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Ethics Review

Is There More to Subjective Cognitive Impairment than Meets the Eye? A Perspective

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Abstract. Multi-disciplinary research has revealed evidence of significant abnormality in a much wider range and level of information processing than that currently definitive for amnestic mild cognitive impairment (MCI). This raises the possibility that the contemporary approach to MCI is inappropriately delimited, and the true nature and extent of brain dysfunction and thus disease burden, underestimated. It follows therefore that the closely related concept of subjective cognitive impairment (SCI) may be similarly constrained. Although research into the wider range of potential brain dysfunction in MCI and SCI is in its infancy, as yet precluding systematic reviews, we present here findings to prompt debate about SCI with respect to its clinical assessment and its personal and societal burden.

Keywords: Mild cognitive impairment, subjective cognitive impairment

INTRODUCTION

Subjective cognitive impairment (SCI) is a disorder in which ostensibly healthy individuals report self-perceived impairment in cognition, usually memory, in the absence of objective evidence on formal neuropsychological assessment [1]. Historically, given the existence of both subjective memory complaints and impaired episodic memory in mild cognitive impairment (MCI), an earlier clinical stage, where subjective memory complaints exist in the absence of detectable objective cognitive deficits, was proposed by Reisberg (see Rodda et al. [2] and Reisberg et al. [3]). Indeed, what is commonly termed SCI is evidence of this. Although the etiology of SCI is heterogeneous, being associated with increasing age [4], depression [5–8], numerous medical illnesses, and various medications [9], there is growing evidence that SCI is associated with increased risk of developing AD [1, 9–12] and of brain changes characteristic of Alzheimer's disease (AD) [2, 13]. These findings lead to the conclusion that SCI is increasingly recognized as a precursor to the earliest stages of AD with a subgroup of patients who will ultimately progress to develop neuropsychological declines consistent with MCI or AD. There are several advantages to studying SCI as if it were a preclinical stage of AD. For example, a pre-MCI stage of a dementing process when patients have more intact cognitive abilities may be more likely to be responsive to treatment than MCI.

Traditionally, preclinical and clinical AD are defined based on objective, standardized, neuropsychological

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assessments. Compared to cognitively healthy aging, MCI is associated with an increased risk of developing AD, especially in the presence of positive biomarker evidence. Thus for some individuals, it represents a point along a cognitive continuum ranging from normality to AD. Not surprisingly, therefore, MCI is a concept and diagnosis derived primarily from, and defined by, measures used to characterize and diagnose AD. Furthermore, the dominant clinical and research priorities for MCI relate to its potential for conversion to AD, the identification of early disease markers, and the development of interventional and preventative schemes to ameliorate personal, societal, and economic-related disease burden.

Defining and diagnosing MCI in terms of acquired impairment in neuropsychological measures of high-level processes such as memory, cognition, language, executive function, and perception (namely those tests used in the diagnosis and definition of AD) has ensured clinical continuity between the two disease entities, and helped establish the link between them. However, such tests tend to be relatively insensitive to the very early stage of disease i.e., in predicting for whom MCI represents prodromal AD. Furthermore, this strategy fails to recognize the potential for breakdown in the integrity of a much wider range of brain functions and in lower or more fundamental levels of information processing with respect to the diagnosis, management, and characterization of MCI, despite emerging research evidence to the contrary. The approach arises perhaps from enduring tacit assumptions that the symptoms of AD (and therefore of MCI) result primarily from the disruption of high level (e.g., cortico-cortical) functions and that if these are preserved then so too are more fundamental levels; and that lower level deficits *per se* do not influence behavior. Arguably, therefore, the original approach to the concept and diagnosis of MCI may have led to its incomplete characterization and underestimation of both individual and social burden. Recent evidence indicates that functional disruption in MCI at group level can be associated with the presence of amnestic deficit *per se,* or specific to the presence of prodromal dementia [14, 15]. Thus the priority given to determining early markers of AD in patients with MCI obscures the fact that individuals with MCI, irrespective of whether or not they develop dementia, may experience a far greater burden of deficits than initially recognized.

