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THE ROLE OF VENTRAL MEDIAL PREFRONTAL CORTEX IN SOCIAL DECISIONS: CONVERGING EVIDENCE FROM fMRI AND FRONTOTEMPORAL LOBAR DEGENERATION

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Abstract

The ventral medial prefrontal cortex (vmPFC) has been implicated in social and affectively influenced decision-making. Disease in this region may have clinical consequences for social judgments in patients with frontotemporal lobar degeneration (FTLD). To test this hypothesis, regional cortical activation was monitored with fMRI while healthy adults judged the acceptability of brief social scenarios such as cutting into a movie ticket line or going through a red light at 2 AM. The scenarios described: (i) a socially neutral condition, (ii) a variant of each scenario containing a negatively-valenced feature, and (iii) a variant containing a positively-valenced feature. Results revealed that healthy adults activated vmPFC during judgments of negatively-valenced scenarios relative to positive scenarios and neutral scenarios. In a comparative behavioral study, the same social decision-making paradigm was administered to patients with a social disorder due to FTLD. Patients differed significantly from healthy controls, specifically showing less sensitivity to negatively-valenced features. Comparative anatomical analysis revealed considerable overlap of vmPFC activation in healthy adults and vmPFC cortical atrophy in FTLD patients. These converging results support the role of vmPFC in social decision-making where potentially negative consequences must be considered.

Keywords

ventromedial prefrontal cortex; social decision-making; frontotemporal dementia

INTRODUCTION

Why don't we cut into the ticket line at a movie theater when our movie is about to start? Why do we know that it is foolhardy to go through a red light at 2AM when there is a policeman on the corner, but more acceptable to go through the same red light at 2AM on the way to an emergency room with a sick child in the car? Humans are social beings who constantly make

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decisions about activities that involve interactions with others, and these decisions are modulated by specific intentions, circumstances, and consequences. In this study, we examined the neural basis for social decision-making with fMRI in healthy adults, and applied these observations to examine the disorder of social cognition that occurs in patients with frontotemporal lobar degeneration (FTLD).

Neurobehavioral studies have identified prominent and disabling social cognitive impairments in patients with frontal and temporal pathophysiology, yet common nomenclature and classification systems rarely identify these characteristics with precision. Furthermore, few models address the synergistic effects of cognitive, social and emotional deficits. For example, patients demonstrate impairments in organizing, tracking, and managing social information as well as their own emotional reactions within changing social contexts that can entail rewards and losses of various kinds. These impairments are expressions of executive dysfunction, emotional dysregulation, and how social outcomes are valued and integrated for decision-making and behavior. Eslinger et al. (1995, 1996) proposed a heuristic taxonomy of *social executors* to advance identification of these converging deficits and the alterations of meaningfulness in social contexts. Social executors refer to shared mechanisms subserving social cognition and executive functions, such as social self-regulation, social self-awareness, and social sensitivity. In similar fashion, neuroeconomic models have recently attempted to incorporate cognitive and emotional variables in decision-making models that are driven by valuation of gains, losses, risks and uncertainties (Fellows, 2007; Glimcher & Rustichini, 2004; Loewenstein et al., 2007; Montague, 2007). Several critical components are thought to contribute to such decision-making in social spheres. A semantic representation of the social context must be understood. A decision-making component involves top-down guidance in the development of a strategy that supports attaining a goal. The value associated with a decision also must be grasped. In social contexts, this value component often depends on an appreciation of the consequences of a decision that entail potential gains vs. losses for self and others, the role of agency, moral concerns, and social emotions. Finally, the consequences of decision-making strategies and their social value must be integrated in a manner that allows comparisons with the social contexts in the environment.

Recent work has begun to map out a large-scale neural network that appears to support the complex set of elements contributing to social decision-making. Decision-making strategies involve dorsolateral prefrontal cortex (dlPFC) and dorsal portions of the anterior cingulate (dACC). An elegant series of fMRI studies has demonstrated the role of dlPFC in the top-down guidance of responses to Stroop-like tasks, theory of mind/intentionality, and social-emotional decisions alike, and has implicated dACC in monitoring conflict and executing an efficient response that discriminates between two competing alternatives (Botvinick, 2007; Botvinick et al., 2001; Carter et al., 1998; Fellows & Farah, 2005; Ochsner & Gross, 2005; Weissman et al., 2008). The value of a decision and its consequences appear to depend in part on ventral-medial prefrontal cortex (vmPFC) (Knutson et al., 2007; Knutson et al., 2005; Taylor et al., 2006; Walton et al., 2004; Wheeler & Fellows, 2008). Finally, a component integrating perception of the social actions, cues and contexts with values and decisions appears to involve temporo-parietal cortex and adjacent superior temporal sulcus (TPC) (Decety & Lamm, 2007; Frith & Frith, 2006; Saxe & Kanwisher, 2003; Saxe & Wexler, 2005; Sugrue et al., 2004). This large-scale neural network is likely to be supported by known neuroanatomic projections between these brain regions (Mesulam, 2000; Price, 2006).

