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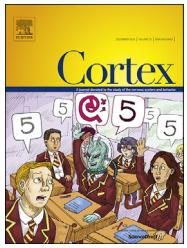

Behavioural neurology

Neuropsychiatric effects of neurodegeneration of the medial versus lateral ventral prefrontal cortex in humans

Edward D. Huey [a,b,c,d,*], *Seonjoo Lee* [d,e], *Adam M. Brickman* [a,c,f], *Masood Manoochehri* [a,c], *Erica Griffith* [a,f], *D.P. Devanand* [b,d], *Yaakov Stern* [a,c,f] *and Jordan Grafman* [g,h]

[a] *Taub Institute and Gertrude H. Sergievsky Center, Columbia University Medical Center, New York, NY, USA*
[b] *Division of Geriatric Psychiatry, Department of Psychiatry, Columbia University, College of Physicians and Surgeons and New York State Psychiatric Institute, New York, NY, USA*
[c] *Department of Neurology, Columbia University, College of Physicians and Surgeons, New York, NY, USA*
[d] *Department of Psychiatry, Columbia University, College of Physicians and Surgeons and New York State Psychiatric Institute, Columbia University, New York, NY, USA*
[e] *Department of Biostatistics, Columbia University, College of Physicians and Surgeons, New York, NY, USA*
[f] *Cognitive Neuroscience Division, Department of Neurology, Columbia University, College of Physicians and Surgeons, New York, NY, USA*
[g] *Brain Injury Research Program, Rehabilitation Institute of Chicago, Chicago, IL, USA*
[h] *Northwestern University, Chicago, IL, USA*

ARTICLE INFO

Article history:
Received 26 March 2015
Reviewed 4 May 2015
Revised 23 June 2015
Accepted 4 August 2015
Published online 15 August 2015

Keywords:
Neurodegeneration
Prefrontal cortex
Neuropsychiatry
Lesion studies

ABSTRACT

Animal evidence suggests that a brain network involving the medial and rostral ventral prefrontal cortex (PFC) is central for threat response and arousal and a network involving the lateral and caudal PFC plays an important role in reward learning and behavioral control. In this study, we contrasted the neuropsychiatric effects of degeneration of the medial versus lateral PFC in 43 patients with Frontotemporal dementia (FTD) and 11 patients with Corticobasal Syndrome (CBS) using MRI, the Neuropsychiatric Inventory (NPI), and the Sorting, Tower, Twenty Questions, and Fluency tests of the Delis-Kaplan Executive Function System (D-KEFS). Deviations in MRI grey matter volume from 86 age-matched healthy control subjects were determined for the patients using FreeSurfer. Multivariate regression was used to determine which brain areas were associated with specific neuropsychiatric and cognitive symptoms. Decreased grey matter volume of the right medial ventral PFC was associated with increased anxiety and apathy, decreased volume of the right lateral ventral PFC with apathy and inappropriate repetitive behaviors, and of the left lateral ventral PFC with poor performance on the sorting and Twenty Questions task in patients with FTD and CBS. Similar to in animal studies, damage to the medial OFC appears to be associated with a

* *Corresponding author*. Taub Institute and Gertrude H. Sergievsky Center, Columbia University Medical Center, 630 W 168th St, P&S Box 16, New York, NY, 10032, USA.
E-mail address: edh2126@cumc.columbia.edu (E.D. Huey).
http://dx.doi.org/10.1016/j.cortex.2015.08.002

disruption of arousal, and damage to the lateral OFC appears to be associated with deficits in trial-and-error learning and behavioral dysregulation. Studies of brain dysfunction in humans are valuable to bridge animal and human neuropsychiatric research.

1. Introduction

Tracing and lesion studies in animals suggests that the medial and lateral ventral prefrontal cortex (PFC) are components of distinct networks with related, but separable, functions (Carmichael & Price, 1995, 1996; Drevets, Price, & Furey, 2008; Haber, Lynd, Klein, & Groenewegen, 1990; Murray, Wise, & Drevets, 2011; Nakano, 2000; Price & Drevets, 2011; Saleem, Miller, & Price, 2014). In this study, we examine the neuropsychiatric and cognitive effects of neurodegeneration of the medial versus lateral ventral PFC in patients with neurodegenerative illness targeting the frontal lobes. The goal of this study is to test whether dysfunction of these brain regions results in neuropsychiatric and cognitive symptoms in humans that are similar to those found in animals.

