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Neuroanatomical correlates of cognitive self-appraisal in neurodegenerative disease

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Abstract

Self-appraisal is a critical cognitive function, which helps us to choose tasks based on an accurate assessment of our abilities. The neural mechanisms of self-appraisal are incompletely understood, although a growing body of literature suggests that several frontal and subcortical regions are important for self-related processing. Anosognosia, or lack of awareness of one's deficits, is common in neurodegenerative dementias, offering an important window onto the brain systems involved in self-appraisal. We examined the neuroanatomical basis of self-appraisal in a mixed group of 39 individuals, including 35 with cognitive impairment due to one of several probable neurodegenerative diseases, using voxel-based morphometry and an objective, neuropsychologically-based measure of self-appraisal accuracy. Self-appraisal accuracy was correlated with tissue content in the right ventromedial prefrontal cortex (vmPFC). We hypothesize that emotional/physiological processing carried out by vmPFC is an important factor mediating self-appraisal accuracy in dementia.

Keywords

Self-awareness; Insight; Anosognosia; Dementia

Introduction

Awareness of our own performance is a critical component of normal cognition that gives us the ability to recognize our limits and choose our activities accordingly. The neural basis self-awareness is incompletely understood, although a growing body of research suggests that several brain regions mediate functions relevant to self-appraisal, including medial prefrontal cortex, insula, anterior cingulate cortex, amygdala and other subcortical regions, and retrosplenial cortex (Gusnard et al., 2001; Kelley et al., 2002; Northoff et al., 2006; Schmitz and Johnson, 2007).

Neurodegenerative diseases offer an important window into the mechanisms underlying self-awareness. Anosognosia, or lack of awareness of one's impairments, is very common in this setting (Mullen et al., 1996; Agnew and Morris, 1998; Zanetti et al., 1999). In contrast to

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classically-described anosognosia for left hemiplegia, which occurs in the setting of right frontoparietal lesions (McGlynn and Schacter, 1989) and appears to relate to insular damage (Karnath et al., 2005), neurodegenerative dementias impair insight into a variety of cognitive and emotional deficits, a form of anosognosia that may have a different neuroanatomical basis. Consistent with the literature supporting an important role for the frontal lobe in self-related processing, several previous studies have indicated that frontal lobe dysfunction, particularly on the right, strongly influences this loss of awareness of impairment (Reed et al., 1993) (Starkstein et al., 1995; Mendez and Shapira, 2005; Vogel et al., 2005; Mimura and Yano, 2006; Salmon et al., 2006; Shibata et al., 2008), although the precise frontal regions associated with this deficit have not been determined. The prior studies examining the neural correlates of self-awareness in dementia measured awareness based on the discrepancy between subjective reports from patients and informants, whose own distress and potential cognitive impairments could be a potential source of inaccuracy (Clare, 2004). In this study, we examined the neuroanatomical correlates of self-appraisal accuracy using voxel-based morphometry and a measurement of self-appraisal that is dependent solely on objective neuropsychological testing, with demographically adjusted scores serving as the standard for comparing patient's self-appraisal ratings.

Methods

Participants

39 consecutively recruited individuals participated. To mitigate the potential contributions of disease-specific effects on self-appraisal, we included individuals with a range of diagnoses, representing a broad range of cognitive abilities, including two cognitively normal individuals, two cognitively normal patients with amyotrophic lateral sclerosis, two patients with mild cognitive impairment, nine patients with probable Alzheimer's disease (AD), ten with frontotemporal dementia (FTD), five with semantic dementia, five with progressive nonfluent aphasia, and four with corticobasal degeneration. Patients were diagnosed using published criteria (McKhann et al., 1984; Neary et al., 1998; Brooks et al., 2000; Petersen et al., 2001; Boeve et al., 2003) after a comprehensive evaluation at the UCSF Memory and Aging Center including neurological history and examination, nursing evaluation, laboratory evaluation, and a previously described neuropsychological assessment of memory, executive function, language, and mood (Kramer et al., 2003). The standard neuropsychological assessment battery includes the MMSE (Folstein et al., 1975), and tests of verbal episodic memory (California Verbal Learning Test (Delis et al., 2000)), visual-spatial function (copy of a modified Rey–Osterrieth figure), confrontational naming (15 items from the Boston Naming Test (Kaplan et al., 1983), a brief syntax comprehension task with five questions requiring subjects to point to pictures corresponding to specific sentences (e.g. point to the picture of the woman being kissed by the man), and five calculations. The Geriatric Depression Scale (GDS, (Yesavage et al., 1983)) is used to assess mood.