We propose that SCI may be associated with dysfunction of a wide range and level of brain functions, just as is found in MCI. By continuing to adopt the traditional clinical and research approach to SCI, we are potentially omitting information not only relevant to the relationship between SCI, MCI, and dementia, but also apposite to our understanding of its signs and symptoms and its effect upon environmental interaction and interpretation, and thus its associated burden on behavior and everyday life. Furthermore, for some individuals with SCI the absence of objective cognitive dysfunction arises simply from the insensitivity of the choice of cognitive test. Evaluating the functional integrity of other aspects and levels of brain function in SCI may reveal subtle associated or even causal changes that are not apparent from neuropsychological testing.

To illustrate these points, the following overview of research-evinced dysfunction in MCI, although not exhaustive or accompanied by meta-analysis, is presented in order to provoke discussion on whether an immediate broader approach to SCI is indicated. As the typical deficit in MCI is in the domain of memory, most studies (such as those described below) have involved participants with amnestic MCI; however, it is important to also acknowledge the existence of forms of MCI in which multiple and various other cognitive domains can be affected, again in the absence of significant disability.

ADDITIONAL DEFICITS IN AMNESTIC MCI

Increasingly apparent is the basis for potential abnormality in an extensive array of fundamental information-processing in MCI compared to cognitively healthy aging. These abnormalities include objectively ascertained disruption to brain physiology, structural and functional integrity, connectivity, the neural synchronization of cortical networks, physiological reactivity, white matter integrity, the default mode network, and the intra-individual variability of processing speed [14, 16–27]. More specifically, impaired visual and visual attention-related processing over a wide range of component operations and levels, including early pre-attentive and later perceptual, is an increasingly common finding in MCI compared to cognitively healthy aging [26, 28, 29–35]. Additional abnormalities include the more rapid decay of visual sensory (iconic) memory [36], abnormalities in pre-attentive change detection and processing [30, 37, 38], motion processing [29, 39, 40], contrast sensitivity function [41], eye movements [42, 43], phasic alerting [14, 44], visuospatial function [45–48], visual search [26, 49], visuospatial perception [50]; attentional control, selective and focused attention [35,

51, 52], the selective inhibition of irrelevant information processing, i.e., cross-modal inhibition [53], and increased perceptual thresholds [30]. However, outcome may depend upon the type of MCI measured and the methodology used [26, 46, 48], and it is possible also that some contribution to these results arises from patients in the early stages of visual variants of AD. Nevertheless, similar dysfunction in visual and attention-related processing is seen in typical AD [54].

Although less commonly measured than visual and attention-related information processing, significant disruption to central auditory processing [55], olfaction [56], taste [57], and somatosensory function [58, 59], together with abnormal multisensory integration [60], cortico-cortical processing [17] and sensory-motor function [61], sleep abnormality [62], and autonomic dysfunction [63], are also apparent in MCI compared to cognitively healthy aging.

As such processes are fundamental requirements for environmental awareness, interaction, interpretation, response, and thus everyday behavior, degradation within these and associated operational networks have the potential for significant negative impact. They are likely also to contribute to, or exacerbate, the characteristic decline in higher level cognitive function in MCI [64–66] and explain the reports of impairments in driving, increased risk of poor balance and falls and difficulties with other instrumental activities of daily living [67–70]. Such abnormality in a range of fundamental operations should alert us to the possibility that AD-related treatments and interventions should not simply be aimed at high-level functions such as memory, cognition, and perception. These results also indicate that, as SCI can represent a pre-MCI/AD stage, it may also be associated with a similar wide range of dysfunction. Indeed, as described below, emerging evidence indicates that this is so.