The medial PFC (MPFC) network involves the more medial and rostral ventral PFC including human BA 10, medial 11, 14, 24, 25, and 32 (Carmichael & Price, 1995, 1996; Haber, et al., 1990; Price & Drevets, 2011). It appears in animals to be preferentially involved in a network that responds to fear and threat (Price & Drevets, 2011). This network includes cochlear – pontine – spinal loops controlling rapid simple startle responses (Lee, Lopez, Meloni, & Davis, 1996), the periaqueductal gray (PAG), which helps to coordinate somatic reactions to fear including the quiescence response in which the animal becomes quiet and withdrawn in response to injury (Bandler, Keay, Floyd, & Price, 2000), and the amygdala (LeDoux, 2007; Price, 2005). There is a large animal literature linking both the amygdala and medial PFC with fear conditioning and extinction [see (Etkin, Egner, & Kalisch, 2011; Marek, Strobel, Bredy, & Sah, 2013) for reviews of this topic]. Lesions of these regions interfere with fear conditioning and extinction in animals (Etkin, et al., 2011; Marek, et al., 2013).

The lateral PFC (LPFC) network involves the more lateral and caudal ventral PFC including human BA lateral 11, 13l, 13m, 13b, 47l, 47m, and 47r (Carmichael & Price, 1995, 1996; Haber, et al., 1990; Price & Drevets, 2011). It receives extensive sensory and limbic inputs in addition to input from areas involved in reward processing including the ventral tegmental area (VTA), nucleus accumbens, and ventral striatum (Carmichael & Price, 1995, 1996). The LPFC network plays important roles in olfactory and gustatory processing and reward and reinforcement learning in primates (Kringelbach & Rolls, 2004; Price, 2005). The LPFC network has been associated with assessing the rewarding or punishing nature of stimuli (Saleem, et al., 2014). Lesions of the lateral ventral PFC in monkeys results in impaired reward learning, but preserved fear conditioning (Kazama, Davis, & Bachevalier, 2014).

We cannot perform brain lesions in humans as we do with animals. However, certain neurodegenerative illnesses in humans result in degeneration and atrophy of the frontal lobes, including Frontotemporal dementia (FTD) and corticobasal syndrome (CBS). The study of these patients can be used as a model for the effects of frontal dysfunction in humans. FTD primarily affects the PFC and the anterior temporal lobes (Seeley et al., 2008), while CBS affects the posterior frontal lobes, anterior temporal lobes, and the basal ganglia (Boeve, 2005). Both illnesses present with neuropsychiatric symptoms and cognitive deficits. Together, these illnesses affect the entire frontal lobes and provide a means to investigate the effects of frontal dysfunction in humans.

Based on findings in animals that the MPFC network is more associated with arousal/threat response, we hypothesize that damage to the MPFC network structures in patients with FTD and CBS will be selectively associated with dysregulation of arousal with excessive arousal (manifesting as anxiety), or decreased arousal (manifesting as apathy) in our subjects. Based on animal findings that the LPFC network is more associated with reward processing, we hypothesize that damage to LPFC network structures will be selectively associated with a decrease in the performance of previously rewarding behaviors (manifesting as apathy), impairment in behavioral regulation (manifesting as inappropriate repetitive behaviors), and deficits in reversal learning (manifesting as poor performance on a sorting task) in patients with FTD and CBS. To test these hypotheses, we administered to caregivers a questionnaire designed to elicit their observations of neuropsychiatric symptoms, the UCLA Neuropsychiatric Inventory (NPI), and we evaluated patients with a sorting test. We performed structural MRI scans on the patients and determined their deviations in grey matter volume from a sample of age matched control subjects.

