

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 amnesic 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.

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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 pre-clinical 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

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 amnesic 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-evidenced 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 amnesic 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 amnesic 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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REFERENCES

- [1] Jessen F, Wolfsgruber S, Wiese B, Bickel H, Mösch E, Kaduszkiewicz H, Pentzek M, Riedel-Heller SG, Luck T, Fuchs A, Weyerer S, Werle J, van den Bussche H, Scherer M, Maier W, Wagner M; German Study on Aging, Cognition and Dementia in Primary Care Patients (2014) AD dementia risk in late MCI, in early MCI, and in subjective memory impairment. *Alzheimers Dement* **10**, 76-83.
- [2] Rodda J, Dannhauser T, Cutinha DJ, Shergill SS, Walker Z (2011) Subjective cognitive impairment: Functional MRI during a divided attention task. *Eur Psychiat* **26**, 457-462.
- [3] Reisberg B, Shulman MB (2009) Commentary on 'A roadmap for the prevention of dementia II: Leon Thal Symposium 2008. 'Subjective cognitive impairment as an antecedent of Alzheimer's dementia: Policy import. *Alzheimers Dement* **5**, 154-156.
- [4] Dik MG, Jonker C, Comijs HC, Bouter LM, Twisk JW, van Kamp GJ, Deeg DJ (2011) Memory complaints and APOE-epsilon4 accelerate cognitive decline in cognitively normal elderly. *Neurology* **57**, 2217-2222.
- [5] van Oijen M, de Jong FJ, Hofman A, Koudstaal PJ, Breteler MMB (2007) Subjective memory complaints, education, and risk of Alzheimer's disease. *Alzheimers Dement* **3**, 92-97.
- [6] O'Connor DW, Pollitt PA, Roth M, Brook PB, Reiss BB (1990) Memory complaints and impairment in normal, depressed, and demented elderly persons identified in a community survey. *Arch Gen Psychiat* **47**, 224-227.
- [7] Jorm AF, Christensen H, Korten AE, Jacomb PA, Henderson AS (2001) Memory complaints as a precursor of memory impairment in older people: A longitudinal analysis over 7-8 years. *Psychol Med* **31**, 441-449.
- [8] Balash Y, Mordechovich M, Shabtai H, Giladi N, Gurevich T, Korczyn AD (2013) Subjective memory complaints in elders: Depression, anxiety, or cognitive decline? *Acta Neurol Scand* **127**, 344-350.
- [9] Reisberg B, Shulman MB, Torossian C, Leng L, Zhu W (2010) Outcome over seven years of healthy adults with and without subjective cognitive impairment. *Alzheimers Dement* **6**, 11-24.
- [10] Edwards ER, Lindquist K, Yaffe K (2004) Clinical profile and course of cognitively normal patients evaluated in memory disorders clinics. *Neurology* **62**, 1639-1642.
- [11] Geerlings MI, Jonker C, Bouter LM, Adér HJ, Schmand B (1999) Association between memory complaints and incident Alzheimer's disease in elderly people with normal baseline cognition. *Am J Psychiatry* **156**, 531-537.
- [12] Jessen F, Wiese B, Bachmann C, Eifflaender-Gorfer S, Haller F, Kölsch H, Luck T, Mösch E, van den Bussche H, Wagner M, Wollny A, Zimmermann T, Pentzek M, Riedel-Heller SG, Romberg HP, Weyerer S, Kaduszkiewicz H, Maier W, Bickel H; German Study on Aging, Cognition and Dementia in Primary Care Patients Study Group (2010) Prediction of dementia by subjective memory impairment: Effects of severity and temporal association with cognitive impairment. *Arch Gen Psychiatry* **67**, 414-422.
- [13] Stewart R, Godin O, Crivello F, Maillard P, Mazoyer B, Tzourio C, Dufouil C (2011) Longitudinal neuroimaging correlates

- of subjective memory impairment: 4-year prospective community study. *Br J Psychiatry* **198**, 199-205.
- [14] Tales A, Leonards U, Bompas A, Snowden RJ, Philips M, Porter G, Haworth J, Wilcock G, Bayer A (2012) Intraindividual reaction time variability in aMCI: A precursor to dementia? *J Alzheimers Dis* **32**, 65-75.
- [15] Bayer A, Phillips M, Porter G, Leonards U, Bompas A, Tales A (2014) Abnormal inhibition of return in mild cognitive impairment: Is it specific to the presence of prodromal dementia? *J Alzheimers Dis* **40**, 177-189.
