 13l or to artifactual spread from the more prominent focus in areas lai and 47s.

The other two regions identified in this correlational set reside in similar portions of the striatum in the left and right hemispheres, respectively (Figs. 1 and 3). This finding is consistent with recently described prefrontal striatal projections in monkeys from the medial network, including areas 24, lai, and 12o [12o is equivalent to 47s in the human, which represents one of four subdivisions of Brodmann area 47 (37)]. Specifically, the ventromedial striatum, including the medial caudate nucleus and the nucleus accumbens, receives input predominately from the areas of the medial network on both the medial wall (e.g., area 24) and the orbital surface [e.g., areas lai and 12o (47s)]. These projections closely mirror the sites of activity within the striatum associated with Persistence in our data (Figs. 1 and 3, regions b and e).

We note a particularly prominent asymmetry in our data, with the foci of correlation being more extensive in the left hemisphere than in the right, primarily manifest in area 47s/lai and the area to which it projects in ventral striatum (see Figs. 1 and 3). Two bodies of information suggest possible sources of this asymmetry, one functional and the other anatomical. Functionally, the task performed by our subjects required a strategic, volitional processing of complex items, which is a type of processing that has been suggested to preferentially engage the left hemisphere (e.g., refs. 41 and 42). Anatomically, an asym-

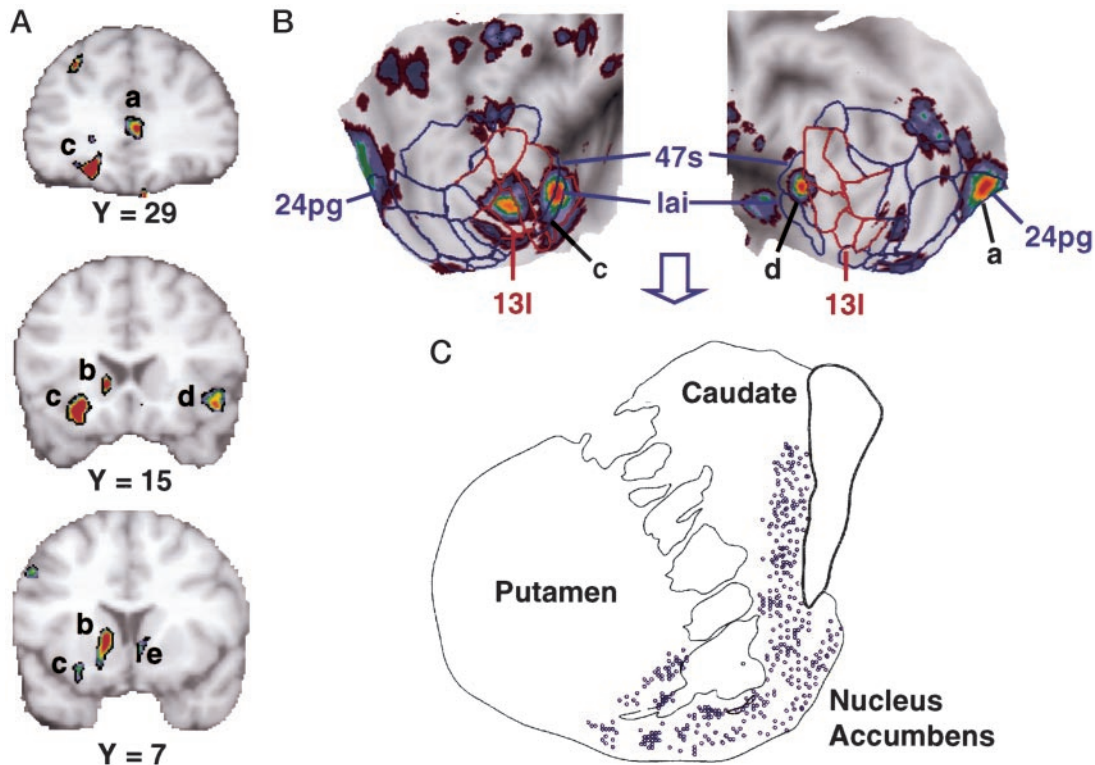


Fig. 3. Two regions (A, b and e) identified in the Persistence correlation reside in portions of the ventromedial striatum (medial caudate nucleus, nucleus accumbens, and ventral putamen). Corticostriatal projections from the medial network of the OMPFC [B, blue grids including areas 24, lai, and 12o (47s in the human)], where three of our correlation foci reside (B, a, c, and d), project directly to these portions of ventromedial striatum. These projections have been recently described in monkeys, and are shown in C [dots represent the distribution of axon terminals labeled by tracers injected in the medial network (31, 37, 38)].

metry in the region of area 47s/lai in the rostral insula and adjacent orbital cortex has been identified in humans, with this area occupying a significantly larger area of cortex in the left hemisphere than in the right in 74% of the 156 cases studied.** This anatomic asymmetry was also confirmed in the majority of the subjects in our sample on their structural magnetic resonance images. (See also *Note in Supporting Text.*)

Circuitry underlying state functionality associated with the personality dimension of Persistence may well extend beyond the areas highlighted in the present discussion (Figs. 1 and 2). Additional candidate areas that were observed in the current study include several temporal and parietal regions shown in Fig. 2. We note, however, that these individual foci are mostly of borderline significance. Future studies should reveal whether they indeed form an integral part of circuitry associated with behavioral persistence.