Self-appraisal testing procedure

Self-appraisal was assessed by adding a self-appraisal task to a battery of additional cognitive tests administered as part of an ongoing project to study dementia. At the beginning of the testing session, participants were informed that they were going to perform a series of tasks and that they would be asked to assess their performance after each task relative to a hypothetical sample of people their age, sex and education. Specifically, they were read the following instructions: “In a few moments we will start to do some tests looking at your thinking abilities. At some points during the testing, I’m going to stop and ask you to tell me how you think you did on the test. When I ask how you did, I’d like you to tell me how well you think you did on the test compared to other people similar to you. I want you to imagine that we gave the same task to 100 healthy people of similar age and with similar levels of education. Imagine

if we then lined them up, based on their scores from best (or highest), to lowest.” They were shown a picture of a bell curve with corresponding percentile rankings at the bottom of the page (Fig. 1). The experimenter proceeded to explain that, on most tests, the majority of healthy age-matched peers would perform at the 50th percentile, with smaller numbers performing above or below average (corresponding locations were pointed to by the experimenter). They were told that, after completing each task, they would have to indicate how they thought they had performed by pointing to where they would be on the bell curve picture. We asked participants to rate themselves after testing rather than before because prior studies have indicated that predictions of cognitive performance on standard neuropsychological tests are inaccurate even in cognitively normal individuals (Eslinger et al., 2005).

Cognitive testing then commenced, and the self-appraisal task was added to selected cognitive tasks including the digit span, spatial span and visual delay memory tasks from the Wechsler Memory Scale-Third Edition (Wechsler, 1997), and the phonemic verbal fluency, design fluency and California Trails tasks from the Delis-Kaplan Executive Function System (DKEFS, (Delis et al., 2001)). These particular tasks were chosen because they spanned a range of cognitive domains and all had published norms, so that subjects' estimates of their performance could be compared with their actual performance, also in terms of percentile rank. The only instructions regarding the tasks were the standard instructions used to explain how the task should be performed, as described in the testing manuals. Participants were not given any information about how well normal people perform on these particular tasks. Immediately after completing each of these cognitive tasks, the bell curve picture was produced and the subject was asked to assess how they had performed in terms of a verbal estimate (average, below average, above average) and then a percentile rank. For example, after the digit span task, they were read the following instructions: “Imagine we gave the test you just took to 100 people your age and with your level of education, and lined them up based on how many numbers they could repeat. Compared with all those people, how do you think you did?” The tester then recorded any comments the subject made, and said: “OK, so can you please tell me whether you think you were average, above average, or below average.” After indicating the response, the tester said: “OK, now here is that graph we looked at earlier. Please point out where you would be on this graph”, and then recorded the response. The verbal ratings were used as a way of assessing whether the participants were using the bell curve in a consistent manner. If participants were inconsistent (for example, if they said they performed below average but rated themselves at the 75th percentile) they were not corrected.

Creation of variables

Mean self-appraisal accuracy—Raw scores on each of the cognitive tasks were converted into percentiles using published norms. Post-test performance estimates were subtracted from actual percentile scores to provide an estimate of the accuracy of self-appraisal. This calculation yields a negative number for participants who overestimate their performance and a positive number for those who underestimate, with zero representing perfect accuracy. The discrepancies were averaged across tasks for each subject, resulting in a mean discrepancy score for each participant.

In an effort to verify that participants were using the bell curve in a way that reflected their true self-appraisal, we compared the verbal ratings to the percentile rankings by converting the verbal ratings to an ordinal numeric scale (1=below average, 2=average, 3=above average).