In the present study, we focus on the contribution of vmPFC to interpreting the value component associated with social decision-making, using converging methods from fMRI studies of healthy adults and patients with vmPFC disease due to FTLD. Some work with subhuman primates and fMRI studies of humans suggests that vmPFC contributes the representation of the values associated with the possible outcomes of a social decision (Elliott

et al., 2003; Harris et al., 2007; Knutson et al., 2007; Knutson et al., 2005; Tom et al., 2007). Evidence consistent with the importance of vmPFC comes from studies of patients with structural insult to the ventral frontal lobe (Adolphs, 2003; Cools et al., 2004; Hornak et al., 2003; Ochsner & Gross, 2005; Rolls et al., 1994). Careful observations have distinguished between decision-making following vmPFC injury compared to disease affecting dlPFC (Fellows & Farah, 2005). Patients with structural disease to ventral regions of the frontal lobe have difficulty on experimental neuropsychological measures that require evaluating positive and negative feedback for the purpose of optimizing future decisions in social contexts (Bechara et al., 2000; Bechara & Van Der Linden, 2005; Britton et al., 2006; Hynes et al., 2006). Other studies emphasize that vmPFC plays a particularly important role in perceiving and monitoring losses, and that these are distinct from the neural substrate important for appreciating the value of gains (Liu et al., 2007; Nieuwenhuis et al., 2007; O'Doherty et al., 2006; Yacubian et al., 2006). Difficulty incorporating negative feedback into social decision-making receives support from studies of patients with vmPFC lesions (Clark et al., 2008; Floden et al., 2008; Wheeler & Fellows, 2008).

Disruption of social decision-making has important consequences in neurodegenerative disease states. Even though intellectual functioning in the form of general knowledge, perception, memory and language may be largely intact, neurological patients with diseases that interfere with social cognition are unemployed and socially isolated. FTLN is a neurodegenerative condition that results in an altered personality and compromises social functioning (Gregory & Hodges, 1993; Miller et al., 1997; Miller et al., 2003; Mychack et al., 2001; Rankin et al., 2005). Emotional processing can be disrupted, and is particularly notable for difficulty recognizing negative emotions (Keane et al., 2002; Lavenex & Pasquier, 2005; Lough et al., 2006; Mendez et al., 2006; Rosen et al., 2006). Clinically, some patients with FTLN can be quite disinhibited, make socially inappropriate comments, and engage in socially unacceptable behaviors (Bozeat et al., 2000; Massimo et al., 2009; Miller et al., 1997; Mourik et al., 2004). Caregivers of FTLN patients consider these to be the most disruptive and difficult behaviors to manage (Massimo et al., 2009). Furthermore, patients often display little insight into the disruptions caused by their behavior, and hence fail to alter their behavior despite significant social and legal consequences.

The basis for the social deficit in patients with FTLN has been experimentally studied with very limited measures to date. One method for examining social functioning involves measures of perspective-taking or Theory of Mind (ToM). ToM tests the interpretation of brief discourses where the patient must place himself/herself in the perspective of an agent in the discourse (first-order ToM), and then switch to adopt the perspective of a viewer of the agent (second-order ToM). Performance is impaired in FTLN, even though knowledge of social rules themselves may be relatively preserved (Gregory et al., 2002; Kipps et al., 2009; Torralva et al., 2007). Since the deficit is most prominent for second-order ToM, this suggests difficulty inhibiting the perspective of the agent while switching to the perspective of the agent's viewer.

Studies using the Iowa Gambling Task (IGT) have shown that FTLN with social cognitive impairment are impaired at interpreting the feedback resulting from a decision to adjust future decisions. In this task, an individual selects a card from one of four available decks. The cards in two of the decks are associated with modest gains and modest losses, and are designed to yield a net positive outcome; the cards in the two remaining decks are associated with larger gains and larger losses, but selections from these decks are designed to lead ultimately to a net loss. Patients with FTLN are impaired in their performance on this measure (Torralva et al., 2007). Thus, they select cards from the decks with large gains and even larger losses. It is unclear whether the deficit here is due to difficulty inhibiting attraction to the large reward, or to a deficit interpreting the consequences of the large loss, or even to impoverished working memory that limits the ability to keep track of prior choices.