Physiological studies related to the OMPFC and striatal areas associated with Persistence in our data, which have been largely conducted in laboratory animals, indicate its importance in reward-related activities, including expectation and detection of reward (for reviews, see refs. 34, 43, and 44). Whereas the nature of the processing occurring in these brain regions is not completely understood, experimental data suggest that it is important for guiding behavior based on contextually relevant incentive-based information.

Functional imaging studies involving reward-related paradigms in humans have complemented this research in laboratory animals (e.g., see refs. 45–48), engaging some, although not all,

of these brain regions. These studies, like most in functional imaging, have reported group-average data. Individual differences in self-reported hedonic responses to various experimental (including pharmacological) manipulations have actually been correlated with changes within portions of OMPFC and its connections, however (47, 49–51). Along with such individual differences in reported experience, it is also potentially relevant that studies on clinical populations, such as subgroups of substance-dependent individuals (52), have suggested that altered functionality of these brain regions may be a source of the incentive-related decision-making and behavioral impairments of these individuals as compared with normal populations.

Incentive-related decision-making and behavioral impairments are not only manifest in such clinical populations, they are also frequently acquired by individuals who have suffered damage to the OMPFC. Specific impairments include a lack of persistence (9), which has been characterized in the Iowa Scales of Personality Change as “the extent to which he/she has difficulty sticking with a task, and completing projects he/she begins” (D. Tranel, personal communication).

Persistence as a specific behavioral phenomenon has been extensively studied. This research has generally been within the context of two relatively distinct psychological traditions, one more experimentally grounded in a learning theory tradition, the other emphasizing inherent individual differences in perception of self (e.g., self-esteem) relative to situational demands in a social psychological tradition (for two excellent reviews, see refs. 10 and 11). Despite such differences, in both of these research settings, persistence has typically been referred to as the extent to which an individual pursues reinforcement that is no longer, or is not immediately, available.

**Price, J. L., Ferry, A., Haut, K. M., Öngür, D., Drevets, W. C. & Botteron, K. N., Society for Neuroscience 31st Annual Meeting, November 10–15, 2001, San Diego, abstr. 83.14.

Efforts at reconciling these approaches have been made by a few researchers considering individual differences in task expectations by using the framework of social learning theory (53, 54). The seven-factor personality model, on which the TCI used for this study is based, might also be regarded as being in this general category. Specifically, it considers individual differences in personality to be related to differences in response biases in neural systems involved in different kinds of learning (55).

Persistence, in the context of the seven-factor model, has been described as reflecting the ability to persevere in the face of partially reinforced responses and to distinguish individuals with regard to their resistance to extinction. Individuals who score high in Persistence tend to endorse being industrious and persevering, whereas those who score low endorse a tendency to give up quickly when not continuously reinforced. In particular, Persistence has been related to the partial reinforcement extinction effect or PREE (56). The PREE refers to an increase in resistance to the extinction of an operant response acquired under partial reinforcement relative to that acquired under continuous reinforcement. It has been documented experimentally in a number of species, including humans (e.g., refs. 57 and

58). This relationship is of interest in the context of our results, in that lesions involving the medial prefrontal cortex and the nucleus accumbens have been shown to abolish the PREE in experimental animals (12, 13).

In conclusion, we have related individual differences on a dimension of personality, Persistence, to a well-known anatomical circuit involving portions of the medial network of OMPFC and its projections to ventral striatum, a circuit that has been associated with prediction and reward as well as emotional motor control. Acquiring an understanding of circuitry that may be associated with such differences, coupled with the knowledge that these differences are, in part, genetically determined, may help develop bridges between genetics, individual differences in behavior, and the brain.

We gratefully acknowledge Deborah Kerr and Russ Hornbeck for their technical contributions to this work. Financial support for this work was received from National Institutes of Health Grants NS 06833 (to M.E.R.), DA 07261 (to D.A.G.), MH 62130 (to C.R.C.), DC 00093 (to J.L.P.), and MH 60974 (to D.C.V.E.), and the Charles A. Dana Foundation.

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