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Topography, Histology, and Semiology in Dementia

Johnson et al¹ provided convincing neuropsychological evidence for a frontal lobe pattern of dementia in patients with pathologically confirmed Alzheimer disease (AD), and were able to correlate this pattern with anatomical evidence of increased frontal lobe burden of neurofibrillary tangles compared with that found in "typical" cases of AD. I have a similar case of a 64-year-old man with a striking progressive frontal lobe syndrome marked by perseverative, retentive, hoarding behavior, radiologically evident bifrontal atrophy (the left side worse than the right side), and an apolipoprotein E (APOE) genotype of APOE3/4 suggesting he may have AD rather than Pick disease (although we presently lack tissue confirmation).

Johnson et al underscore a point I tried to make, in a 1992 article titled "Asymmetric Cortical Degeneration Syndromes,"² that the cognitive profile of degenerative cortical dementia is dictated by the topography of pathology more than by its histology. This is true not only for frontotemporal dementia, but for progressive aphasia, visual syndromes, apraxic syndromes, and so forth. A second point I tried to make was that the various asymmetric cortical degenerative syndromes could be more closely related to one another than their disparate clinical profiles would otherwise suggest, because the only real difference between them was one of topography, analogous to different stroke syndromes. Through 1992, the gist of the debate centered around whether these were truly focal syndromes, or "generalized dementia,"³ implying (incorrectly) that dementia itself was a nonspecific, "generalized" pattern of cognitive impairment. The discovery of chromosome 17-related dementias helped to vindicate the contention that the cognitive differences between different dementia syndromes could be of important diagnostic significance, and that the focal-vs-generalized debate was irrelevant.

We can classify cortical dementia syndromes according to their cognitive profile, neuropathological findings, and, increasingly, their genetic bases. We have learned that there are general correlations between these 3 categories, but there are many exceptions. Alzheimer disease usually causes "Alzheimer dementia" and relates to APOE, or a less common genetic factor, but AD can also produce a progressive visual syndrome, frontal

lobe syndrome, aphasic syndrome, or apraxic syndrome, and, in some cases, may relate to a *tau* gene mutation.⁴ Johnson et al¹ suggest their cases may represent a frontal lobe "variant" of AD. This may be, but the authors probably recognize that variants also exist for Pick disease, corticobasal ganglionic degeneration, nonspecific degeneration, and probably for every degenerative disease that affects the cerebral cortex. It may be instead that factors that determine histologic condition are, in turn, influenced by a second factor that influences topography. As well-illustrated by Johnson et al,¹ the modern approach to the diagnosis of dementia must be guided by an open mind and data, and must not be misguided by historical bias.

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In reply

We recently identified a subgroup of patients with a frontal variant of AD who had early and disproportionate impairments on tests of frontal lobe functioning and also a greater than expected degree of neurofibrillary tangle, but not neuritic senile plaque, pathology in the frontal cortex.¹ Dr Caselli raises the point that the cognitive profile of cortical dementias is dictated more by the location of the pathological lesions than by the histological features. Dr Caselli also highlights, however, that genetic and neuropathological heterogeneity may also have an increasingly important role in explaining phenotypic differences.

It is clear that the areas of the brain subserved by higher level cognitive processing are particularly vulnerable to the effects of aging and neurodegenerative diseases. In fact, the frontal cortex is affected not only in AD but also in frontotemporal dementia, vascular dementia, and dementia with Lewy bodies. And in some variants of neurodegenerative disorders, the frontal cortex may have more burden than usual, such as in the frontal variant of AD¹ or frontal variant of

frontotemporal dementia.² While the regional topography of vulnerability is common across these disorders, the underlying molecular and cellular mechanisms most likely differ. As the frontal variant of AD showed a greater than expected degree of one classic marker of AD (ie, neurofibrillary tangles), it is also likely that different mechanisms of neurodegeneration are involved. For example, the frontal variant of AD may have distinct and early initiation factors targeted to the frontal cortex that may precede neurofibrillary tangles and/or follow a, yet, unidentified alternative pathogenic pathway (eg, apoptosis in neurons or perhaps glia). Other studies have also demonstrated differential vulnerability of morphology, cell layers, and cortical circuits in AD.³⁻⁵

Our recent article illustrates one approach to studying the mechanisms giving rise to atypical presentations of AD. That is, after identifying cortical brain regions that are differentially vulnerable, we can further study the molecular cascades that contribute to this brain region and cortical circuit vulnerabilities. It is possible that the subgroup-specific changes may create a signature of vulnerability and, in turn, generate unique and fundamental changes in cognition and/or behavior. The fundamental goal of dementia research is to identify the most vulnerable circuits, the functional consequences on cognition, early markers, and potential interventions. There

fore, probing circuit-specific functions may play an increasing role in contemporary neurology.

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