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# Mild Cognitive Impairment – Prospects for Prognosis and Management

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## ABSTRACT

*The term mild cognitive impairment (MCI) has traditionally been used to refer to a transitional period between normal cognitive function and clinically probable Alzheimer's disease (AD). Many studies report high reversion rates, however, with some 30% to 50% of those diagnosed with MCI reverting to "normal" cognition at subsequent follow-up. The detection of differentiable predisposing factors, reflected in the dichotomy between the annual reversion rate to normal cognition and the conversion rate to dementia, indicates that there are modifiable factors that may be contributing to cognitive decline. The clinical prospect for dementia and the presence of these predisposing factors have together made a strong case for early diagnosis and therapeutic intervention. Current efforts seek to identify tools capable of resolving the causal ambiguities inherent in MCI and to develop therapeutic avenues addressing such underlying aspects before long lasting and irreversible cognitive loss. This review explores three arenas for which there is especial promise for determining and modulating prognosis: in the diagnostic realm, novel neuroimaging procedures and biomarkers and, in the domain of therapy, network based non-invasive neurostimulation therapies. Particular examples include novel structural and dynamical MRI procedures for assessing connectivity and its alterations during disease, inflammation and miRNA markers, and non-invasive procedures for rehabilitating deteriorating brain functions. The advances occurring in these select areas indicate that the determination of MCI's multi-etiology is a realistic goal that can ground prognosis assessment and therapeutic outcome.*

## Keywords

Mild cognitive impairment, Resting state fMRI, Dementia, Amnestic MCI, Hippocampal memory network.

## Introduction

The term mild cognitive impairment (MCI) has traditionally been used to refer to a transitional period between normal cognitive function and clinically probable Alzheimer's disease (AD) [1-3]. The inference behind this understanding has thus causally linked a measured decline in cognitive ability over time with a clinically defined entity having a high probability of transition to dementia. Among those identified as having MCI, this presumption has been buttressed by a documented 5% to 10% annual rate of progression to dementia, a rate much higher than the 1% to 2% incidence per year observed within the general population.

Challenging this coupling, however, many studies report high reversion rates, with some 30% to 50% of those diagnosed with MCI reverting to "normal" cognition at subsequent follow-up [4-6]. Multiple factors have been discovered that are associated with improved likelihood of reverting to a normal cognitive status, including single domain impairment, the presence of depression, use of anticholinergic medications, and an absence of the apolipoprotein E ε4 allele, among others [6]. It has become increasingly clear, therefore, that mild cognitive impairment is a concept encompassing much more than a preclinical state of AD and useful in itself as a clinical and research entity [2].

Besides a principal cognitive impairment that may characterize MCI as amnestic or non-amnestic, or one involving several cognitive domains, each of these clinical presentations can also have multiple etiologies. For example, although a

neurodegenerative process could be the etiology of a patient with amnestic MCI, memory impairment might also evolve from other conditions such as ischemia, trauma, or metabolic disturbance [7]. Accompanying these conditions may be additional factors that exacerbate the presentation, such as psychiatric illness [8,9], or somatic conditions like cardiovascular disease [9].

Various medical disorders are also known to have a positive association with MCI, including Parkinson Disease, traumatic brain injury, cerebrovascular rupture, and Huntington disease [6,10]. In these cases, symptoms usually manifest first followed by cognitive impairment later. In other instances, the cognitive impairment or behavioral symptoms can manifest early and typically prior to the disease course. This latter set is often observed in disorders primarily affecting cognition, such as Alzheimer disease, vascular dementia, Lewy body disease, prion disease, and frontotemporal dementia. In these disorders, there is frequently a prodromal stage displaying MCI symptoms, which can go undiagnosed but later progress to dementia.

In view of these widely varying manifestations, the Diagnostic and Statistical Manual of Mental Disorders 5th Edition [11] currently classifies MCI as a "mild neurocognitive disorder not substantially interfering with instrumental activities of daily living and displaying a subjective and objective decline from a previous level of functioning in 1 or more of 6 cognitive domains". These domains have been specified as learning and memory, social functioning, language, visuospatial function, complex attention, and executive functioning. On the other hand, because the prevailing understanding of the term "mild cognitive impairment" has often referred to a decline in the ability to learn new information or recall stored information, this has led to a broad distinction in classification of MCI as either "amnestic" or "nonamnestic, where amnestic MCI refers to impairment purely in one's ability to recall stored information and nonamnestic MCI refers to an impairment in 1 or more of the other cognitive domains, with memory remaining relatively intact [6].

The detection of differentiable predisposing factors, reflected in the dichotomy between the annual reversion rate to normal cognition and the conversion rate to dementia, indicates that there are modifiable factors that may be contributing to cognitive decline. In conjunction with these predispositional aspects, the differential prognosis of influencing factors from various etiological groups have made a strong case for early diagnosis and therapeutic intervention. Accordingly, major research efforts have sought to identify tools capable of resolving the causal ambiguities inherent in MCI and to develop therapeutic avenues addressing such underlying aspects before long lasting and irreversible cognitive loss.

