Symptoms of Frontotemporal Dementia Provide Insights into Orbitofrontal Cortex Function and Social Behavior

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ABSTRACT: Recent investigations into the brain substrates of behavioral changes in frontotemporal dementia (FTD) demonstrate that the orbitofrontal cortex (OFC) plays a crucial role in normal social and emotional behavior. The initial symptoms of FTD reflect the early involvement of OFC as well as the disruption of an associated network involving the insula, striatum, and medial frontal lobes. As predicted by patients with other types of OFC lesions, FTD patients show impairments involving stimulus-reward reversal learning, response inhibition, and ability to judge the appropriateness of their behavior in the social context. While the natural reward system remains intact in these patients, that is, patients will seek out directly rewarding stimuli, such as food and sex, with progressive OFC dysfunction they lose the ability to process complex stimulus-reward contingencies. These abnormalities are apparent in their social interactions, which break down early in the disease. Also, deficits in emotion recognition and empathy have been directly linked to OFC atrophy in these patients. In contrast, some patients with early FTD show intact cognitive skills, including memory and executive functioning. Here, we review the behavioral and neuropsychological changes that accompany OFC atrophy in FTD and argue that phylogenetically new neurons found in this region, called von Economo neurons, are selectively vulnerable in FTD.

KEYWORDS: orbitofrontal cortex; frontotemporal dementia; social behavior

Frontal-variant frontotemporal dementia (FTD) is a devastating neurodegenerative disease in which the first brain region to show atrophy is the orbitofrontal cortex (OFC)[1] (see FIG. 1). In keeping with this anatomy, the first symptoms of FTD typically involve behavioral alterations, changes in personality, and impairments in social interactions. This disorder progresses slowly and is associated with gradual atrophy and dysfunction of the frontal and/or anterior temporal lobes with a relative sparing of the posterior brain. Once considered

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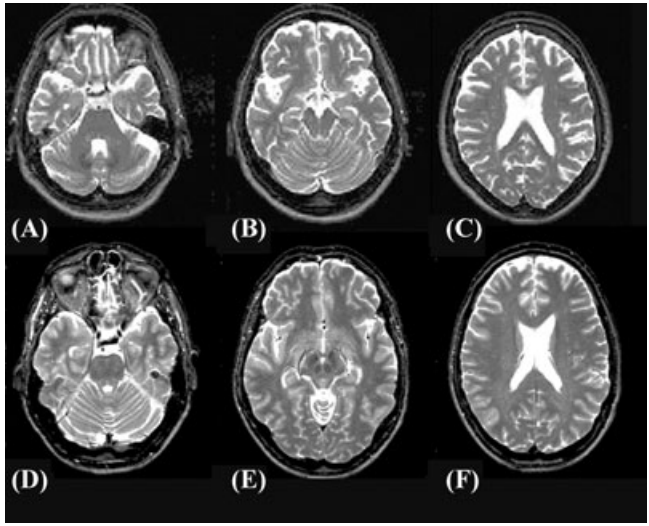

FIGURE 1. T2-weighted magnetic resonance images of a patient in the early stages of FTD (**A-C**) showing relatively selective OFC atrophy and a healthy age-matched control subject (**D-F**) for comparison.

rare, it is now accepted that FTD is at least as common as Alzheimer's disease (AD) in patients under 65 years of age[2–4] On post-mortem examination, FTD shows selective atrophy, gliosis, and neuronal loss in the frontal and anterior temporal regions. Histologically, FTD has two main subtypes, one associated with tau inclusions (Pick's disease) and the other with ubiquitin-TDP-43 positive/tau-negative inclusions.[5]

In this paper, we review the behavioral and neuropsychological changes that accompany OFC atrophy in FTD and argue that phylogenetically new neurons found in this region, called von Economo neurons, are selectively vulnerable in FTD.