- [16] Bai F, Liao W, Watson DR, Shi Y, Wang Y, Yue C, Teng Y, Wu D, Yuan Y, Jia J, Zhang Z (2011). Abnormal whole-brain functional connection in amnesic mild cognitive impairment patients. *Behav Brain Res* **216**, 666-672.
- [17] Golob EJ, Miranda GG, Johnson JK, Starr A (2001) Sensory cortical interactions in aging, mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging* **1**, 755-763.
- [18] Babiloni C, Visser PJ, Frisoni G, De Deyn PP, Bresciani L, Jelic V, Nagels G, Rodriguez G, Rossini PM, Vecchio F, Colombo D, Verhey F, Wahlund LO, Nobili F (2010) Cortical sources of resting EEG rhythms in mild cognitive impairment and subjective memory complaint. *Neurobiol Aging* **31**, 1787-1798.
- [19] Haller S, Nguyen D, Rodriguez C, Emch J, Gold G, Bartsch A, Lovblad KO, Giannakopoulos P (2010) Individual prediction of cognitive decline in mild cognitive impairment using support vector machine-based analysis of diffusion tensor imaging data. *J Alzheimers Dis* **22**, 315-327.
- [20] Li H, Liang Y, Chen K, Li X, Shu N, Zhang Z, Wang Y (2013) Different patterns of white matter disruption among amnesic mild cognitive impairment subtypes: Relationship with neuropsychological performance. *J Alzheimers Dis* **36**, 365-376.
- [21] Missonnier P, Herrmann FR, Michon A, Fazio-Costa L, Gold G, Giannakopoulos P (2010) Early disturbance of gamma band dynamics in mild cognitive impairment. *J Neural Trans* **117**, 489-498.
- [22] Binnewijzend MA, Schoonheim MM, Sanz-Arigita E, Wink AM, van der Flier WM, Tolboom N, Adriaanse SM, Damoiseaux JS, Scheltens P, van Berckel BN, Barkhof F (2012) Resting-state fMRI changes in Alzheimer's disease and mild cognitive impairment. *Neurobiol Aging* **33**, 2018-2028.
- [23] Bai F, Zhang Z, Yu H, Shi Y, Yuan Y, Zhu W, Zhang X, Qian Y (2008) Default-mode network activity distinguishes amnesic types of MCI from healthy ageing: A combined structural and resting-state functional MRI study. *Neurosci Lett* **438**, 111-115.
- [24] Zhu DC, Majumdar S, Korolev IO, Berger KL, Bozoki AC (2013) Alzheimer's disease and amnesic mild cognitive impairment weakens connections within the default-mode network: A multi-modal imaging study. *J Alzheimers Dis* **34**, 969-984.
- [25] Gorus E, De Raedt R, Lambert M, Lemper J-C, Mets T (2008) Reaction times and performance variability in normal aging, mild cognitive impairment and Alzheimer's disease. *J Geriatric Psychiatry Neurol* **21**, 204-218.
- [26] McLaughlin PM, Borrie MJ, Murtha SJE (2010) Shifting efficacy, distribution of attention and controlled processing in two subtypes of mild cognitive impairment: Response time performance and intraindividual variability on a visual search task. *Neurocase* **16**, 408-417.
- [27] Phillips M, Rogers P, Haworth J, Bayer A, Tales A (2013) Intra-individual reaction time variability in mild cognitive impairment and Alzheimer's disease: Gender, processing load and speed factors. *PLoS One* **8**, e65712.
- [28] Van Dam NT, Sano M, Mitsis EM, Grossman HT, Gu X, Park Y, Hof PR, Fan J (2013) Functional neural correlates of attentional deficits in amnesic mild cognitive impairment. *PLoS One* **8**, e54035.
- [29] Graewe B, Lemos R, Ferreira C, Santana I, Farivar R, De Weerd P, Castelo-Branco M (2013) Impaired processing of 3D motion-defined faces in mild cognitive impairment and healthy aging: An fMRI study. *Cereb Cortex* **23**, 2489-2499.
- [30] Bublak P, Redel P, Sorg C, Kurz A, Förstl H, Müller HJ, Schneider WX, Finke K (2011) Staged decline of visual processing capacity in mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging* **32**, 1219-1230.
- [31] Redel P, Bublak P, Sorg C, Kurz A, Förstl H, Müller HJ, Schneider WX, Perneczky R, Finke K (2012) Deficits of spatial and task-related attentional selection in mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging* **33**, 195.e27-195.e42.
- [32] Alegret M, Boada-Rovira M, Vinyes-Junqué, Valero S, Espinosa A, Hernández I, Modinos G, Rosende-Roca M, Mauleón A, Becker JT, Tárraga L (2009) Detection of visuoperceptual deficits in preclinical and mild Alzheimer's disease. *J Clin Exp Neuropsychol* **31**, 860-867.