Mean cognitive performance—Theoretically, if all subjects rated themselves at the same level, for instance rating themselves conservatively as performing at the level of an average person, those with the worst performance on cognitive testing would be expected to show the greatest error in self-appraisal just because they were most impaired. In order to ensure that

the analysis represented self-appraisal, rather than cognitive performance on the tasks we used, we averaged the percentile ranks for performance on all the cognitive tasks to create a variable representing overall cognitive performance, which was entered as a covariate in regression analyses examining the association between self-appraisal scores and regional brain morphology.

Image acquisition—Structural MR images were acquired using a 1.5-T Magnetom VISION system (Siemens Inc., Iselin, NJ), a standard quadrature head coil and previously described sequences (Rosen et al., 2002) to obtain (i) scout views of the brain for positioning subsequent MRI slices, (ii) proton density and T2-weighted MRIs and (iii) T1-weighted (MP-RAGE) images of the entire brain. MP-RAGE images were used for analysis.

Image analysis: voxel-based morphometry (VBM)—VBM was used to identify regions where gray matter content correlated with self-appraisal accuracy. VBM of gray matter images was accomplished with SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/>), using standard preprocessing and standard brain templates and prior probability maps for spatial normalization and segmentation, multiplication of the gray matter images by the Jacobian determinants used in normalization to preserve the original amount of gray matter signal in each region of the image, and smoothing with a 12 mm FWHM isotropic Gaussian kernel. VBM analyses was conducted using a “covariates only” model that included self-appraisal discrepancy, diagnosis (using binary coding for each diagnosis vs. controls), mean cognitive performance, age, sex, and total intracranial volume (calculated as the sum of the modulated gray, white and CSF volumes, used as a surrogate for head size) as covariates. Statistical significance for VBM was evaluated at $p < 0.05$ corrected for multiple comparisons using family-wise error correction (Friston et al., 1996), although the data are displayed using the commonly used $p < 0.001$ threshold.

The research protocol was approved by the UCSF committee on human research and all subjects gave informed consent before participating.

Results

Group characteristics

Table 1 shows the demographic and cognitive data for the participants, grouped according to diagnosis as cognitively normal subjects (Controls and ALS), AD spectrum patients (MCI and AD), and FTD spectrum patients (FTD, SD, PNFA, CBD). Data are shown for the six tasks for which subjects predicted their performance, as well as for several tasks from our standard neuropsychological assessment battery tapping other domains, including verbal memory, language, visuospatial processing, calculations and mood. As would be expected, patients in AD and FTD groups performed more poorly than ALS and control subjects.

Self-appraisal

We performed several analyses to examine how the participants handled the self-appraisal task. Self-appraisal varied across individuals in a predictable pattern. The majority estimated themselves near average, with smaller numbers estimating themselves above or below average. This was true in both the AD spectrum and FTD spectrum patients, although it is notable that the AD spectrum patients showed a trend toward rating themselves lower than average, and this did not appear to be the case in the FTD spectrum patients (Fig. 2). The correlations between these percentile-based self-assessments and the verbal self-appraisals (average, below average, above average) across the group were high and statistically significant for all six cognitive tasks ($r > 0.8$, $p < 0.001$ in each case). We also examined correlations between verbal and percentile ratings by diagnosis using average verbal and percentile ratings across all tasks, and

found that the correlations were high in both AD spectrum and FTD spectrum patients ($r > 0.9$, $p < 0.05$ in both groups). These data indicate that even subjects with dementia appeared to use the percentile rating system appropriately. In addition, average self-assessment was moderately correlated with performance, so that decreasing performance was associated with decreasing self-estimation ($r = 0.430$, $p < 0.001$), indicating that participants were somewhat sensitive to their performance, with more poorly performing subjects rating themselves as performing more poorly.

Self-appraisal accuracy

Despite the general trend of decreasing self-estimation with decreasing performance, when compared with actual performance most individuals overestimated their abilities resulting in a negative discrepancy (Fig. 3). Thus, self-appraisal was not adjusted to a degree commensurate with actual cognitive impairment. Cognitive performance and self-appraisal accuracy (i.e. the actual performance minus self-appraisal) were correlated ($r = 0.542$, $p < 0.001$). It can be seen from Fig. 3 that, although controls, ALS patients and MCI patients showed the best performance and the smallest discrepancies between self-appraisal and performance, there was no strong association between one particular neurodegenerative diagnosis and self-appraisal accuracy. In order to examine whether additional cognitive variables might account for self-appraisal accuracy beyond performance on the six targeted tasks, we performed partial correlations between each of the variables from the standard cognitive assessment listed in Table 1 and self-appraisal accuracy, controlling for average performance across the six cognitive tasks used for self-appraisal. None of the variables in Table 1 showed a significant correlation with self-appraisal accuracy after accounting for the cognitive scores used for the self-appraisal judgments.