In an earlier study, we examined the contribution of ToM and control over perspective-taking to social decision-making using standard cartoon vignettes presenting social dilemmas (Guilford's Cartoon Predictions test) (Eslinger et al., 2007). Patients selected the most appropriate of three possible outcomes to a social dilemma such as finding a fly in soup in a restaurant. FTLD patients with a social disorder were disproportionately impaired in comparison to patients with semantic dementia and progressive non-fluent aphasia as well as age-matched control participants. This impairment was significantly correlated with difficulty on measures of ToM, cognitive flexibility, and empathy ratings. Moreover, a regression analysis showed that the strongest predictor of social decision-making was the measure of cognitive flexibility. By comparison, others have not found a relationship between executive functioning and ToM impairments (Gregory et al., 2002; Lough et al., 2001; 2006), possibly due to differences in the battery of measures used to ascertain executive functioning. Disrupted social behavior in FTLD thus may be due in part to poor executive resources such as impaired cognitive flexibility that limit the perspective-taking needed to participate in social interactions, although these observations do not clarify the relative roles of difficulty controlling attraction to a prominent feature of the environment and/or a deficit interpreting the negative consequences and potential losses associated with a decision.

Cortical atrophy in patients with a social disorder due to FTLD is typically found in frontal and anterior temporal regions, with prominent disease in the right medial frontal lobe (Miller et al., 1991; 1993; Rosen et al., 2002). Direct correlations of personality and behavioral changes with cortical atrophy have been rare (Massimo et al., 2009; Rankin et al., 2006; Rosen et al., 2005; 2006; Williams et al., 2005). In a direct correlation of social decision-making with cortical atrophy in FTLD, poor judgments of social dilemmas were correlated with atrophy in vmPFC as well as mid-lateral temporal cortex in the right hemisphere (Eslinger et al., 2007). Thus, vmPFC appears to be a critical hub in the networks related to inhibitory control and interpreting the consequences of a decision for potential gains and losses, and particularly the incorporation of negative feedback into social decision-making

The purpose of this experiment was to investigate the role of vmPFC in interpreting the value of contextual features of social scenarios. We achieved this by developing a novel measure that manipulated the context of familiar social situations, such as accidentally denting a car that is brand new vs. an old clunker, and receiving back too much change at a store that is overpriced vs. a charitable thrift shop. Common contingencies were created to be positive and result in a perceived social gain versus negative and result in a perceived social loss. We presented these scenarios to healthy controls in order to monitor vmPFC activation with BOLD fMRI while subjects judged the acceptability of positively- and negatively-valenced scenarios. In a parallel behavioral study, we administered the same scenarios to patients with FTLD in order to measure their pattern of decision-making and judgment of acceptable actions. In addition, we tested the hypothesis that anatomical areas of fMRI activation in the healthy adults would overlap with cerebral atrophy detected in the FTLD patients with social disorder. Constrained by the fMRI activation patterns of healthy adults, we sought to relate the decision-making abilities of the FTLD sample directly to their cortical atrophy. Given the clinical intransigence of FTLD patients in social situations and their particular insensitivity to negative emotions, we predicted that these findings would demonstrate a critical role for vmPFC in the interpretation of negatively-valenced feedback during social decision-making.

METHODS

Subjects

Participants in the fMRI study included 18 young, healthy adults (mean $\pm$ SD age = 25 ± 4.2 ; mean $\pm$ SD education = 16 ± 1.3).

In the behavioral study, 19 patients were diagnosed with behavior-variant frontotemporal dementia (bvFTD), a form of FTLT with a prominent disorder of social and executive functioning, according to a modification of published criteria (McKhann G et al., 2001; Neary D et al., 1998; The Lund and Manchester G, 1994). Other causes of dementia were excluded by clinical exam, blood and brain imaging tests. Two independent examiners established consensus diagnoses for members of the FTLT group. Clinical participants were alert and cooperative. Healthy senior participants (n = 19) served as controls for the FTLT group, and were matched as closely as possible for age and education (Table 1). The FTLT sample was slightly younger than controls ($p < .03$) and had lower Mini Mental State Exam scores ($p < .007$), but did not differ in educational level. Informed consent was provided by all participants and caregivers of FTLT patients according to a protocol approved by the Institutional Review Board at the University of Pennsylvania.