CHARACTERISTICS OF FTD

The Neary Criteria[6] for FTD define this syndrome as a behavioral disorder characterized by early decline in social and personal conduct, emotional blunting, and loss of insight. Neuroimaging studies suggest that early in the illness, FTD patients show predominantly right frontal, anterior insular, and anterior cingulate involvement with pronounced OFC atrophy.[2,7,8] FTD has a strong male predominance (about 64%), often begins before the age of 60 years, and shows a fast but variable progression to death, with mean estimates ranging from 2.3 to 8.7 years from first symptoms.[2,9,10] These patients are frequently misdiagnosed with psychiatric disorders or other neurological diseases.[11] Rankin *et al*.,[12] however, demonstrated that examiner ratings of

patient behavior after only 1 hour of testing were useful for discriminating FTD patients from other types of dementia. FTD patients exhibited excessive calmness or ease during the evaluation, a subset exhibited disinhibited behavior, and many lost respect for personal boundaries.

ANATOMY OF THE OFC

The OFC occupies the ventral portion of the prefrontal cortex (PFC) and is made up of five cytoarchitectonic sub-regions: frontopolar area 10, area 11 in the anterior boundary, area 13 at the posterior boundary, area 14 medially, and area 47/12 at the lateral boundary.[13] The OFC is also among the few brain regions, and the only frontal region, that receives projections from all the sensory modalities.[14] It is extensively connected to the limbic system, receiving direct projections from the amygdala, cingulate gyrus, parahippocampal cortex, and hippocampus.[15] Therefore, its anatomical placement gives the OFC information from all of the senses and the emotion and memory systems.

The OFC is selectively vulnerable in FTD: in a study of 12 FTD patients, the three mildest patients showed no detectable frontal atrophy, while six patients with moderate atrophy showed significant atrophy in the OFC and right insula[1] (see FIG. 2). The patients with the most severe atrophy showed diffuse involvement of the entire frontal region, including white matter. These results support the hypothesis that the OFC and insula are the most vulnerable regions in FTD. In addition, the behavioral symptoms that are seen early in FTD include functions that are known to rely on intact OFC, such as complex decision making and perseveration, as discussed below.

OFC AND REWARD PROCESSING

Patients with OFC damage or dysfunction show two characteristic behaviors: perseverative responses to previously rewarding stimuli and deficits in complex decision making. Perseveration is one of the first deficits to be described in monkeys with OFC lesions, such that lesioned monkeys are unable to inhibit responding to an object that was previously associated with a reward when the reward contingencies are reversed and a previously unrewarded stimulus is now the key to the reward.[16] This deficit in stimulus-reward reversal learning is found in patients with OFC damage,[17] but not in patients with damage limited to the dorsolateral PFC.[18] Perseveration also disrupts performance on the Iowa gambling task by patients with OFC lesions.[19] In this task, participants are asked to choose cards from one of four decks, with some cards winning and some losing hypothetical money. Two of the decks consistently yield small gains and smaller losses, while the other two yield large gains but even greater losses. Healthy controls quickly learn that the best strategy is to stick to the