Voxel-based morphometry

Adjusting for the influence of covariates including cognitive performance and diagnosis, self-appraisal discrepancy was positively correlated with tissue content in the right posterior/medial orbitofrontal cortex, with the peak on the medial wall of the frontal lobe in a region often referred to as ventromedial prefrontal cortex (vmPFC; $x, y, z = 8, 18, -14$; Fig. 4; cluster size of 25 voxels at $p < 0.05$ corrected).

Because nearly all values for the discrepancy were negative, larger values (closer to zero) indicate less impairment, so that larger vmPFC volume was associated with more accurate self-appraisal.

Discussion

The chief finding in this study is that accuracy of self-appraisal for cognitive performance is correlated with gray matter content in the right vmPFC. Specifically, reduced vmPFC volume is associated with greater overestimation of cognitive performance. This relationship, which was identified using an objective, neuropsychologically-based assessment of self-appraisal, is independent of cognitive performance scores and diagnosis. The finding adds to a growing body of evidence supporting a role for ventromedial frontal structures in self-appraisal. We propose that the relationship suggests an important role for emotional and/or physiological signals in self-appraisal for cognitive performance.

Several studies in patients with dementia have demonstrated relationships between impaired self-appraisal and right frontal hypometabolism (Reed et al., 1993) (Starkstein et al., 1995; Mendez and Shapira, 2005; Vogel et al., 2005). Recent studies have highlighted in particular links between anosognosia and posterior orbitofrontal regions (Salmon et al., 2006) with the region identified in one study overlapping almost precisely with the location of our finding

(Shibata et al., 2008). All of these prior studies used questionnaires assessing abilities in everyday life and looked at discrepancies between patients' assessments of their abilities and the corresponding assessments of informants. In contrast our study used objective neuropsychological data and evaluated self-appraisal for specific cognitive tasks. Because of the nature of the measurement, our study is closer to classical studies of metacognition (Nelson and Narens, 1994), some of which have used measures similar to ours (Kruger and Dunning, 1999). It is thus notable that one prior study of patients with focal frontal lobe lesions found that impaired self-appraisal, measured using accuracy of feeling-of-knowing judgments (FOK, a commonly used measure of metacognition), was associated with lesions in the right vmPFC (Schnyer et al., 2004). Although the findings in the literature concerning the neuroanatomy of anosognosia provide compelling evidence linking self-appraisal and right hemisphere structures, our study provides only limited additional support for a specific relationship with the right hemisphere. While only the right vmPFC surpassed the statistical threshold in our analysis, examination of the data at a less stringent statistical threshold also suggested a possible relationship for left sided structures. Thus right vs. left hemisphere roles in self-appraisal could not be adequately resolved in our dataset.

The relationship between self-appraisal accuracy and vmPFC has also been highlighted in functional MRI (fMRI) experiments. A study of patients with traumatic brain injury (TBI) who had impaired awareness of their own abilities showed abnormal activation in the vmPFC during a self-evaluation task (Schmitz et al., 2006). Impaired self-awareness in this study also appeared to be more closely associated with right hemisphere injury than left. In a study of patients with MCI, activity in the vmPFC during the same self-evaluation task was correlated with awareness of abilities in daily life (Ries et al., 2007). Although the locus of activation in these studies was 2 to 3 cm anterior to the vmPFC region highlighted in our results, the task used in those studies was different, requiring patients to evaluate the relevance of adjectives to them (e.g. tall, daring, etc.), rather than requiring them to evaluate their cognitive performance. In addition, it should be noted that the region identified in our study is difficult to study with fMRI because of magnetic susceptibility artifacts (Gorno-Tempini et al., 2002). That said, one fMRI study found that activation in a vmPFC region only about 1 cm anterior to the site identified here was correlated with accuracy of FOK judgments (Schnyer et al., 2005). Thus, ample evidence is accumulating to support the association between self-appraisal and the vmPFC.

