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Review

Magnetic resonance spectroscopy in mild cognitive impairment: Systematic review and meta-analysis

Q1 Shankar Tumati[a,b,*], Sander Martens[a,b], André Aleman[a,b]

[a] Neuroimaging Center, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[b] Department of Neuroscience, University Medical Center Groningen, Groningen, The Netherlands

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ABSTRACT

Research using proton magnetic resonance spectroscopy (MRS) can potentially elucidate metabolite changes representing early degeneration in Mild Cognitive Impairment (MCI), an early stage of dementia. We integrated the published literature using meta-analysis to identify patterns of metabolite changes in MCI. 29 MRS studies (with a total of 607 MCI patients and 862 healthy controls) were classified according to brain regions. Hedges' g was used as effect size in a random effects model. N-Acetyl Aspartate (NAA) measures were consistently reduced in posterior cingulate (PC), hippocampus, and the paratrigonal white matter (PWM). Creatine (Cr) concentration was reduced in the hippocampus and PWM. Choline (Cho) concentration was reduced in the hippocampus while Cho/Cr ratio was raised in the PC. Myo-inositol (mI) concentration was raised in the PC and mI/Cr ratio was raised in the hippocampus. NAA/mI ratio was reduced in the PC. NAA may be the most reliable marker of brain dysfunction in MCI though mI, Cho, and Cr may also contribute towards this.

Contents

* Corresponding author at: Neuroimaging Center, P.O. Box 196, 9700 AD Groningen, The Netherlands. Tel.: +31 50 3634955.
E-mail address: s.tumati@umcg.nl (S. Tumati).

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1. Introduction

With an aging population that is getting increasingly older, the prevalence of dementia is increasing. Unfortunately, the diagnosis of dementia is typically made at a stage in which the underlying pathology has reached an advanced and irreversible state. In the past decade, Mild Cognitive Impairment (MCI) has been identified as an early stage on the path towards dementia, and it may thus be important to predict the development of dementia at a stage when it can still be treated, thereby stopping or at least delaying the progression to dementia. The criteria for the diagnosis of MCI, however, are still under active development. In order to understand the pathophysiology of this early stage of cognitive deterioration, research using neuroimaging is necessary. Besides volumetric analyses of grey and white matter, based on Magnetic Resonance Imaging (MRI) scans, and functional MRI of brain activation differences, neuroimaging using proton magnetic resonance spectroscopy (MRS) can yield information regarding metabolite changes in the brain representing early degeneration.

The criteria for the diagnosis of MCI were defined for the first time in 1999 by Petersen and colleagues with the purpose of capturing the prodromal state of Alzheimer's Disease (AD) (Petersen et al., 1999). The criteria consist of having a memory complaint that is corroborated by an informant and is documented by appropriate testing. In addition, the subject should be normal in other cognitive domains, be unimpaired in daily living and not demented. However, observations suggested that subjects with memory complaints may eventually progress not only to AD but also to other forms of dementia or psychiatric ailments (Petersen et al., 2001; Dubois and Albert, 2004). In 2004, the criteria were therefore expanded to include amnestic MCI (aMCI) and non-amnestic MCI (naMCI) with impairments in either a single domain or multiple domains accounting for diverse etiologies that cause memory impairments (Winblad et al., 2004). Reports of prevalence of MCI vary widely, ranging from 3 to 42%, with an increasing frequency observed from the age of 65 to 85 years. The majority of the cases are of the amnestic type. This cohort of individuals has an annual conversion rate to AD of 3–17%, which is much higher than that for the general population (1–2%) (Ward et al., 2012). However, the outcomes of MCI are not consistent. While most MCI patients progress to dementia, a part of this cohort remains stable. That is, these patients are impaired, but do not progress to dementia. A small fraction may even improve to be categorized as no longer being impaired (Fisk and Rockwood, 2005; Palmer et al., 2008; Ritchie, 2004; Schonknecht et al., 2005; Solfrizzi et al., 2004).

Being a relatively new disorder, MCI continues to be characterized, with the diagnostic criteria being regularly updated to reflect the improved understanding of the disease (Albert et al., 2011). An important drawback of the current criteria is that they capture a clinical syndrome and not the disease. As a result, individual studies often use various definitions for the diagnosis of MCI (Matthews et al., 2008). This results in the use of a definition of MCI that is inconsistent across studies that in turn affects meaningful interpretation of the outcomes from various studies. This inconsistency may be an important reason for the variable results among epidemiological studies, and there is thus a clear need for standard criteria for the diagnosis of MCI (Ward et al., 2012). As the burden of AD is projected to increase in the near future, the interest in MCI as a predictor has also increased manifold (Petersen et al., 2009). Research on biomarkers, such as brain abnormalities, can ultimately benefit reliability and early identification of the condition. Moreover, research on the neural basis of MCI could contribute to the necessary knowledge for developing evidence-based interventions.

MRS is a novel technique that provides a detailed picture of the in vivo biochemistry of the brain (Duarte et al., 2012). To that end, a standard MRI scanner is used to acquire the spectrum that reflects the concentration of metabolites in the brain. Unfortunately, only a few metabolites in the brain are present in sufficiently large concentrations to be detected by MRI scanners approved for safe use in humans. The detection of the metabolites is partly dependent on the strength of the field, with higher field strengths required to detect metabolites present in low concentrations. The metabolites that are present in high concentrations and thus most commonly studied are N-Acetyl Aspartate (NAA), choline (Cho), creatine (Cr), myo-inositol (ml), and glutamate and glutamine (Glx). Each of these metabolites is sensitive to a different pathological process in the brain. NAA is thought to be synthesized only within neurons and its concentration reflects neuronal density and viability (Block et al., 2002; De Stefano et al., 1995). It has a peak at 2.0 ppm in the spectra (Pouwels and Frahm, 1998). The choline signal is mainly contributed by the presence of free glycerophosphocholine and phosphocholine. These compounds are immobile when part of the cellular membrane, but become mobile and contribute to the Cho signal when the cell membrane has broken down (Klein, 2000). The Cho signal has a peak at 3.2 ppm and is a marker for membrane integrity (Miller et al., 1996). Creatine and phosphocreatine are markers for energy metabolism with a peak at 3.03 ppm. The levels of Cr are thought to be fairly constant and hence used as a reference value (Pouwels and Frahm, 1998), though there are reports disputing this claim (Kreis et al., 1993; Li et al., 2003). Myo-inositol is an osmolyte and has a role in the second messenger system. It has a peak at 3.55 ppm and it is a marker for glial activation (Fisher et al., 2002). Glutamate and glutamine (Glx), key amino acids in the brain, appear as a single peak at 2.1–2.3 ppm in the spectrum. The peak can be resolved into individual wavelets in high-field MRI or less accurately by post-processing methods. A second smaller peak is also seen at 3.75 ppm (Duarte et al., 2012; Mountford et al., 2010). Zhu and Barker (2011) provide a recent review on MRS.

Magnetic resonance spectroscopy has many advantages. The MRS spectrum is easily obtained from a conventional MRI machine requiring relatively little time. It is possible to obtain spectrum either from a single voxel (SV) of interest or from multiple areas (Multivoxel Spectroscopy (MVS)) simultaneously making it

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