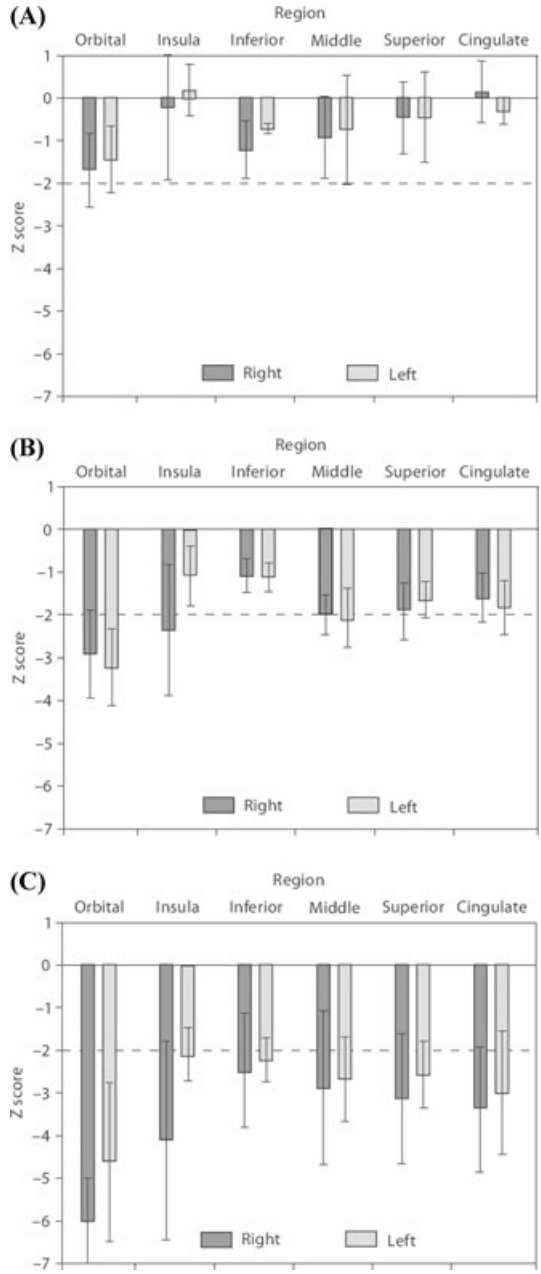

FIGURE 2. Mean regional volumes by patient subgroup: **(A)** mild atrophy (n = 3), **(B)** moderate atrophy (n = 6), and **(C)** severe atrophy (n = 3). Values are expressed in z scores derived from control mean and standard deviation values. Error bars indicate plus or minus two standard errors of the mean. Reprinted with permission from Perry *et al*. (2006).[1]

more conservative decks, but patients with OFC damage continue to choose cards from the risky decks until they lose all their "money." Recently, this task was administered to 20 patients with FTD who also showed impairments similar to those seen in OFC patients relative to age-matched controls.[20] Furthermore, in a study of autonomic responses during the Iowa gambling task, control participants showed an increase in skin conductance just before they chose a card from one of the high-risk decks, while OFC patients failed to show any anticipatory response.[21] Once the choice was rewarded or punished, however, patients showed skin conductance responses that were equivalent to those seen in controls. Bechara *et al*.[22] further demonstrated that autonomic responses can still be affected by learning in OFC patients, suggesting that the deficit seen in the patients stems from an inability to associate patterns of environmental stimuli with autonomic responses.

Accounting for these findings, the OFC is thought to bind situations with consequences, or, more specifically, to learn how stimuli will affect the organism emotionally and physically. Thus it can predict and create a resultant autonomic state in the presence of particular circumstances. This theory, which proposes that the OFC contributes to decision making by integrating and evaluating bodily signals is known as the somatic marker hypothesis.[23] In the presence of OFC impairment, patients are unable to choose between alternatives because the emotional consequences are not differentiable: the patient can no longer use "gut feelings" when weighing options, and all decisions, regardless of their importance or triviality, become arbitrary. This deficit in the ability to predict emotional consequences of behavior may explain why patients with FTD can often describe the consequences of their actions with complete emotional neutrality. For example, in our FTD population, one patient was able to describe in perfect detail the distressed emotional reaction that his spouse displayed when he said something injurious to her, without remorse or any indication that he realized he could avoid hurting her in the future by monitoring his language. FTD patients are also unable to judge the relative seriousness of consequences. For example, another patient used company funds to purchase illicit materials online because he did not want his wife to find out about his penchant for lewd material. This example demonstrates that the patient did not realize that the consequences of embezzling money at work were far more serious than his wife's anger, highlighting the deficit in weighing options seen in patients with FTD.

DIRECT MEASURES OF CHANGING STIMULUS-REWARD CONTINGENCIES

As predicted by patients with OFC lesions, early FTD patients show impairments in shifting strategies based on changing stimulus-reward associations. For example, in a recent study of FTD patients who were unimpaired on classic

frontal-executive tests, the patients demonstrated a select impairment on the "flanker" test of attentional control.[24] On this test, participants indicated the direction of a centrally presented arrow as quickly and as accurately as possible. The central arrow was flanked on both sides by arrows either pointing in the same direction (congruent condition) or opposite direction (incongruent condition). FTD patients showed reduced accuracy and speed on incongruent trials. In another study of early FTD patients with intact performance on frontal-executive tests, the patients showed difficulty in reversing previously learned visual discriminations when reinforcement contingencies changed.[25] These same patients also showed slowed deliberation times and increased risk taking on a decision-making task. The deficits demonstrated by the early FTD patients in these two studies may arise from impairment in adjusting strategies based on trial-by-trial changes in stimuli and their associated reinforcement value, with reinforcement value defined as the emotional response associated with correct and incorrect responding. This process was attributed to OFC activity based on the results of a recent functional magnetic resonance imaging (fMRI) study of brain activity during various conditions of the flanker test.[26]