Materials and Procedure

Participants judged 20 social situations and scofflaws (i.e., minor infractions of the law) such as “Rolling through a red light at 2am” and “Cutting into the ticket line at a movie theater”, on a 5-point acceptability scale (1 defined as “Definitely No” through 5 defined as “Definitely Yes”). These core scenarios were then presented for judgment when biased by negatively-valenced contingencies (e.g., “Rolling through a red light at 2am *when there is a police car at the intersection*”) and positively-biased contingencies (e.g., “Rolling through a red light at 2am *when rushing a sick child to the emergency room*”). In developing this task, ratings of social familiarity were first judged by a group of 15 adults and the remaining items then biased in a positive or negative manner. These biasing features were judged by another set of 15 adults to be positive or negative in their social value based upon their social-acceptability and – unacceptability. Then the wording was adjusted so that the positive features differed from baseline to roughly the same extent as the negative features, according to judgments of a different group of 15 adults. During the experiment, participants rated these biased scenarios on the same 5-point acceptability scale as the core social situations. These scenarios were presented under two instruction conditions. The conditions included rule-based instructions (i.e., “Should everyone do this all of the time?”) and similarity-based instructions (i.e., “Is this generally ok?”). This manipulation was administered in order to bring out differences that may be attributable to insensitivity to perceived legal and social rules. Therefore, controls rendered judgments about all of the scenarios under the 2 instructional conditions while in the scanner, with the order of instructional condition randomly determined in order to minimize judgment contamination as a result of fixed administration order. In behavioral testing, FTLT patients similarly rendered judgments about all of the scenarios under the 2 instructional conditions. This occurred during two test sessions, typically separated by one month. This was necessary in order to minimize fatigue effects. As with the controls, the order of instructional condition was randomly determined in order to minimize judgment contamination as a result of a fixed administration order. Subsequently, as noted below, we found little evidence that this manipulation resulted in any significant difference in patient performance or imaging results, so the results were averaged across these two conditions for the positively-biased and negatively-biased scenarios.

For statistical analyses of the behavioral data, the core scenario ratings were used as each participant’s baseline judgment, and difference scores then were computed for the positively-biased and negatively-biased scenarios. Multivariate analysis of variance was employed to analyze these data, and post-hoc comparisons were performed with t-tests.

Imaging Methods

Functional imaging of young adults—The experiment was carried out at 3T on a Siemens Trio scanner (Siemens Medical Systems, Erlangen, Germany). Each imaging study began with

a 3D MPRAGE protocol (TR=1620 msec, TE=30 msec, 192×256 matrix), acquiring 1 mm isotropic voxels to determine regional anatomy. BOLD fMRI images were then acquired to detect alterations in blood oxygenation accompanying increased mental activity. All images were acquired with fat saturation, 3 mm isotropic voxels, flip angle of 15° , TR=3000 msec, TE_{eff}= 30 msec, and a 64×64 matrix, acquiring 45 contiguous axial slices through the entire brain every 3 sec.

Individual subject data were then prepared for analysis using SPM2, developed by the Wellcome Trust Centre for Neuroimaging (<http://www.fil.ion.ucl.ac.uk/spm/software/spm2>). The images in each subject's time series were registered to the initial image in the series. The images were then aligned to a standard coordinate system using the MNI152 average brain template. The data were spatially smoothed with an 8 mm FWHM isotropic Gaussian kernel to facilitate statistical analyses and to account for local variations in sulcal anatomy across participants. Low-pass temporal filtering was implemented, and we controlled for auto-correlation with a first-order auto-regressive method.

A random-effects model was used to analyze neural activation for each type of social scenario. Event onset times were convolved with a canonical hemodynamic response function to estimate their potential contribution to the fMRI data. We assessed the specificity of the consequences and risks of these scenarios using closely matched contrasts. Thus, we contrasted the main effects associated with positively- and negatively-valenced scenarios with each other. These analyses were performed in each individual, and these contrasts were then entered into a second-level analysis to assess group effects. We used a statistical threshold of $p < .01$ to generate the images. Subsequently, we used a cluster extent threshold of >20 voxels and a z-score criterion, such that clusters were considered significant if their peak voxel exceeded a z-score of 3.09.

Regions of interest (ROIs) were identified using the vmPFC cluster identified in the Negative > Positive contrasts summarized in Table 2. They were extracted using the MarsBaR toolbox in SPM2. This averages the time series across the cluster, and uses information about conditions in order to extract a parameter estimate for each condition. After ROIs were determined, the percent signal change was extracted separately from the Positive and Negative main effects.