There are data from previous studies on the neuroanatomical associations of neuropsychiatric symptoms in patients with neurodegenerative illness and brain injury to support these hypotheses. In one such study in patients with neurodegenerative disease, apathy was associated with atrophy in the right ventromedial PFC and aberrant motor behavior with the right dorsal anterior cingulate cortex extending laterally to the supplemental motor area (Rosen et al., 2005). Other studies have linked degeneration of the ventromedial PFC with apathy in patients with Alzheimer's disease (Benoit et al., 2002; Craig et al., 1996; Migneco et al., 2001) and FTD (Peters et al., 2006), and also with the lateral PFC in FTD (Zamboni, Huey, Krueger, Nichelli, & Grafman, 2008) (note, however, that 15 of the patients in this study were included in the current study as well). In studies of brain injury resulting in focal lesions, apathy has been associated with medial and lateral PFC lesions (Knutson et al., 2014), and anxiety with damage to structures involved in the MPFC network (Knutson et al., 2013). Apathy has been associated

with strokes of the medial PFC (Jorge, Starkstein, & Robinson, 2010).

A limitation of previous studies on the neuroanatomy of psychiatric symptoms in neurodegenerative disorders and brain lesions is that both imaging measures and psychiatric symptoms are highly co-linear (e.g., atrophy in one region is associated with atrophy in adjacent regions and psychiatric symptoms such as anxiety and depression often co-occur). In the current study we utilized a statistical method, multivariate regressions, which accounts for the co-linearity of our neuropsychiatric and imaging measures, to best determine which brain areas are associated with which neuropsychiatric symptoms.

2. Material and methods

2.1. Participants

We performed MRI scans in 86 healthy control subjects and 43 patients with FTD and 11 patients with CBS. We studied patients with FTD and CBS because with these two diagnoses, the patients had involvement of all parts of the frontal cortex. We included patients with both behavioral and language variants of FTD as there is significant symptomatic and anatomic overlap between these variants. The FTD and CBS patients were seen as part of an ongoing research study on FTD and CBS in the Cognitive Neuroscience Section of the National Institute of Neurological Disorders and Stroke (NINDS) of the NIH, Bethesda, MD and diagnosed by standard clinical criteria (Armstrong et al., 2013; Rascovsky et al., 2011). We required all subjects to have an assigned research durable power of attorney prior to admission to the protocol and the assigned individuals gave written informed consent for the study. The patients gave assent for the study. All aspects of the study and the consent procedure were approved by the NINDS Institutional Review Board. Demographic and selected clinical data on the patients and control subjects is presented in Table 1.

To establish a robust normative MRI map, we performed MRI scans and extensive neuropsychological testing on 86 healthy control subjects between the ages of 40 and 77 through their participation in a separate study at Columbia University Medical Center ("Exploring cognitive aging using reference ability neural networks", PI: Yaakov Stern). These subjects were screened to not have any neurological or psychiatric illness and to be cognitively intact (Table 1). Informed consent was obtained from the subjects, and all procedures were approved by the Columbia IRB.

Table 1 – Characteristics of 54 patients and 86 control subjects. Numbers with parentheses are means with standard deviations. T-tests are between the patients and control subjects.

	Patients	Control subjects	T-test p-value
Age	61 (8.9)	59.3 (10.2)	.32
Education	15.5 (2.9)	16.2 (2.5)	.13
Male	52%	52%	N/A
DRS-2 Total	106.9 (24.3)	139.9 (2.8)	>.01
Mean scaled score D-KEFS sorting score (10 is normal)	6.5 (2.7)	N/A	N/A

2.2. Measures

The NPI was administered to all of the FTD and CBS patients. This is a scale in which a knowledgeable informant is interviewed on the development of a range of neuropsychiatric symptoms by the patient since the onset of the illness (Cummings et al., 1994). We also administered the Mattis Dementia Rating Scale (MDRS-2) (Mattis, 1976) to assess general cognition and the card sorting test from the Delis-Kaplan Executive Function System (D-KEFS) (Delis, Kaplan, & Kramer, 2001) to assess executive functions in patients who could understand the test instructions.