- [33] Deiber M-P, Ibañez V, Missonnier P, Herrman F, Fazio-Costa L, Gold G, Giannakopoulos P (Aging) (2009) Abnormal-induced theta activity supports early directed-attention network deficits in progressive MCI. *Neurobiol* **30**, 1444-1452.
- [34] Okonkwo O, Wadley VG, Ball K, Vance DE, Crowe M (2008) Dissociations in visual attention deficits among persons with mild cognitive impairment. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn* **15**, 492-505.
- [35] Levinoff EJ, Saumier D, Chertkow H (2005) Focused attention deficits in patients with Alzheimer's disease and mild cognitive impairment. *Brain Cog* **57**, 127-130.
- [36] Lu ZL, Neuse J, Madigan S, Doshier BA (2005) Fast decay of iconic memory in observers with MCI. *Proc Natl Acad Sci U S A* **102**, 1797-1802.
- [37] Tales A, Haworth J, Wilcock G, Newton P, Butler S (2008) Visual mismatch negativity highlights abnormal pre-attentive visual processing in mild cognitive impairment and Alzheimer's disease. *Neuropsychologia* **46**, 1224-1232.
- [38] Mowszowski LI, Hermens DF, Diamond K, Norrie L, Hickie IB, Lewis SJ, Naismith SL (2012) Reduced mismatch negativity in mild cognitive impairment: Associations with neuropsychological performance. *J Alzheimers Dis* **30**, 209-219.
- [39] Yamasaki T, Horie S, Muranaka H, Kaseda Y, Mimori Y, Tobimatsu S (2012) Relevance of *in vivo* neurophysiological biomarkers for mild cognitive impairment and Alzheimer's disease. *J Alzheimers Dis* **31**, S137-S154.
- [40] Raquel L, Figueiredo P, Santana I, Simões MR, Castelo-Branco M (2012) Temporal Integration of 3D coherent motion cues defining visual objects of unknown orientation is impaired in amnesic mild cognitive impairment and Alzheimer's disease. *J Alzheimers Dis* **28**, 885-896.
- [41] Risacher SL, Wudunn D, Pepin SM, MaGee TR, McDonald BC, Flashman LA, Wishart HA, Pixley HS, Rabin LA, Paré N, Englert JJ, Schwartz E, Curtain JR, West JD, O'Neill DP, Santulli RB, Newman RW, Saykin AJ (2013) Visual contrast sensitivity in Alzheimer's disease, mild cognitive impairment, and older adults with cognitive complaints. *Neurobiol Aging* **34**, 1133-1144.
- [42] Qing Y, Wang T, Su N, Xiao S, Kapoula Z (2013) Specific saccade deficits in patients with Alzheimer's disease at mild

- to moderate stage and in patients with amnesic mild cognitive impairment. *AGE* **35**, 1287-1298.
- [43] Dmitry L, Manzanares C, Zola SM, Buffalo EA, Agichtein E (2011) Detecting cognitive impairment by eye movement analysis using automatic classification algorithms. *J Neurosci Methods* **201**, 196-203.
- [44] Tales A, Snowden R, Haworth J, Wilcock G (2005) Abnormal spatial and non-spatial cueing effects in mild cognitive impairment and Alzheimer's disease. *Neurocase* **11**, 85-92.
- [45] Mandai PK, Joshi J, Saharan S (2012) Visuospatial perception: An emerging biomarker for Alzheimer's disease. *J Alzheimers Dis* **31**, S117-S135.
- [46] Fernandez-Duque D, Black SE (2006) Attentional networks in normal ageing and Alzheimer's disease. *Neuropsychology* **20**, 133-143.
- [47] Vannini P, Almkvist O, Dierks T, Lehmann C, Wahlund LO (2007) Reduced neuronal efficacy in progressive mild cognitive impairment: A prospective fMRI study on visuospatial processing. *Psychiatry Res* **156**, 43-47.
- [48] Tales A, Snowden R, Phillips M, Haworth J, Porter G, Wilcock GK, Bayer A (2011) Exogenous phasic alerting and spatial orienting in mild cognitive impairment compared to healthy ageing: Study outcome is related to target response. *Cortex* **47**, 180-190.
- [49] Tales A, Bayer A, Haworth J, Snowden R, Philips M, Wilcock G (2011) Visual search in mild cognitive impairment: A longitudinal study. *J Alzheimers Dis* **24**, 151-160.
- [50] Mandal P, Joshi J, Saharan S (2012) Visuospatial perception: An emerging biomarker for Alzheimer's disease. *J Alzheimers Dis* **31**, S117-S135.