Structural imaging of FTLN patients—High resolution structural MRI scans were available for a subset of 8 FTLN patients to establish cortical atrophy using a modulated version of voxel-based morphometry (VBM). This subsample did not differ from the remaining FTLN sample in any demographic variables. Images were acquired by a SIEMENS Trio 3T MRI scanner in all 8 patients. First, a novel symmetric diffeomorphism procedure was used to normalize high-resolution T1-weighted MR images for shape and intensity (Avants & Gee, 2004) using a local template consisting of 8 healthy seniors and 8 patients. We used high dimensional normalization and template-based cortical segmentation to quantify gray matter changes. A spatially dense mapping, or correspondence, between the template and a population of experimental images was first computed. The brain image was modeled as a dense continuum, sampled at individual voxels, that was accompanied by a transformation model that preserved neighborhood relationships among voxels even under very large deformations. This strategy enabled a high resolution, smoothly flowing deformation of these voxels into the corresponding voxels of the template and was able to capture both large-scale atrophy and more subtle, focal disease effects. Moreover, this mapping process was fully unbiased. Unlike standard methods that map a brain to a template unidirectionally, the mapping we generated was based on a bidirectional algorithm that builds unbiased maps from the set of experimental brains into a template and, simultaneously, from the template into the population of experimental brains. The symmetry achieved in this optimization significantly improves normalization compared to unidirectional template mapping (Beg & Khan, 2007). These types

of high-dimensional, unbiased maps, called symmetric diffeomorphisms (Avants & Gee, 2004; Avants et al., 2008) also benefited normalization accuracy because of the reduced variance in the probable location of a structure following deformation. With this approach, we had the advantage of being able to perform statistical contrasts between groups at a higher spatial resolution, and with greater statistical confidence, than was previously achieved with parametric or elastic methods. Parametric and elastic methods are limited because they cannot guarantee that neighboring voxels are maintained, while at the same time capturing highly deforming transformations that align both the large-scale features as well as the local topography of the brain. The reduced variance in the estimated location of the neuroanatomy achieved by a symmetric diffeomorphic approach also reduced the amount of smoothing required in the final statistical treatments of these data. The statistical superiority of symmetric diffeomorphisms, relative to available parametric and elastic methods, has been established experimentally in the propagation of neuroanatomic labels across a population of elderly and neurodegenerative brains (Avants et al., 2008) and in localizing activation in small brain structures such as the hippocampus (Miller et al., 2005). The resulting images were then segmented using FAST (Zhang et al., 2000) which labeled the brain volumes into gray matter, white matter, CSF, and other with inhomogeneity correction. Gray matter images were then multiplied by their corresponding jacobian registrations to template space, which resulted in normalized, spatially varying estimates of gray matter volume for each subject (Avants & Gee, 2004). Gray matter images were subsampled to 2mm x 2mm voxel sizes, and then warped into MNI space using the jacobians of the MNI space-warped template. Images were smoothed with a 4mm FWHM Gaussian filter, and contrasted with a cohort of 8 age-matched controls using an independent samples t-test in SPM5, constrained by a mask of the fMRI activation clusters identified in the healthy adult sample while undertaking decisions about acceptable actions in the negatively-valenced social scenarios. The analysis included all voxels containing any gray matter in the volume, thus resulting in a true whole brain analysis. Implicit masking (i.e., use of a dummy value to exclude voxels with a value of 0) was used to ignore zeros, and global calculation was omitted. We set a statistical threshold for identifying significant gray matter atrophy at the $p < 0.05$ FDR level with a cluster extent of 20 adjacent voxels.

RESULTS

Decision-Making in Healthy Adults

Behavioral results—Figure 1 shows that young controls rated the actions in the positive feature protocols as more acceptable, and the actions in negative feature protocols as less acceptable, during the functional neuroimaging protocol. Statistical analysis of acceptability judgments for the positively-valenced scenarios and the negatively-valenced scenarios, relative to acceptability judgments for the baseline scenarios, revealed a significant difference [$t = 11.23$, $p < 0.0001$]. There was no difference between judgments made under rule-based conditions or similarity-based conditions, and judgments of positively- and negatively-valenced scenarios did not interact with the rule-based or similarity-based instruction conditions.

Imaging results—Judgments of the negative social scenarios, relative to the positive social scenarios, revealed significant activation in vmPFC and right IPC (Figure 2). The location of activated clusters and the coordinates of peak voxels in these clusters are summarized in Table 2. Figure 2 also illustrates the percent signal change during the negatively-biased scenarios and the positively-based scenarios at the peak voxel in the activated vmPFC cluster. This distribution of activation was confirmed during the rule-based instruction condition and during the similarity-based instruction condition (see Table 2) and did not differ when rule-based vs. similarity-based conditions were specifically contrasted. Significant vmPFC activation was not detected for the positively-valenced scenarios relative to the negatively-valenced scenarios,

although this contrast revealed significantly greater activation in left IPC and left superior temporal cortex (see Table 2)

Judgments in FTLN Patients and Relationships with Cortical Atrophy

Neutral Scenarios—Mean acceptability ratings on the unbiased scenarios did not differ between the FTLN patients and the age-matched controls, nor for rule or similarity conditions, and there was no interaction effect.

