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COMMENTARY PAPER OF THE MONTH

Imaging apathy in Alzheimer's disease

Theleritis and co-workers should be commended for producing the most comprehensive review on the neuroimaging correlates of apathy in Alzheimer's disease (AD). The authors assessed studies using different imaging modalities such as structural neuroimaging with three-dimensional magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), single photon emission tomography (SPECT), and positron emission tomography (PET). This scholarly review will be an excellent resource for future publications on neuroimaging in apathy.

The authors made the important comment that depression is a relevant confounder of apathy in AD. A study that included 319 patients with AD diagnosed apathy on 37% based on a diagnostic algorithm, and 24% of the patients with apathy had major or minor depression (Starkstein *et al.*, 2001). This important confounder has been rarely controlled for in most imaging studies. As also mentioned by Theleretis *et al.*, severity of dementia is another important confounder, as the frequency of apathy was reported to increase from 14% among patients with mild AD to 61% among patients with severe AD (Starkstein *et al.*, 2006). Nevertheless, imaging studies differ widely in the severity of dementia of AD patients recruited, which may account for some of the heterogeneous findings. Other important limitations of these studies are the use of different instruments to assess apathy in AD, the use of severity rating scales for making a diagnosis rather than a more appropriate structured psychiatric interview, and the lack of standardized diagnostic criteria for apathy.

The anterior cingulate emerged as the region most frequently reported to show structural or metabolic abnormalities (e.g. in five of the ten SPECT studies included in the review, in five of the six structural studies, but in only one of the five PET studies). The authors discussed how dysfunction of the anterior cingulate, as part of a putative brain circuit, may underlie apathy in AD. As mentioned by the authors, the anterior cingulate has been considered to play an important role in the initiation of cognitive and behavioral activities as well as in monitoring behavior as part of an "executive control network." Nevertheless, association does not mean causation, and future longitudinal studies should further clarify the role of the anterior cingulate in the mechanism of apathy in AD. It is also important to note that other cortical areas have been associated with the presence of apathy in AD, for example changes in cortical regions such as the orbital and dorsolateral regions of the frontal lobe and the right temporal lobe, subcortical structures such as the ventral putamen, head of the caudate, the medial thalamus, and the ventral tegmental area, as well as changes in the frontal lobe white matter. While changes in these regions may be subsumed under the concept of dysfunction of a "distributed frontal-subcortical network," this concept requires further clarification.

I would like to briefly mention other potential mechanisms of apathy in AD. First, there is a clear symptom overlap between apathy and depression, which accounts for a sizeable proportion of patients with apathy in AD. Among those patients with apathy and no depression, severity of dementia should be considered, as patients progressively lose the capacity to engage in their usual hobbies, have increasing problems with their activities of daily living, and due to memory and language deficits become more socially isolated. Therefore, it is highly likely that the syndrome of apathy in AD may have different causes ranging from psychological to pure biological factors. As suggested by Theleretis *et al.*, longitudinal studies are needed to determine whether the anterior cingulate is a significant predictor of apathy in AD, as well as to validate subgroups of patients with apathy in AD with different underlying mechanisms.

Conflict of interest

None.

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