- [51] Perry RJ, Hodges JR (2003) Dissociation between top-down attentional control and the time course of visual attention as measured by attentional dwell time in patients with mild cognitive impairment. *Eur J Neurosci* **18**, 221-226.
- [52] Sorg C, Myers N, Redel P, Bublak P, Riedl V, Manoliu A, Pernecky R, Grimmer T, Kurz A, Förstl H, Drzezga A, Müller HJ, Wohlschläger AM, Finke K (2012) Asymmetric loss of parietal activity causes spatial bias in prodromal and mild Alzheimer's disease. *Biol Psychiatry* **71**, 798-804.
- [53] Drzezga A, Grimmer T, Peller M, Wernke M, Siebner H, Rauschecker JP, Schwaiger M, Kurz A (2005) Impaired cross-modal inhibition in Alzheimer's disease. *PLoS Med* **2**, e288.
- [54] Tales A, Porter G (2008) Visual attention-related processing in Alzheimer's disease. *Rev Clin Gerontol* **18**, 229-243.
- [55] Rahman TTA, Mohamed ST, Albanouby MH, Bekhet HF (2011) Central auditory processing in elderly with mild cognitive impairment. *Geriatr Gerontol Int* **11**, 304-308.
- [56] Sun GH, Raji CA, MacEachern MP, Burke JF (2012) Olfactory identification testing as a predictor of the development of Alzheimer's disease: A systematic review. *Laryngoscope* **122**, 1455-1462.
- [57] Steinbach S, Hundt W, Vaitl A, Heinrich P, Förster S, Bürger K, Zahnert T (2010) Taste in mild cognitive impairment and Alzheimer's disease. *J Neurol* **257**, 238-246.
- [58] Stephen JM, Montañó R, Donahue CH, Adair JC, Knoefel J, Qualls C, Hart B, Ranken D, Aine CJ (2010) Somatosensory responses in normal aging, mild cognitive impairment, and Alzheimer's disease. *Neural Transm* **117**, 217-225.
- [59] Metzger FG, Polak T, Agha Zadeh Y, Ehrlis AC, Fallgatter AJ (2012) Vagus somatosensory evoked potentials – A possibility for diagnostic improvement in patients with mild cognitive impairment. *Dement Geriatr Cog Disord* **33**, 289-296.
- [60] Wu J, Yang J, Yu Y, Li Q, Nakamura N, Shen Y, Ohta Y, Yu S, Abe K (2012) Delayed audiovisual integration of patients with mild cognitive impairment and Alzheimer's disease compared with normal aged controls. *J Alzheimers Dis* **32**, 317-328.
- [61] Yan, J, Rountree S, Massman P, Doody R, Li H (2008) Alzheimer's disease and mild cognitive impairment deteriorate fine movement control. *J Psychiatr Res* **42**, 1203-1212.
- [62] Westerberg C, Mander B, Florczak S, Weintraub S, Mesulam M, Zee PC, Paller KA (2012) Concurrent impairments in sleep and memory in amnesic mild cognitive impairment. *J Int Neuropsychol Soc* **18**, 490-500.
- [63] Collins O, Dillon S, Finucane C, Lawlor B, Kenny RA (2012) Parasympathetic autonomic dysfunction is common in mild cognitive impairment. *Neurobiol Aging* **33**, 2324-2333.
- [64] Rizzo M, Anderson SW, Dawson J, Myers R, Ball K (2000) Visual attention impairments in Alzheimer's disease. *Neurology* **54**, 1954-1959.
- [65] Cowan N (1988) Evolving conceptions of memory storage, selective attention, and their mutual constraints within the human information processing system. *Psychol Bull* **104**, 163-191.
- [66] Fukui T, Lee E (2009) Visuospatial function is a significant contributor to functional status in patients with Alzheimer's disease. *Am J Alzheimers Dis Other Dement* **24**, 313-321.
- [67] Shin MB, Han SJ, Jung JH, Kim JE, Fregni F (2011) Effect of mild cognitive impairment on balance. *J Neurol Sci* **305**, 121-125.
- [68] Aggarwal NT, Wilson RS, Beck TL, Bienias JL, Bennett DA (2006) Motor dysfunction in mild cognitive impairment and the risk of incident Alzheimer's disease. *Arch Neurol* **63**, 1763-1769.
- [69] Salek Y, Anderson N, Sergio L (2011) Mild cognitive impairment is associated with impaired visual-motor planning when visual stimuli and actions are incongruent. *Eur J Neurol* **66**, 283-293.