Positive and Negative Bias—Negatively-biased scenarios were judged to be much more acceptable by FTLN patients than age-matched controls, although positively-biased scenarios were rated equally acceptable by FTLN patients and older controls (Figure 1). We evaluated judgments statistically with a MANOVA, using a group (2 – controls, FTLN patients) X scenario (2 – positive, negative) X instruction condition (2 – rule, similarity) design. Analysis revealed a significant main effect for group [$F = 5.717$; $df\ 1,34$; $p=.022$], a main effect for judgments of positive vs. negative bias scenarios [$F = 159.724$; $df\ 1, 34$; $p<.0001$], and a group X scenario interaction [$F = 5.044$; $df\ 1,34$; $p=.031$]. Post-hoc tests confirmed that the FTLN patients and controls differed in their judgments of the negatively biased scenarios ($t = 3.423$, $p<.002$), with the FTLN patients showing less of a change from their neutral scenario ratings and hence less sensitivity to negative social biases. There were no significant group differences for the positive bias contingencies. This pattern obtained under both rule and similarity instruction conditions as well. Furthermore, we could find no correlations between measures of disease severity on the MMSE and judgment ratings. Hence, the specific dissociation of less sensitivity to negatively valenced social scenarios was not related to severity of cognitive decline.

Cortical atrophy in FTLN patients—The overlap between fMRI activations in healthy adults judging negatively-biased scenarios and the areas of cortical atrophy in FTLN patients is illustrated in Figure 3. A large cluster ($k = 148$) was detected in the vmPFC region (peak coordinate 2, 48, -10; $z\ score = 3.69$, $p <.0001$).

DISCUSSION

Converging analysis of functional brain activation patterns in healthy adults and anatomical changes in FTLN patients with prominent social cognitive deficits supports an important role for the vmPFC in mechanisms of social decision-making, particularly when potentially negative consequences must be considered. The fMRI studies in healthy adults showed significant activations in vmPFC during their judgments of negatively-valenced social scenarios relative to positively-valenced social scenarios. Patients with FTLN and social disorder were specifically impaired at judging the acceptability of actions in these negatively-valenced social scenarios, as they did not differ from controls in their judgments of positively-valenced scenarios. Furthermore, when constrained by a mask of the fMRI activations of healthy adults during negatively-valenced judgments, FTLN patients showed significant cortical atrophy in the vmPFC that overlapped with the fMRI activations. These findings provide converging support for the claim that vmPFC contributes to social judgments involving negatively-biased scenarios. Progressive damage to this region, therefore, may be implicated as an important substrate for the deficits underlying disordered social comportment in FTLN such as disinhibition and difficulty interpreting potential risks associated with social interactions.

The vmPFC region is thought to be particularly vulnerable in FTLN (Seeley et al., 2008). Prior work has related disease in this region to impulsivity and poor inhibitory control as well as to limited cognitive and response inhibition (Massimo et al., 2009; Rosen et al., 2005). There has

been considerable debate about the role of this region in the problematic social disorder of patients with FTLD. Some work emphasizes that vmPFC plays a critical role in processing the interpretation of any affective value associated with the possible outcome of a social decision (Elliott et al., 2003; Knutson et al., 2007; Knutson et al., 2005; Tom et al., 2007). Patients with vmPFC disease thus may have difficulty evaluating feedback during decision-making that incorporates value (Adolphs, 2003; Bechara et al., 2000; Bechara & Van Der Linden, 2005; Hornak et al., 2003; Ochsner & Gross, 2005; Rolls et al., 1994). This may also entail poor contingency-based learning and reversal learning that has been shown to be impaired with orbital frontal lesions (Rolls et al., 1994; Hornak et al., 2003; Floden et al., 2008). Other studies emphasize a more selective role for vmPFC. These data underscore a particularly important role for vmPFC in perceiving and monitoring risks and potentially associated losses (Liu et al., 2007; Nieuwenhuis et al., 2007; O'Doherty et al., 2006; Yacubian et al., 2006). Difficulty incorporating negative feedback into social decision-making receives support from studies of patients with vmPFC lesions (Clark et al., 2008; Fellows & Farah, 2005; Floden et al., 2008; Wheeler & Fellows, 2008). Our observations are more consistent with this latter hypothesis. From this perspective, FTLD patients may have bizarre, disinhibited behavior in part because they are relatively insensitive to the negative feedback and risky consequences associated with displaying disruptive behavior. Furthermore, we do not think that vmPFC activation is necessarily related to decision-making independent of value because an identical decision-making component was also present in the baseline condition.