Our findings also relate to a broader literature linking frontal regions with self-related processing in general. Early studies highlighted medial prefrontal regions anterior and dorsal to the location of our finding (Gusnard et al., 2001), but subsequent studies have implicated a broad network of insular and ventral and medial frontal regions, along with the amygdala and other subcortical structures and retrosplenial cortex, in self-related processing (reviewed in (Schmitz and Johnson, 2007; Seeley and Sturm, 2007)). The vmPFC is one of several regions responsible for tracking the current physiological state of the body (Critchley et al., 2000), and these functions have been linked by some to a construct referred to as the “minimal self,” which is conceptualized as a representation of the moment-to-moment state of the body (James, 1890; Gallagher, 2000; Seeley and Sturm, 2007). Others have construed the ventromedial frontal regions, along with other regions involved in emotional appraisal, as evaluating stimuli relevant for survival, and thus relevant to the self (Schmitz and Johnson, 2007). According to both of these approaches, ventral frontal and subcortical regions are more important for self-related processing “in the moment,” while more introspective judgments about the self, particularly those representing the self longitudinally, are attributed to more dorsomedial frontal and retrosplenial regions (Buckner and Carroll, 2007; Schmitz and Johnson, 2007; Seeley and Sturm, 2007). While our self-appraisal task does not tap strongly into longitudinal representations of the self, it does require some introspection and maintenance of impressions about one's performance beyond the immediate present. Thus, one interpretation of our finding is that, while more dorsal regions may be important for higher level, introspective judgments

about the self, some judgments of this type are also critically dependent on regions responsible for tracking the physiological state of the body, and these physiological signals, or the neural processing that generates them, are used to inform higher level self-appraisal.

In this study, we did not assess patients' broad assessments of their abilities in everyday life, which might be more representative of longitudinal representations of the self; however, in prior studies, we have shown a moderate degree of correlation between this more general type of judgment and the self-appraisal methods used in this study (Williamson et al., 2009). This observation, combined with prior studies in dementia, MCI, and TBI indicating that anosognosia measured using broader assessments of patients' everyday abilities is correlated with pathology (Salmon et al., 2006; Shibata et al., 2008) and physiological activity (Schmitz et al., 2006; Ries et al., 2007) in vmPFC suggests that self-appraisal judgments of the type assessed here may be an important basis for maintenance of one's perception of one's abilities over time.

As for the nature of the link between neural processing in the vmPFC and self-appraisal, we can only speculate. We hypothesize that events signifying poor performance on cognitive testing, such as errors or prolonged searching for responses, generate error signals that are mediated by vmPFC and associated with physiological arousal. This would be generally consistent with the role of medial and orbital frontal structures in marking deviations from expected outcomes (Ridderinkhof et al., 2004; Schultz, 2006). In this case the deviation would be one's own actual vs. expected performance. In this way, the vmPFC could contribute to self-appraisal in a fashion analogous to its contribution to reversal learning, extinction, and similar processes. The degree to which such signals are generated may vary depending on how important the task or the errors are perceived by the individual to be. Some support for this idea comes from studies demonstrating autonomic reactivity in response to one's own errors (Hajcak et al., 2003; Critchley et al., 2005). In one fMRI study, errors on trials resulting in large monetary losses were associated with greater activation in vmPFC compared with errors on trials with small monetary losses (Taylor et al., 2006). Furthermore another study of self-awareness in dementia demonstrated that FTD, which is characterized by very poor insight into one's impairments, causes significant impairment in online monitoring of errors compared with other neurodegenerative dementias (O'Keefe et al., 2007). Future research will be required to further investigate whether there is a specific relationship between error monitoring and self-appraisal accuracy.