2.3. Structural MRI (sMRI)

All MRI scans were acquired during a single session of a 3.0T GE MRI scanner at NIH (for the patients) or a 3.0T Philips Achieva scanner at Columbia Medical Center (for the control subjects). Scan parameters for NIH were TE/TR = 3/6.5 ms, Flip angle 8°, In-plane resolution = 256×256 voxels, 1 mm slice thickness, 140–180 slices, field of view = 240 mm. Scan parameters for Columbia were the same except TE/TR = 3/6.6 ms. At each session, a scout T1-weighted image was acquired to determine patient position. Using each individual's T1-weighted MPRAGE image global and regional brain volume were derived using FreeSurfer software, version 5.1 (http://surfer.nmr.mgh.harvard.edu/). This version of FreeSurfer utilizes a longitudinal image processing framework in which an individualized template is created for each subject and this template is used to initialize segmentation algorithms. This procedure has been shown to reduce variability compared to independent processing (Jovicich et al., 2013; Reuter, Schmansky, Rosas, & Fischl, 2012). Use of the longitudinal image processing framework has been demonstrated to result in good volume reproducibility of individual brain structures between scanners of three different manufacturers (GE, Siemens, and Philips, mean intraclass correlation coefficient .939 to .998, Dice coefficient for spatial overlap range from .90 to .95, absolute volume reproducibility errors range from 1.8 to 3.8%) (Jovicich, et al., 2013). Brain volume calculations paralleled the procedures of Walhovd et al. (Walhovd et al., 2011) to automatically assign a neuroanatomical label to each voxel in the MRI, with results comparable to manual labeling (Fischl et al., 2002; Fischl et al., 2004) . From this labeling, volumetric regions of interest (ROI) were defined (Kennedy et al., 2009). The calculated volume within each region was adjusted for variations in individual global brain volume with a measure of total intracranial volume (ICV) using the atlas-based normalization scaling factor as a proxy for ICV (Buckner et al., 2004). All of the FreeSurfer ROIs were used with the exception of the frontal and temporal pole ROIs. The frontal and temporal poles are not measured directly in FreeSurfer. Rather they are designated using exclusionary criteria — the frontal and temporal regions are defined and the remaining portion is designated the pole (Desikan et al., 2006).

Our group and others have found the FreeSurfer frontal and temporal pole values to be unreliable in patients with significant anterior frontal and temporal brain atrophy (Su et al., 2013). The boundaries of the lateral OFC were the rostral and caudal extents of the lateral orbital gyrus, and the midpoint of the olfactory sulcus and the lateral bank of the lateral orbital sulcus. The boundaries of the medial OFC were the rostral and caudal portions of the medial orbital gyrus, and the cingulate cortex and the medial bank of the superior frontal gyrus (Desikan, et al., 2006).

2.4. *Data analysis*

First, we determined the gender-specific mean volume and standard deviations of values in the control subjects. We next assigned each patient an "atrophy map" of z-scores of the degree of volume loss in each of our 80 (40 in each hemisphere) ROIs compared to our age-matched control subjects with zero mean and one standard deviation. To test the effect of volume loss on the NPI scores, we then entered these z-scores into a multivariate regression. For model selection, we used Least Absolute Shrinkage and Selection Operator (LASSO) regularization. Multivariate regression with LASSO regularization achieves sparsity in the estimated model by interpreting variables with non-zero regression coefficients as truly associated with the dependent variable. The model we considered was $y_{ip} = \alpha_p + \sum_{j=1}^{Q} \beta_{jp} x_{ij} + \epsilon_{ip}, \quad i = 1, \ldots, n, \; p = 1, \ldots, P$ where n was the number of individuals, Q was the number of ROIs, and P was the number of non-imaging outcome measures. The possible confounding variables age and total Mattis Dementia Rating Scale 2 (Mattis, 1976) score were included as covariates. We applied multivariate linear regression with LASSO regularization using the lars R package for model selection (Benjamini & Yekutieli, 2001; Efron, Hastie, Johnstone, & Tibshirani, 2004), and the model coefficients were corrected for multiple comparison (Benjamini & Yekutieli, 2001).

3. Results

The ROI volumes were normally distributed in the control subjects (96% of the ROIs had a non-significant Kolmogorov–Smirnov test at a 5% significance level). We compared the ROI volumes of the FTD and CBS patients to our age- and gender-matched mean normative volumetric data. These data are presented graphically in Fig. 1. Fig. 2 shows the heat map of results from the multivariate linear regression with LASSO regularization. To understand the selective associations, we applied biclustering on the estimated coefficients that LASSO selected using hierarchical cluster analysis with complete linkage. Significant associations are noted as colored boxes on the heat map in Fig. 2. In a whole brain analysis, the 2 ROIs that showed the strongest negative association with the total NPI were the right lateral OFC and medial OFC. Decreased volume in the right lateral OFC was selectively associated with increased aberrant (repetitive) motor activity and decreased volume of the right medial OFC with increased anxiety. Both regions were associated with apathy. Most associations shown in Fig. 2 did not survive Bonferroni correction (Table 2). However, it should be noted that a Bonferroni correction to correct for 43 comparisons is very strict and greatly increases the threshold for statistical significance.