INABILITY TO ADAPT TO CHANGING REINFORCEMENT MAY LEAD TO DISINHIBITION

Based on their reviews of OFC functional and lesion studies, Kringelbach and Rolls[27] propose that the OFC flexibly processes reward and punishment values of stimuli in the environment and adapts behaviors contingent on the changing nature of these reinforcers. Based on their model, patients with OFC damage, such as early FTD patients, may produce socially inappropriate actions or comments because they are unable to adapt their behavior when there is a conflict between immediate personal and delayed gratification values, particularly when social reward cues must be inferred from minimal or complex input.[28] Socially inappropriate behavior is common in FTD and can include sexually charged comments or otherwise offensive speech, theft, and public urination or masturbation.[29] Additional evidence for a direct role of OFC in disinhibition comes from studies of patients with OFC lesions[30] and from a study by Peters and colleagues[31] that reported a specific association between disinhibition and posterior orbitofrontal hypometabolism in FTD.

NATURAL REWARD SYSTEM

The natural reward system modulates the drive to seek out directly rewarding stimuli, such as food, sex, and water, by monitoring internal cues (satiety) and external cues in the surrounding environment. OFC lesions have been

shown to leave the natural reward system intact: animals with complete removal of OFC will still work for natural rewards[32] and will learn that a neutral stimulus predicts reward.[33] Without the ability to code and react to changing values of reinforcement, however, OFC atrophy may lead to behaviors, such as overeating. In fact, alterations in eating behavior have frequently been observed in patients with FTD, including an increased preference for sweet foods,[34] and recent research by Woolley and colleagues[35] suggests that a right orbitofrontal-insula-striatal circuit may be necessary for normal regulation of feeding and satiety. Patients with FTD, semantic dementia (SD), progressive non-fluent aphasia, progressive supranuclear palsy, AD, and normal controls were presented with a constant volume of sandwiches for 1 hour at lunchtime. Six of the patients with FTD, but none of the other participants, overate. Five of these six patients spontaneously reported to the experimenter that they were full during the lunch but nevertheless continued to eat, and all six showed normal primary taste processing. These overeating patients showed the greatest preference for the sweet jelly sandwich from among the other five sandwich choices. The overeating patients did not differ from the other patients on any cognitive variables, including tests of language and executive functioning, but they did show greater behavioral disturbances, as rated by their caregivers, involving euphoria, apathy, disinhibition, aberrant motor behavior, and aberrant sleep behavior. Using voxel-based morphometry (VBM) to compare cortical atrophy in the overeating patients to the non-overeating patients and the controls, the authors identified greater atrophy in right rostral OFC, right ventral insula, and right striatum in the overeating patients.

These findings are supported by a study conducted by Whitwell and colleagues,[34] in which the neural correlates of altered eating behavior in 13 patients with FTD and three with SD, as rated by their caregivers, were measured. Increased preference for sweet foods was associated with marked gray-matter reductions in OFC bilaterally and right anterior insula, and increased food consumption was associated with OFC bilaterally. Based on single-neuron recording studies in the macaque and functional neuroimaging studies in humans, Rolls has proposed that the OFC represents the reward value of taste, and further, that the reward value declines when the individual has eaten to satiety.[36,37] The abnormal eating behaviors frequently observed in FTD, such as a change in food preference toward sweet foods and continued eating after satiety is experienced, are likely manifestations of the early OFC involvement associated with this disease.

