Supplemental Text

Regression-Based Norms

Regression-based norms[9,e-50] can be helpful when baseline cognition was not documented. This approach estimates expected cognition with patient variables (e.g., education[9,e-50]), and infers decline when performance is lower than expected. But even the best estimates of premorbid IQ only account for 22-24% of the variance in speed and memory,[e-51] and cannot estimate a person's idiosyncratic profile of strengths and weaknesses across domains. As such, regression-based norms are useful, but the gold standard for estimating decline is comparison to baseline function.

Segmentation of Hippocampal Subfields and Thalamic Nuclei

Advances in MR imaging and analysis will inform models of cognitive deficits. For instance, ultra-high field imaging (e.g., 7.0 Tesla) may allow better segmentation of critical structures, such as the hippocampus and thalamus. Indeed, given separable patterns of hippocampal subfield atrophy / modifications across different neurologic conditions (for review,[33] for MS[28,34]), and links between specific subfields and different basic mnemonic processing functions,[33] increased spatial resolution and MRI segmentation techniques may inform our understanding of disease-related memory deficits. Likewise, the thalamus is not homogeneous, but instead a collection of nuclei synapsing with separable functional networks. Ability to segment nuclei, along with improved imaging of dynamic links between grey matter and associated white matter tracts over time, may improve understanding of cognitive deficits (as recently discussed[35]).

DMTs as Protective Factors

DMTs help prevent physical disability by reducing disease activity and cerebral atrophy,[e-52] and evidence suggests that early DMT treatment may also reduce risk of cognitive decline (e.g.,[e-53]). Although early work showed that interferon β-1a (versus placebo) protected against decline on a composite measure of processing speed and memory,[e-54] subsequent clinical trial results for cognition have been inconsistent (see review[e-55]). One explanation has been use of the PASAT as the sole cognitive measure, which has several limitations (Table 1). The SDMT is recommended as a more sensitive outcome, with guidelines for clinically-meaningful change.[13] Future trials may also consider differential treatment effects across cognitive domains (speed, memory).

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