To further explore the relationship between executive functions and medial versus lateral OFC volume, we performed linear regressions on the ability of the patients' z-score volume deviation from gender-matched controls in the left and right lateral versus medial OFC to predict performance on the following D-KEFS sub-tests: Sorting, Tower Test, Trails, 20 Questions, and Fluency. Each D-KEFS subtests test gives several summary measures (Delis, et al., 2001). To avoid bias in selection of a summary measure for our analysis, we used the mean of the scaled score summary performance measures for each measure in the analysis. The overall regressions were significant: Sorting [R Square = .227, Adjusted R Square = .181, $F(4,34) = 2.88$, $p = .039$] and 20 Questions [R Square = .243, Adjusted R Square = .163, $F(4,38) = 3.04$, $p = .029$]. The best predictor of sorting and 20 Questions test performance was volume in the left lateral OFC (Table 3). All other regressions were not significant.

4. Discussion

Our results mostly support our hypotheses and agree with previous studies showing an association between damage to the ventral PFC and apathy, disinhibition, and aberrant motor behavior (Arnould, Rochat, Azouvi, & Van der Linden, 2013; Bruen, McGeown, Shanks, & Venneri, 2008; Hornberger, Geng, & Hodges, 2011; Rosen, et al., 2005). The whole-brain multivariate regression showed many significant findings (Fig. 2), but the right lateral and medial OFC showed the strongest negative association with the total NPI. Degeneration of the right medial OFC, associated with arousal/threat response in animals, was associated with increased anxiety and apathy in our subjects. Degeneration of the right lateral OFC, associated with reward processing, was selectively associated with apathy and inappropriate repetitive behaviors, and the left lateral OFC with poor performance on tests of trial-and-error learning [Sorting and Twenty Questions (Fig. 2, Table 3)]. Previous studies have shown a similar laterality with degeneration of the left PFC more closely associated with language and cognitive deficits and of the right with behavioral and neuropsychiatric symptoms (Mychack, Kramer, Boone, & Miller, 2001).

While we have argued that the MPFC and LPFC syndromes are clinically separable, we have also posited that they overlap on the symptom of apathy (Fig. 2). A possible explanation for this finding is that disruption of reward processing associated with LPFC network dysfunction and disruption of arousal associated with MPFC network dysfunction could both lead to decreased interest in previously enjoyed activities, resulting in a similar symptom (apathy), but with different neuroanatomical and functional origins. We also found that apathy and anxiety both increase with greater medial PFC atrophy. This suggests that these symptoms do not lie on opposite ends of a spectrum of arousal, but rather that while they both may be related to disruption of normal arousal, they can co-exist and are both are associated with neurodegeneration of the medial PFC. Further research can determine ways in which apathy associated with dysfunction of MPFC and LPFC networks may