EMOTION RECOGNITION AND EMPATHY: DISRUPTIONS IN REWARD PROCESSING IMPAIR SOCIAL COGNITION IN FTD

Arguably the most complex web of reinforcement schedules is found in social interactions. Our ability to recognize emotions in others and to infer their mental states provides us with social cues for appropriate behavior and

allows us to receive social rewards and avoid punishment. Patients with FTD are particularly insensitive to social cues and their rewarding or punishing values. FTD patients are impaired in the recognition of both facial and vocal expressions of emotions,[38] and this impairment is more severe than in patients with AD.[39] Tests tapping the cognitive processes important for recognizing these cues show some promise for the early diagnosis of FTD.[40]

Empathy is a complex cognitive and emotional process involving the ability to recognize and feel the emotional response of another individual. Empathy promotes social engagement, provides cues important for appropriate social conduct, and has been shown to be lacking in FTD patients.[41] Using VBM-determined cortical atrophy, Rankin and colleagues[42] provided evidence that the OFC may be required for normal empathy. They demonstrated that right medial OFC volume was strongly related to loss of cognitive and emotional empathy in a sample of 123 patients with neurodegenerative disease, including 30 with FTD. If patients are unable to evoke or process the autonomic responses inherent during emotional experiences in themselves, their capacity to feel or recognize emotions in others would necessarily be impoverished. This disconnection between "gut feelings" and reward processing in FTD may explain how empathy is lost with OFC atrophy.

Empathy is a complex process, however, and there are multiple dissociable systems involved in the experience of empathy and related social processes.[43] For example, empathy may be disrupted after amygdala damage because of an impairment in both the recognition and experience of emotion,[44] and dorsomedial PFC may be particularly important for the mental attribution of intentions.[45]

Gregory and colleagues[46] showed that the related concept of theory of mind (i.e., the ability to infer other people's mental states, thoughts, and feelings) was impaired in FTD and that the degree of impairment showed a strong concordance with OFC damage. The FTD patients studied by Gregory and colleagues were impaired on several tests of theory of mind, with about half of patients impaired on tests that tap the ability to make cognitive inferences about what story characters were thinking (e.g., "what does character x think character y knows?") and 74% impaired on a more complex "faux pas" detection test that requires integrating the mental and emotional states of two individuals in order to process embarrassment (e.g., recognizing that character x should not have unintentionally done something because it may be hurtful to character y). Patients with bilateral OFC lesions and intact medial PFC tested using a similar battery showed a select impairment in the more complex "faux pas" detection test.[47] These results suggest that the OFC may play a role in inferring the mental state of another person from external cues and likely plays a critical role in comparing the emotional value of an inferred mental state with the value of other internal or external stimuli. The disruption of these cognitive mechanisms in FTD may explain why patients with this disease commonly seem unconcerned about the feelings of their loved ones.

OFC ATROPHY IN THE CONTEXT OF A LARGER NETWORK

Increasing the complexity of this story, the initial symptoms of FTD may reflect the early involvement of an associated network involving the insula, striatum, and medial frontal lobes, in addition to the OFC. Recently, direct correlations between OFC atrophy and the behavioral changes in FTD have been reported. In a study of 62 patients with FTD and SD, Rosen and colleagues[48] examined the neural correlates of caregiver ratings of behavior with regional differences in cortical atrophy using VBM. Specific behaviors in FTD, including apathy, disinhibition, repetitive compulsive behaviors, and overeating, correlated with atrophy in the right frontal, insular, striatal, and anterior temporal regions. The average of these four behavioral disturbances also correlated with tissue loss in right inferior and medial frontal cortex, including OFC, as well as with tissue loss in the right caudate head and the right anterior insula. Additional unique effects were observed for apathy with the ventromedial superior frontal gyrus, disinhibition with the subgenual cingulate gyrus, and aberrant motor behavior with the right dorsal anterior cingulate cortex (ACC). The brain-behavior correlations observed in this study suggest that the right OFC regulates behavior in concert with predominantly right-sided network involving the insula and striatum.