- [70] Frittelli C, Borghetti D, Iudice G, Bonanni E, Maestri M, Tognoni G, Pasquali L, Iudice A (2008) Effects of Alzheimer's disease and mild cognitive impairment on driving ability: A controlled clinical study by simulated driving test. *Int J Geriatr Psychiat* **24**, 232-238.
- [71] Wang Y, Risacher SL, West JD, McDonald BC, MaGee TR, Farlow MR, Gao S, O'Neill DP, Saykin AJ (2013) Default-mode network connectivity in older adults with cognitive complaints and amnesic mild cognitive impairment. *J Alzheimers Dis* **35**, 751-760.
- [72] Maestu F, Baykova E, Ruiz JM, Montejó P, Montenegro M, Llanero M, Solesio E, Gil P, Yubero R, Paul N, Pozo F, Nevado A (2011) Increased biomagnetic activity in healthy elderly with subjective memory complaints. *Clin Neurophysiol* **122**, 499-505.
- [73] Selnes P, Fjell AM, Gjerstad L, Bjørnerud A, Wallin A, Due-Tønnessen P, Grambaite R, Stenset V, Fladby T (2012) White matter imaging changes in subjective and mild cognitive impairment. *Alzheimers Dement* **8**, S112-S121.
- [74] Peter J, Lukas S, Abdulkadir A, Boecker H, Heneka M, Wagner M (2014) Gray matter atrophy pattern in elderly with subjective memory impairment. *Alzheimers Dement* **10**, 99-108.
- [75] Scheef L, Spottke A, Daerr M, Joe A, Striepens N, Kölsch H, Popp J, Daamen M, Gorris D, Heneka MT, Boecker H, Biersack HJ, Maier W, Schild HH, Wagner M, Jessen F (2012) Glucose metabolism, gray matter structure, and memory decline in subjective memory impairment. *Neurology* **79**, 1332-1339.
- [76] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Jr., Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens

- P, Carrillo MC, Thies B, Weintraub S, Phelps CH (2011) The diagnosis of dementia due to AD: Recommendations from the National Institute on Ageing-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 263-269.
- [77] Department of Health (2009) Living well with dementia: A national dementia strategy. <https://www.gov.uk/government/publications/living-well-with-dementia-a-national-dementia-strategy>
- [78] Dubois B, Feldman HH, Jacova C, Cummings JL, Dekosky ST, Barberger-Gateau P, Delacourte A, Frisoni G, Fox NC, Galasko D, Gauthier S, Hampel H, Jicha GA, Meguro K, O'Brien J, Pasquier F, Robert P, Rossor M, Salloway S, Sarazin M, de Souza LC, Stern Y, Visser PJ, Scheltens P (2010) Revisiting the definition of Alzheimer's disease: A new lexicon. *Lancet* **9**, 1118-1127.
- [79] Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR Jr, Kaye J, Montine TJ, Park DC, Reiman EM, Rowe CC, Siemers E, Stern Y, Yaffe K, Carrillo MC, Thies B, Morrison-Bogorad M, Wagster MV, Phelps CH (2011) Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 280-292.
- [80] Abdulrab K, Heun R, Abdulrab K, Heun R (2008) Subjective memory impairment. A review of its definitions indicates the need for a comprehensive set of standardised and validated criteria. *Eur Psychiatry* **23**, 321-330.
- [81] Henriksen K, O'Bryant SE, Hampel H, Trojanowski JQ, Montine TJ, Jeromin A, Blennow K, Lönneborg A, Wyss-Coray T, Soares H, Bazenet C, Sjögren M, Hu W, Lovestone S, Karsdal MA, Weiner MW; Blood-Based Biomarker Interest Group (2013) The future of blood-based biomarkers for Alzheimer's disease. *Alzheimers Dement* **10**, 115-131.
- [82] Selnes P, Aarsland D, Bjørnerud A, Gjerstad L, Wallin A, Hessen E, Reinvang I, Grambaite R, Auning E, Kjærvi VK, Due-Tønnessen P, Stenset V, Fladby T (2013) Diffusion tensor imaging surpasses cerebrospinal fluid as predictor of cognitive decline and medial temporal lobe atrophy in subjective cognitive impairment and mild cognitive impairment. *J Alzheimers Dis* **3**, 723-736.
- [83] Stern Y (2012) Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol* **11**, 1006-1012.
- [84] Liu Y, Cai Z-L, Xue S, Zhou X, Wu F (2013) Proxies of cognitive reserve and their effects on neuropsychological performance in patients with mild cognitive impairment. *J Clin Neurosci* **20**, 548-553.
- [85] Lin P-J, Neuman PJ (2013) The economics of mild cognitive impairment. *Alzheimers Dement* **9**, 58-62.