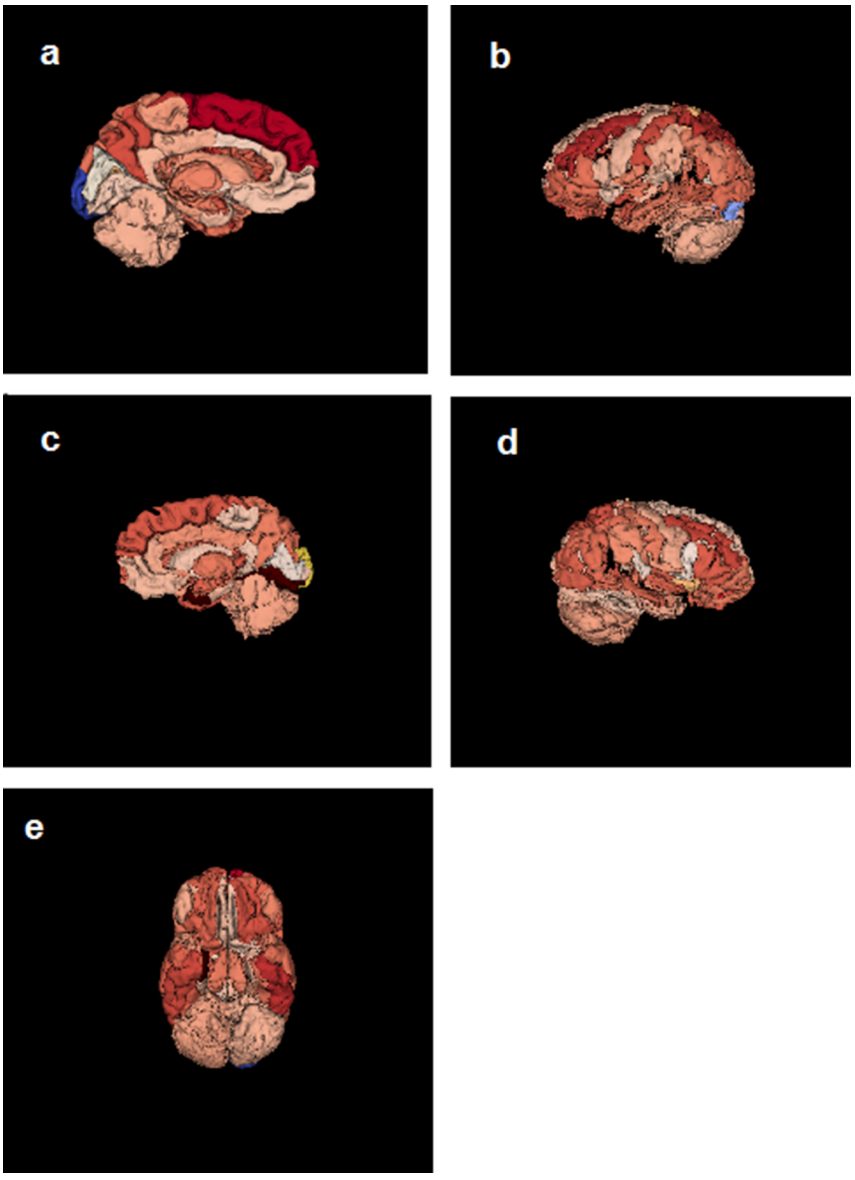

Fig. 1 – Heat map of areas of volume deviation from normal control subjects in our patients with FTD and CBS. Colors represent the mean cortical volume z-score deviation for a given region for the patients compared to the control subjects. The darker the red, the greater the grey matter volume reduction compared to control subjects. Blue represents the one region with greater volume in the patients than the control subjects (the left lateral occipital gyrus). The z-score deviation ranged from −1.77 for the left superior frontal gyrus to .04 for the left lateral occipital gyrus. Fig. 1a and b show the medial and lateral aspects of the left hemisphere, Fig. 1c and d show the medial and lateral aspects of the right hemisphere, Fig. 1e shows the ventral brain.

clinically differ, or if differs depending on the stage of the illness.

Previous animal and human studies indicate that the ventral PFC plays an important role in reward learning and behavioral control. The lateral PFC is activated by the performance of the sorting test, a test of reward learning, in humans (Buchsbaum, Greer, Chang, & Berman, 2005; Ezekiel, Bosma, & Morton, 2013). Damage to the lateral ventral PFC has been linked to repetitive and impulsive behaviors in mice (Mar, Walker, Theobald, Eagle, & Robbins, 2011) and optogenetic stimulation of the lateral ventral PFC suppresses compulsive behaviors in mice (Burguiere, Monteiro, Feng, & Graybiel, 2013). The lateral PFC appears to play an important role in representing the associations between rules and expected reward outcomes (Dixon & Christoff, 2012). Disruption of this process appears to be clinically associated with inappropriate repetitive behaviors, as observed in the current study. Our group recently examined repetitive behaviors in a separate population with penetrating TBI and found that damage to the lateral PFC was the only brain area selectively associated with the development of inappropriate repetitive behaviors in the TBI patients (submitted).