Apathy, defined as a lack of interest, lethargy, social and emotional withdrawal, and reduced speech output, is almost universally prevalent in FTD patients to some degree[49] and seems to rely mainly on medial PFC function. While apathy is almost universally present, other behavioral disturbances vary considerably among patients, reflecting the heterogeneity of the pathology and its anatomical distribution. In an effort to characterize different manifestations of the disease, two distinct behavioral syndromes have been described, including an apathetic subtype, characterized by a generalized loss of interest in activities and volition, loss of social emotions, and decreased pain response; and a disinhibited subtype, characterized by an increased preference for sweet foods, hyperorality, exaggerated sensory responses, repetitive motor behavior, and increased apathy.[50] Other behaviors include stereotyped or ritualized behaviors, such as repetitive organization of objects into groups, hoarding, or repetition of a story or catch phrase. Caregivers report personality changes, such as increased submissiveness or rigidity, or shifts in their attitudes or values, such as a change in religious beliefs.[51–53] As the disease progresses and atrophy encompasses more and more frontal and temporal regions, the number and severity of behavioral impairments increase, and impairments in executive functioning emerge.[49,54,55] With relatively spared medial temporal and parietal lobes, FTD patients retain their visuospatial skills and the ability to learn new information, in contrast to the classic presentation of AD.[56,57]

INTACT COGNITIVE SKILLS EARLY IN THE DISEASE

Like patients with OFC lesions, early in the disease, many FTD patients show few measurable cognitive deficits. Widely used bedside cognitive screening instruments, such as the Mini-Mental State Examination (MMSE), are insensitive to the early stage impairments of FTD.[58] Certain newer batteries have shown minimal success in differentiating early FTD patients, as a group, from early AD patients.[59–61] These batteries have been less successful in differentiating frontal variant patients and AD patients than batteries that include caregiver-rating scales of behavior.[62,63]

Like patients with OFC lesions, early FTD patients can perform in the normal range on traditional "frontal executive" tests, such as tests of concept formation, working memory, verbal fluency, planning, or complex sequencing. As the disease progresses, however, impairments on frontal-executive tests typically emerge and can be useful for differential diagnosis.[54,57,64] The approach patients take and the errors they make may be more useful for diagnosis than the overall achievement scores.[65] Normal performance on these executive tests relies heavily on the functioning of lateral PFC.[66] When performance on these tests is preserved in FTD, the disease process may be predominantly affecting orbitofrontal or dorsomedial areas.[55]

SELECTIVELY VULNERABLE CELLS: VON ECONOMO NEURONS AND FTD

Compelling evidence regarding the exact locus of early degeneration has recently been reported by Seeley *et al*.[67] (see FIGS. 3 and 4). Von Economo neurons (VENs), formerly called "spindle cells," are a group of recently evolved neurons primarily in the ACC and the frontoinsular (FI) cortex in humans, great apes, and whales, all creatures with complex social behaviors. These cells are large bipolar cells, found in cortical layer Vb, with only a single large basal dendrite, and thus are easily distinguished from pyramidal cells. Extensively described and mapped by von Economo and Koskinas,[68] these neurons have arisen only within the last 15 million years in hominids. As a result, they may be particularly vulnerable to disease and dysfunction. They are largest and most numerous in humans, declining in density in hominids with approximately the phylogenetic distance from humans; that is, the larger the distance between the hominid and humans, the fewer VENs are found in that species.[69]

The right FI cortex has about 30% more VENs than the left FI,[70] leading to the hypothesis that VENs are involved in processes that are more reliant on right than left hemisphere activity. These functions include emotional and social processes. In fact, this right-sided bias in VEN numbers may account for the MRI-based findings that cortical gray matter is greater in the right