SCI: ADDITIONAL ABNORMALITIES BEYOND NEUROPSYCHOLOGICAL DEFICITS

Associations between SCI and direct measures of underlying brain changes are emerging. There is evidence of objective SCI-related changes in fundamental processing, e.g., default-mode network disruption [71], alterations in brain neural synchronization and function [13, 18, 72], changes in white [73] and gray matter [74], volumetric and metabolic changes [2, 75], and change in visual contrast sensitivity function [41] and divided attention [2]. Thus readily measurable abnormality in the functional integrity of a range and level of processing occurs in SCI independently of what appears to be objectively normal cognitive processing. This may contribute to the self-reports of memory changes even if neuropsychological test results are 'normal'.

Despite such research-related findings in MCI and SCI (and indeed in AD), the potential for abnormality in such a wide range and level of brain function is not taken into account or addressed in the new proposals for the diagnostic criteria for MCI or SCI aimed at promoting earlier detection [77]. Similarly, whereas the importance of cognitive decline is recognized in the English National Dementia Strategy ([77], and see also [78–82]), the potential for and impact of a wider range of deficits is not, despite their potential to influence behavior, disease burden, fitness to work, frailty, social isolation, coping strategies, social exclusion, loss of independence, and the provision of appropriate care. Neither are they recognized with respect to the development of early disease markers, or the development of disease interventions, or the measurement and interpretation of their efficacy. Furthermore, as SCI *per se* has for many people both functional and emotional significance, extending diagnostic testing could also help in determining for whom SCI and MCI is not related to early AD. In addition, such investigation has the potential to highlight deficits in processing that may adversely affect behavior and quality of life and increase disease burden, irrespective of whether SCI signals pre-dementia or not.

Another factor influencing the early diagnosis of dementia in MCI and SCI is that cognitive function may be maintained, namely performance on standard neuropsychological measures may be within the normal range despite underlying pathology, due to cognitive reserve and re-organizational and compensatory strategies [83, 84]. By limiting the investigation of cognitive reserve to high-level cognitive function (i.e., with respect to the same neuropsychological tests used in the diagnosis of AD), we are limiting our potential to fully understand its basis and to find new ways of identifying early signs of significant disease in those with high reserve.

ACTION

Arguably, as the potential benefits of intervention and treatment of pre-dementia AD are recognized, the evidence presented here indicates that the concept of, and clinical and research approach to SCI should be expanded by an immediate strategy of testing a wider range of brain function in both clinical practice and

research. More specifically, such a strategy is likely to benefit the individual and society with respect to an increased awareness and understanding of SCI and the range of brain functions that may be detrimentally affected and their consequence for behavior, irrespective of whether they are specific to the presence of neurodegenerative change. Against such an approach is the fact that currently there are no proven effective disease modifying treatments for AD irrespective of its stage (i.e., SCI and MCI). Thus the benefit to the individual or society in striving for increased knowledge in this area and the substantial economic cost of such research and the development of new tests can be questioned. Nevertheless, arguably the more we learn about SCI and indeed MCI and AD, the greater the potential to reduce the economic burden of these conditions, even in the current absence of successful intervention (e.g., see Lin and Neuman [85]). Furthermore, the majority of research studies examining brain function in MCI and SCI have been cross-sectional in nature. This paucity of longitudinal studies renders it difficult to determine whether abnormality in the novel aspects of information processing in MCI or SCI described above, results from the disproportionately poorer performance of those patients for whom MCI or SCI represents pre-dementia, or whether it more generally accompanies amnestic or cognitive dysfunction *per se*. Similarly, longitudinal study of SCI performance on established neuropsychological tests are essential in order to discriminate whether a score that is outside the normative range represents an early stage of decline from a premorbid level or a lifelong and stable individual difference.

Study replication levels are also low which precludes the performance of meta-analysis and thus associated measures of validity, reliability, and specificity. The evidence presented emphasizes the need for a longitudinal approach.

We therefore invite debate with respect to whether the current approach to SCI should be changed immediately in response to growing research evidence suggesting a much wider range and level of brain dysfunction in MCI and AD than had previously been recognized. Alternatively, should we await the outcome of additional longitudinal studies before making such a decision—or is there no need for our approach to SCI to change at all?

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