While most of the associations in Fig. 2 are negative (i.e., a decrease in volume in the region is associated with an

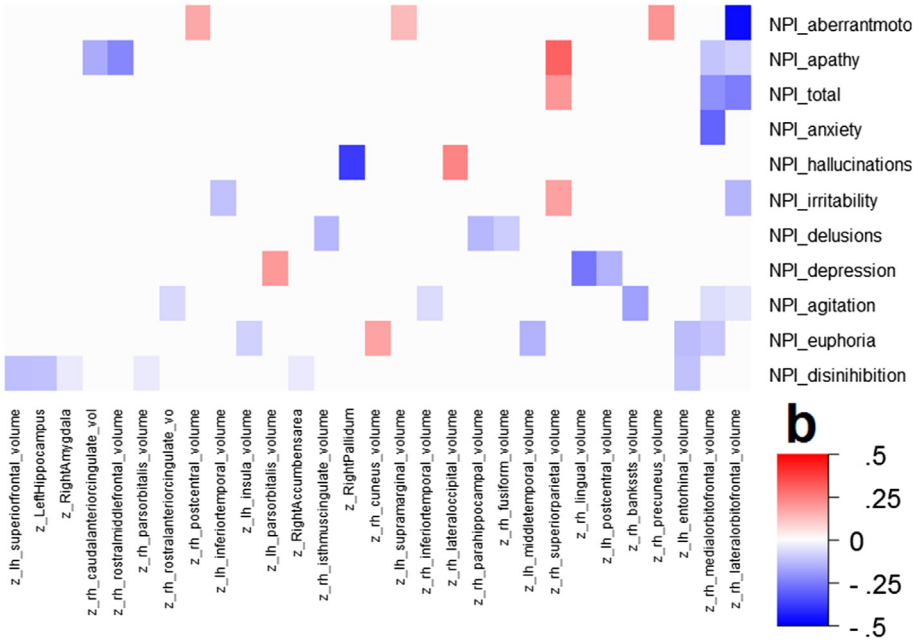

Fig. 2 – Whole-brain associations between the NPI and regional volumes. Cold colors represent negative associations (i.e., the score on the NPI increases, representing more severe psychiatric symptoms, as the regional volume decreases). Hot colors represent the converse (NPI score decreases with decreasing regional volume). The color scale represents standardized coefficients, which are equivalent to partial correlation coefficients. Only ROIs with significant positive or negative associations with the NPI or NPI subscales are shown in the figure. Rh = right hemisphere, lh = left hemisphere. See (Desikan, et al., 2006) for anatomical definitions of regions.

Table 2 – Bonferroni-corrected results for the 43 coefficients represented in Fig. 1. The 95% confidence interval for the following coefficients did not include 0.

Symptom measure	ROI	*b*	Multiple comparison 95% CI	
			.581%	99.419%
NPI_aberrantmotor	z_rh_lateralorbitofrontal_volume	−.476	−.715	−.251
NPI_anxiety	z_rh_medialorbitofrontal_volume	−.303	−.525	−.150
NPI_total	z_rh_superiorparietal_volume	.203	.011	.432
NPI_apathy	z_rh_superiorparietal_volume	.307	.025	.616
NPI_depression	z_lh_parsorbitalis_volume	.196	.032	.407
NPI_hallucinations	z_rh_lateraloccipital_volume	.240	.121	.520

Table 3 – Regression results for effect of ROI volume on summary Sorting and 20 Questions task measures.

Sorting	*B*	Std. Error	Beta	*t*	*p*
Constant	7.27	.68		10.67	.00
Left lateral OFC volume	.80	.41	.47	1.97	.06
Right lateral OFC volume	−.26	.64	−.11	−.40	.70
Left medial OFC volume	−.21	.43	−.12	−.49	.63
Right medial OFC volume	.54	.57	.27	.95	.35
20 Questions	***B***	**Std. Error**	**Beta**	***t***	***p***
Constant	7.73	.79		9.85	.00
Left lateral OFC volume	.83	.47	.45	1.76	.09
Right lateral OFC volume	−.45	.72	−.16	−.62	.54
Left medial OFC volume	.67	.49	.31	1.38	.18
Right medial OFC volume	−.25	.63	−.11	−.40	.67

increase in the neuropsychiatric symptom), some are positive (i.e., greater volume in the region is associated with an increase in the neuropsychiatric symptom). The reasons for these positive findings are unclear, but may reflect that some of the neuropsychiatric symptoms measured may reflect different ends of a behavioral spectrum. For example, the strongest positive association, between right precuneus volume and aberrant motor activity, could reflect that degeneration of the right precuneus is associated with decreased overall motor activity, both normal and aberrant. However, further research using other measures of neuropsychiatric symptoms will be needed to test this hypothesis.