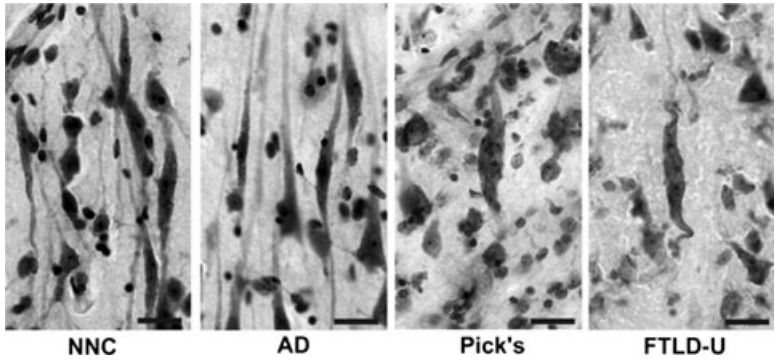

FIGURE 3. VEN swelling and dysmorphism in FTD. VENs in non-neurological control subjects (NNC) and AD patients showed prominent clustering, smooth contours, and slender, tapering somata. In FTD, VENs were often solitary, swollen (especially in Pick's disease), or showed twisting and kinking of proximal dendrites (both Pick's and frontotemporal lobar degeneration with ubiquitin inclusions (FTLD-U)). Cresyl violet stain. Scale bars = 20 μm. Photomicrographs are oriented with the pial surface at the top. Reprinted with permission from Seeley *et al*. (2007).[8]

than the left frontal cortex.[71,72] VENs also appear later in development—only about 15% of them are present at birth—and they continue to migrate and differentiate until age four.[73] At birth, the right hemisphere shows only 6% more VENs than the left, reinforcing the notion that VENs play a special role in social and emotional behavior.

In humans, VENs have a large, elongated, symmetrical cell body with an apical dendrite extending toward the pial surface of the cortex and a single basal dendrite extending toward the underlying white matter.[69] In the ACC, VENs are about four times larger than their neighboring pyramidal cells.[74] This large size suggests that the cells are involved in the rapid relay of information to and from the frontal cortex. VENs cluster close to small arterioles, suggesting that they have high metabolic requirements and may be more prone to injury from oxidation over time.[67]

As mentioned above, the FI is one of the key areas in which VENs have been found. Further evidence underscoring the role of the FI in social behavior can be found in fMRI studies: Bartels and Zeki[75] found that when participants viewed images of loved ones, there was more neural activity in the FI than when they viewed images of mere acquaintances, while Lamm, Batson, and Decety[76] found that greater activity in the insular cortex correlated with greater empathy. In addition, the medial part of Brodmann's Area 10 has been shown to be preferentially active when participants are required to choose a course of action affecting the lives of others.[77]