The results fit well with the known anatomic connectivity of vmPFC in a network of temporal and frontal regions subserving social judgments and decision-making. Reciprocal projections via the uncinate fasciculus link vmPFC with the amygdala and the temporal polar region. These areas are important for processing negatively-biased emotions related to fear, anger and disgust (Adolphs & Spezio, 2006; Phelps & LeDoux, 2005), and the modulation of psychosomatic and emotion-related responses through paralimbic interactions appears to be disrupted in FTLD (Kipps et al., 2009). Our study may not have implicated these regions because we did not assess negative emotions per se, but evaluated judgments of social scenarios with a risk of evoking negative social consequences. Nevertheless, anterior temporal regions are known to be atrophic in some FTLD patients, including the patients participating in this study, and the right temporal variant of FTLD is associated with a disruption of social behavior (Bozeat et al., 2000; Kipps et al., 2009; Liu et al., 2004; Rankin et al., 2003; Snowden et al., 2001; Zahn et al., 2009).

vmPFC is also linked to social perception and integration regions of the superior temporal sulcus and temporo-parietal junction via the superior frontal-occipital fasciculus. We found that right IPC is activated during judgments of negative scenarios in young adults. We also observed IPC and posterior-superior temporal activation in the left hemisphere during the contrast of fMRI activations associated with judgments involving positive scenarios compared to negative scenarios. In the context of neuroeconomic models of decision-making and game theoretic approaches to social decisions, vmPFC is thought to play a crucial role in the continual accounting of "value", an affect-related component that modulates the probabilities associated with decisions and their potential outcomes, while IPC plays a role in integrating multiple sources of information for the purpose of contextualizing and scene-setting (Decety & Lamm, 2007; Moll et al., 2003; Saxe, 2006; Saxe & Kanwisher, 2003). We are reluctant to implicate IPC directly in the value component of judgments of social scenarios since IPC was not significantly atrophied in the FTLD patients we examined. Our fMRI observations thus implicate IPC and the temporal-parietal junction in judgments of social scenarios, confirming prior work, and the basis for the lateralized involvement depending on the negative or positive polarity of the social scenario should be pursued in future work.

vmPFC is also linked to a decision-making network involving dlPFC and dACC, areas with which it is reciprocally interconnected. This is well-studied in Stroop-like cognitive tasks and

other cognitive measures involving decision-making (Botvinick et al., 2001; Carter et al., 2000; Carter & van Veen, 2007; MacDonald et al., 2000), and the role of strategic decision-making in social disorders is beginning to be pursued (Fletcher, 1995; Massimo et al., 2009; Moll et al., 2003; Weissman et al., 2008). dlPFC appears to be important in probability assessments during top-down decision-making that contribute to planning, organizing, and regulating behavior, and the precise region implicated within dlPFC appears to depend in part on the complexity of the task (Badre et al., 2005; Badre & Wagner, 2004). Reciprocal projections via the cingulum fasciculus also relate vmPFC to dACC, an area important for selective attention, initiation and regulation of response to action. Grabenhorst et al. (2008) showed dissociations between affective value of stimuli (vmPFC and pregenual cingulate activations) and binary decision-making independent of affective value (medial PFC and dACC). Additional work is needed to determine whether specific aspects of the decision-making process are elicited by social decisions compared to cognitive decisions. For example, brain regions may be recruited by FTLN patients during performance of this task that differ from the recruitment pattern seen in controls, and this may compensate for FTLN patients' orbital frontal atrophy. In addition, given the limited size of the FTLN sample for anatomical studies, confirmatory data analysis are needed.