Cautions apply when comparing the effects of human lesions with animal studies. The most common animal fear learning lesion paradigm is to pair a conditioned stimulus (CS, such as a tone) with an unconditioned stimulus (US, such as a

shock) and examine the effects of lesions on conditioning or extinction. In patients with neurodegenerative illness, as in the current study, there is no clear CS or US. We are more likely assessing the effects of dysfunction of core systems involved in arousal, motivation, and reward. Thus, the direction of specific associations may differ between animal and human studies. For example, damage to the medial PFC can reduce fear conditioning in animals (Burgos-Robles, Vidal-Gonzalez, & Quirk, 2009; Vidal-Gonzalez, Vidal-Gonzalez, Rauch, & Quirk, 2006), but is associated with increased anxiety in humans in the current study.

A limitation of the current study is that the control and patient scans were collected on different scanners, which could have biased the results. However, we believe this is unlikely to account for our results for several reasons: 1. Reliability of the Freesurfer 5.1 processing algorithm between GE and Phillips scanners appears to be good (Jovicich, et al., 2013), 2. All scans were individually examined for scan quality prior to Freesurfer processing and discarded if poor quality, 3. The regional volume differences we observed conform to the differences that would be expected between FTD and CBS patients and healthy controls (i.e., frontal, anterior temporal, and peri-central sulcus). Systematic differences in scan quality or scanner manufacturer would be unlikely to reproduce these disease-specific differences. 4. The specific associations between neuropsychiatric symptoms and brain regions that we report agree with the previous literature, including studies we have performed using different methods (Zamboni, et al., 2008).

Generalizing from animal constructs to human psychiatric disorders is a stated goal of the NIMH Strategic Plan and the Research Domain Criteria (RDoC) project (Cuthbert & Insel, 2013). Historically, this has proven difficult as many neuropsychiatric symptoms are specific to humans, so generalizing from animal constructs (such as limbic dysfunction induced by olfactory bulbectomy in rats) to human neuropsychiatric symptoms (such as depressed mood) has been difficult. Studies of brain dysfunction in humans, such as the current study, can help translate between animal and human research by providing a more direct analogy of animal research in humans (e.g., comparing the effects of limbic dysfunction induced by olfactory bulbectomy in rats to damage to the limbic system in humans induced by neurodegeneration) (Huey & Lieberman, 2012). Neuropsychiatric symptoms are common and diverse in neurodegenerative disorders, making these disorders a good lesion model (Levenson, Sturm, & Haase, 2014). 85% of Alzheimer's disease patients, and essentially all patients with Huntington's disease, FTD, and Lewy Body Dementia will develop neuropsychiatric symptoms at some point in their illness including depression, agitation, compulsions, anxiety, or psychosis (Barnes et al., 2012; Chow et al., 2012; Lyketsos et al., 2011; Snowden et al., 2012; Thompson et al., 2012).

5. Conclusions

We have demonstrated in patients with neurodegenerative illness that damage to the medial OFC was associated with an increase in anxiety and apathy. Damage to the lateral OFC was associated with apathy, inappropriate repetitive behaviors, and impairment in trial-and-error learning. These findings generally agree with previous human lesion studies and findings in animals that a network involving the medial OFC is preferentially involved with arousal and fear and that a network involving the lateral OFC is preferentially associated with reward learning. Studies of brain dysfunction in humans are valuable to bridge animal and human research on neuropsychiatric symptoms (Insel & Quirion, 2005).

Acknowledgments

We thank Holly Moore for her comments, our patients and their families, and Michael Tierney, Alyson Cavanaugh, and Karen Detucci for their work with the patients at NINDS. This work was supported by the Intramural Program of NIH/NINDS, NIH/NINDS grants R00NS060766 and R01NS076837 (EDH), the Irving Institute of Columbia University (EDH), and NIH/NIA grant R01AG038465 ("Exploring Cognitive Aging Using Reference Ability Neural Networks", YS).

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