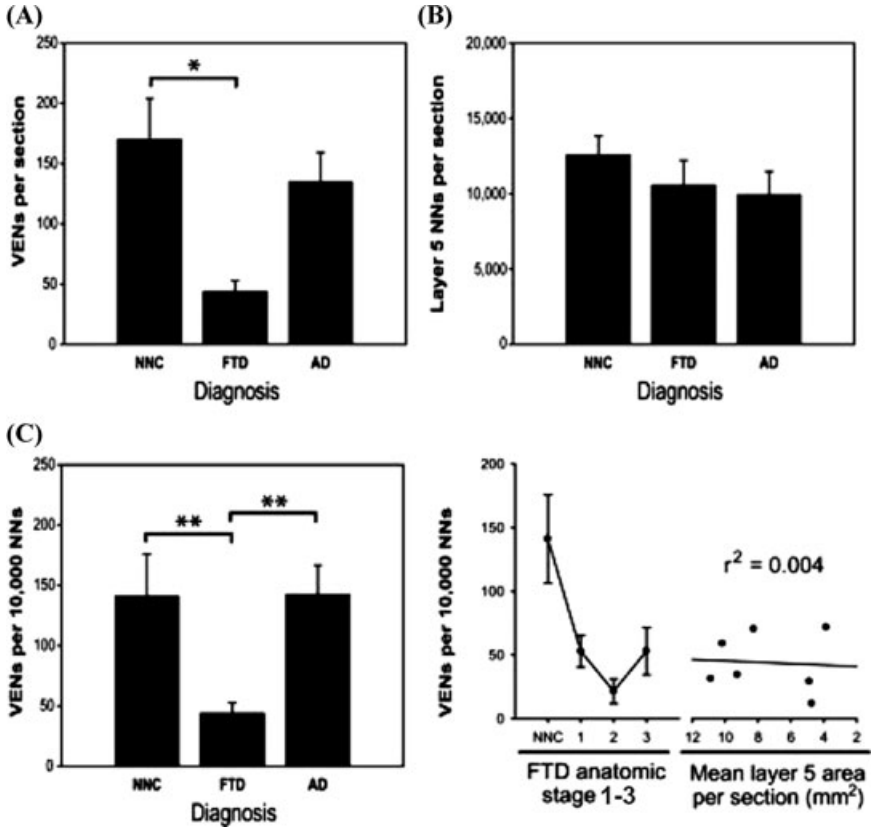

FIGURE 4. Severe, selective, disease-specific, and early loss of VENs in FTD. **(A)** VENs per section were reduced by 74% in FTD compared with non-neurological subjects (NNC) ($^{*}P < 0.005$, Tukey's test after F-test for three-group analysis of variance [ANOVA]). **(B)** Layer 5 neighboring neurons (NNs), in contrast, showed a mild, statistically nonsignificant reduction in FTD, similar to that seen in AD. **(C)** VEN per 10,000 NN estimates indicated selective VEN depletion in FTD compared with NNC subjects and patients with AD ($^{**}P < 0.05$, Tukey's tests after F-test for three-group ANOVA). **(D)** Even mild stages of FTD-related atrophy were accompanied by marked VEN dropout. Mean Layer 5 area per ACC section, used here as a local marker for disease severity, had no bearing on the VEN/10,000 NN ratio, further suggesting that VEN selectivity occurred across FTD stages. Error bars reflect the standard error of the mean. Reprinted with permission from Seeley *et al*. (2007).[8]

NEUROTRANSMITTERS: VASOPRESSIN, DOPAMINE, AND SEROTONIN

Receptors expressed on VENs include the vasopressin 1a receptor, the dopamine D3 receptor, and the serotonin 2b receptor. Vasopressin is a

neurotransmitter that has been strongly linked to the formation of social bonds.[78] The dopamine D3 receptor has been implicated in reward-seeking behavior, including drug addiction.[79] Though not playing a direct role in creating the rewarding effects of psychostimulants, D3 receptors seem to be involved in the motivation to self-administer drugs where significant effort must be expended in order to receive the drug, that is, where the cost of the drug is high. D3 receptors seem to modulate the effect that environmental stimuli have on drug-seeking behavior, while having no influence on natural reinforcers, such as food or sex.[79] Finally, serotonin in the OFC has been shown to contribute to cognitive flexibility.[80] When serotonin is depleted selectively from the PFC, perseverative responses to previously rewarding stimuli are observed.[81] A more recent study has confirmed the role of OFC serotonin in inhibition of prepotent reponses.[82] The serotonin 2b receptor is also numerous in the human stomach and intestines, where it contributes to peristalsis.[83] The activation of these receptors in the gut, then, may contribute to the signaling of danger or threat, and this information may be rapidly integrated by VENs.

Recent work has demonstrated severe, selective, and early loss of VENs in patients with FTD[67] (see FIGS. 3 and 4). Compared to healthy age-matched controls, patients showed a 74% reduction in VENs, while neighboring layer V pyramidal cells were not significantly depleted. While a previous study has shown that VENs are lost in AD as well, Seeley *et al*.[67] showed that early in AD, this VEN loss is not detectable, suggesting that the selective loss of VENs in FTD is a defining feature of the disease.

FUTURE DIRECTIONS

Patients with early FTD show marked behavioral changes and functional declines, and as such, it follows that there are impaired underlying processes that could theoretically be tapped by objective measures. There is a clear clinical need to develop neuropsychological tests that are sensitive to the impaired cognitive processes of early FTD, both to improve methods for early and accurate diagnosis and to better evaluate the efficacy of new treatments. Some initial progress toward this goal has involved adapting tests with demonstrated sensitivity to OFC dysfunction, specifically tests of emotion recognition, theory of mind, attention, and decision making. These tests measure various aspects of processing emotional or social cues, their reinforcement value, and the flexible use of those cues to guide behavior.

In addition, finding a direct link between VEN activity and social behavior will allow scientists to develop computational models of OFC function. FTD offers a unique window into the mechanisms by which these cells facilitate social interactions and complex behavior. Understanding how OFC damage affects decision-making processes will not only inform neuroscientists about the OFC itself, but will also be of interest to economists, anthropologists,

psychologists, and individuals who hope to understand how humans are able to function in a world of seemingly infinite choices.

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