In summary, vmPFC activation appears to play a crucial role in evaluating the negative consequences of social decision-making, and progressive disease in this area contributes to the disruptive social behavior of patients with FTLN. The direct contrast with positively-biased social scenarios in the fMRI study and the patient study emphasize that specific role of vmPFC in evaluations of the negative consequences of risky behavior. This conclusion is based on converging observations from fMRI studies of healthy adults and anatomic studies of patients with FTLN. While we do not think that vmPFC activation is related to decision-making independent of value because an identical decision-making component was also present in the baseline and positively-biased conditions, additional work is needed to examine these processes in a manner that is less confounded by task-related factors such as explicit decisions. It would also be useful in future work to assess subgroups of FTLN patients with a social disorder due to disease selectively affecting frontal and temporal regions in order to examine specific components of this social process. Findings support the conclusion that the vmPFC is likely to be important in how negative contingencies are considered and valued in decision-making, and thus how potential risks are incorporated into the regulation of adaptive behavior. Findings from studies with converging evidence such as ours can begin to elucidate mechanisms that comprise an important dimension of social executive function and apply this to patients with FTLN who appear to be particularly vulnerable to neurodegenerative changes in vmPFC.

Research Highlights

The purpose of this experiment was to investigate the role of ventral medial prefrontal cortex (vmPFC) in interpreting the value of contextual features of social scenarios.

We tested the hypothesis that anatomical areas of fMRI activation in vmPFC of healthy adults would overlap with cerebral atrophy detected in the FTLN patients with social disorder.

Comparative anatomical analysis revealed considerable overlap of vmPFC activation in healthy adults and vmPFC cortical atrophy in FTLN patients.

The vmPFC activation appears to play a crucial role in evaluating the negative consequences of social decision-making, and progressive disease in this area contributes to the disruptive social behavior of patients with FTLN.

These converging results support the role of vmPFC in social decision-making where potentially negative consequences must be considered.

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FIGURE 1.
MEAN ($\pm$ SEM) PROFILE OF DECISION-MAKING BY HEALTHY YOUNG ADULTS DURING THE fMRI EXPERIMENT AND BY FTLD PATIENTS AND AGE-MATCHED OLDER CONTROLS IN THE BEHAVIORAL EXPERIMENT¹

NOTE

1. Graphed scores are differences for judgments of positively- and negatively-valenced scenarios relative to judgments of baseline scenarios in each individual. All judgments differ significantly from baseline except for FTLD patients' judgments of scenarios with a negative social value. FTLD patients differed significantly from controls' judgments only for negatively-biased scenarios. See text for details.

FIGURE 2.
fMRI ACTIVATION FOR JUDGMENTS OF NEGATIVELY-VALENCED SCENARIOS
RELATIVE TO POSITIVELY-VALENCED SCENARIOS

FIGURE 3. ANATOMICAL OVERLAP OF CORTICAL ATROPHY IN FTLD PATIENTS WITH SOCIAL DISORDER (SHOWN IN BLUE) WITH fMRI ACTIVATIONS IN HEALTHY ADULTS UNDERTAKING JUDGMENTS OF NEGATIVE SOCIAL SCENARIOS (SHOWN IN ORANGE).

TABLE 1

MEAN ($\pm$ S.D.) CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF PATIENTS WITH FRONTOTEMPORAL LOBAR DEGENERATION

	FRONTOTEMPORAL LOBAR DEGENERATION	HEALTHY SENIORS
AGE (yrs)	62.38 $\pm$ 12.30	72.55 $\pm$ 6.85
GENDER	6F 13M	11F 8M
EDUCATION (yrs)	14.00 $\pm$ 2.80	16.48 $\pm$ 2.06
DISEASE DURATION (mos)	57.23 $\pm$ 26.90	NA
MMSE (max=30)	25.71 $\pm$ 6.38	29.00 $\pm$ 0.93

TABLE 2

fMRI CORTICAL ACTIVATION IN HEALTHY ADULTS DURING ACCEPTABILITY JUDGMENTS OF SOCIAL SCENARIOS

Cluster Locus (Brodmann Area)	Coordinates of Peak Voxel			Z-Score
	X	Y	Z	
NEGATIVE > POSITIVE				
Bilateral ventral medial prefrontal (11)	4	16	-4	3.27
Right inferior parietal (7)	40	-28	48	3.94
NEGATIVE > POSITIVE RULE-BASED				
Bilateral ventral medial prefrontal (11)	-8	40	-12	3.40
Right inferior parietal (7)	36	-20	52	3.36
NEGATIVE > POSITIVE SIMILARITY-BASED ^I				
Bilateral ventral medial prefrontal (11)	4	16	-4	2.97
Right inferior parietal (7)	44	-24	52	3.34
Left lateral temporal (21)	-60	-56	-8	3.41
POSITIVE > NEGATIVE				
Left inferior parietal (7)	-28	-56	52	3.60
Left inferior parietal (7)	-40	-32	36	3.56
Left superior temporal (22)	-32	-52	16	3.76
Left superior temporal (22)	-28	-16	-8	3.55

NOTE

^I Analysis conducted at p<0.05 height threshold.