Prior studies have suggested that cognitive abilities such as executive function and memory predict self-appraisal accuracy in patients with dementia (Mangone et al., 1991; Lopez et al., 1994; Michon et al., 1994; Migliorelli et al., 1995; Souchay et al., 2002). Similarly, in our study a measure of cognitive performance comprised of tasks sensitive to executive function, working memory and episodic memory was correlated with self-appraisal accuracy. By factoring these cognitive abilities out of our VBM analysis, we identified brain regions that contribute unique variance in self-appraisal accuracy beyond these cognitive abilities. We would suggest, as others have, that self-appraisal accuracy is likely to be the product of multiple processes (McGlynn and Schacter, 1989; Agnew and Morris, 1998; Morris and Hannesdottir, 2004), including cognitive factors tracked by traditional tests, and physiological and emotional factors highlighted above that are more difficult to quantify. Future studies should attempt to identify the relative contributions of these different factors using them as predictors of an independent measure of self-appraisal in multivariate models.

Several limitations to the study should be noted. First, the low number of normal controls leaves open the possibility that the relationship between vmPFC and self-appraisal may be seen in neurodegenerative disease, but not normal controls. In particular, cognitive impairment resulted in the majority of participants overestimating their performance. In normal individuals,

self-appraisal may be more likely to include underestimates, which may have a different anatomical and physiological basis. More work in normal individuals and larger patient groups examining the neuroanatomical correlates of self-appraisal will be helpful in this regard. In addition, the task described here is somewhat abstract, and factors other than self-appraisal ability, such as motivation or unmeasured cognitive functions, may have contributed to the variability we examined. Our findings that participants' verbal self-appraisals corresponded very well with their percentile ratings, that patients with more severe impairment tended to give lower estimates of their performance, and that there were no correlations between self-appraisal accuracy and cognitive functions not targeted by our analysis, such as language, verbal memory or visuospatial abilities, suggest that patients understood and performed the task as intended. It is important that future work continue to take these factors and other relevant cognitive and emotional functions into account. In addition, more control tasks, such as rating of non-cognitive abilities (Banks and Weintraub, 2008), could help to ensure that tasks such as this one truly assess the intended functions.

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Fig. 1.
Bell curve picture used to help patients estimate their performance.

Fig. 2. Histogram of self-appraisal ratings in each of the major diagnostic groups and across the entire group of participants.

Fig. 3. Cognitive performance, in terms of percentile vs. discrepancy between cognitive performance and self-appraisal.

Fig. 4. Regions where gray matter content is correlated with self-appraisal accuracy (independent of actual performance).

Table 1

Demographics and neuropsychological test results for cognitively normal (CN) participants and patients in the AD and FTD diagnostic spectra.^a

	CN (N=4)	AD (N=13)	FTD (N=22)
Age	53.3 (22.5)	61.4 (8.5)	66 (6.3)
Males/Females	3/1	11/2	16/6
Education (years)	17.5 (0.7)	16.8 (3.9)	15.8 (3.2)
MMSE (max=30)	28.3 (0.9)	25.1 (4.3)	23.9 (5.2)
CVLT-MS (max=9)			
Trial 4	7.5 (1.7)	5.1 (2.7)	4.7 (2.6)
19' Free Recall	7.5 (0.6)	2.6 (2.5)	3.1 (2.9)
Abbreviated BNT (max=15)	13.8 (1.5)	12.2 (3.4)	10 (4.4)
Syntax Comprehension (max=5)	4.5 (0.6)	3.9 (1.6)	4.1 (1.2)
Modified Rey–Osterrieth Copy (max = 17)	15 (0.8)	13.2 (4.5)	14.3 (2.5)
Calculations (max=5)	4.5 (0.6)	3.9 (1.1)	4 (1.4)
GDS (max=30)	6.5 (6.2)	8.5 (8.3)	7.5 (4.3)
WMS Digit Span Percentile	75.5	38	30
WMS Spatial Span Percentile	79	33.7	35.1
WMS Visual Delay Percentile	62	26.4	20.5
DKEFS Verbal Fluency Percentile	65.7	42.9	21.4
DKEFS CA Trails Percentile	46.5	25.5	30.3
DKEFS Design Fluency Percentile	70.3	37.5	35.9
Average Performance Percentile (6 self-appraisal tasks)	64.8	33.6	27.3

^a CN includes Controls and ALS; FTD includes FTD, SD, PNFA and CBD; AD includes AD and MCI.