Clinical assessment employing a cognitive battery has been the standard approach adopted for detection of MCI, usually following self or family member reporting of cognitive difficulty [6,12]. Etiological determinations and intervention, on the other hand, have proved more difficult, limiting their use to clinical trials or exploratory research. Significant progress during the past decade in the development of procedures for distinguishing underlying MCI causes have nonetheless made diagnostic outcomes more certain and therapeutic intervention more promising [13-15]. The prospects for objective assessment and management in the clinical realm, therefore, have opened an avenue to resolution of the question of whether a salutary prognosis is obtainable and which factors may need to be addressed to achieve it. Indeed, prognosis is at the heart of current thinking on MCI. There are numerous treatable factors, which when present can contribute to MCI, including metabolic deficiencies, depression, and polypharmacy, among others [6].

This paper will review three arenas for which there is especial promise for prognosis including, in the diagnostic realm, novel neuroimaging procedures and biomarkers and, in the domain of therapy, network based non-invasive neurostimulation therapies. The selection of these arenas is intended to offer a window into the expanding arena of MCI prognosis by providing an up to date focus on how well current advances in select areas of MCI research can facilitate the determination of etiology and how that determination in turn can inform successful therapy.

## Neuroimaging for MCI Diagnosis

Current neuroimaging techniques – magnetic resonance imaging (MRI), cerebral blood flow-single photon emission computed tomography (CBF-SPECT), fluorodeoxyglucose-positron emission tomography (FPET), and diffusion tensor imaging (DTI) - are essential and to date widely employed for the structural evaluation of MCI subjects. For these subjects, imaging procedures have two goals. First, the identification of non-dementia causes of cognitive decline – e.g., a brain tumor - and so provision for a differential diagnosis for AD. Second, for putative cases of AD, neuroimaging can both help predict the likelihood of developing dementia and assess neurodegenerative progression. Structural brain imaging can thus provide diagnostic information not only about the etiological basis of the pathology causing cognitive decline but also make inferences about long term dementia prognosis [6].

MRI or computerized tomography can be useful, for example, in assessing overall brain structure, which can eliminate the possibility of conditions that are due to vascular or trauma effects. By revealing white matter, hyperintensities or ischemic small vessel changes cognitive impairment can be distinguished from vascular dementia or other causes. With T1-weighted MRI the topographic distribution of cortical and subcortical atrophy can also be assessed. Subsequent follow-up examinations can record disease progression by determining structural tissue changes based on calculations of volume changes. Employing these volumetric and morphometric techniques, for instance, it is possible to assess whether the CA1 region of the hippocampus is structurally compromised, a key indicator of amnestic mild cognitive impairment [16].

Besides these traditional applications, new structural MRI procedures are building on fundamental principles affecting image acquisition and advanced mathematical transformation

methods for feature extraction. Coupled with improved procedural methods for registration and processing current advances are enabling submillimetric resolution in short periods of acquisition time and providing novel multi-parametric assays [17,18]. In the case of diffusion tensor imaging, for example, MRI can document hydrogen-based changes in the MRI signal at a microstructural level, providing measurements of the restricted diffusion of water in tissue and thus the obtaining of neural tract images. In patients with mild cognitive impairment, diffusion tensor imaging has detected tract abnormalities in brain regions that include the hippocampus, thalamus, and posterior white matter.

Increasingly, structural imaging is being supplemented by functional and dynamical imaging procedures for the assessment of functional or dynamic impairments that may give rise to MCI symptoms. Positron emission tomography (PET) scanning using F-fluorodeoxyglucose is a traditional but still frequently used method of dynamical imaging for assessing brain activity. In this procedure F-fluorodeoxyglucose uptake is used to assess tissue specific glucose usage, where consumption corresponds to increased or decreased uptake of the radioactive tracer. Patients displaying glucose hypometabolism within the temporal or parietal lobes have a higher risk of progression from MCI to dementia. Due to its emphasis on metabolic integrity, PET scanning is more reflective of changes in neural functional capacity and so is more sensitive than structural MRI imaging for diagnosing "early" dementia consistent with MCI [19].

Most growth in methodological development has occurred in the functional assessment of brain activity. Central to these approaches is functional MRI (fMRI), which monitors neural activity indirectly by measuring the BOLD signal originating from the brain vasculature. Despite the slowness of the BOLD signal, which is slightly over a hundred fold slower than the neural activity it measures, the high spatial resolution (nearly 1 mm) of the procedure enables the recording of sources of activity within very narrow spatial zones.

Building on this capability tools for functional brain diagnosis are rapidly acquiring new ways of assessing functional impairments. These now include techniques for making inferences about interregional connectivity and causal relationships – termed functional and effective connectivity, respectively. Functional connectivity determinations extend fMRI measurements of brain activity by providing likelihood estimates of functional associations between neural activity zones, capturing deviations from independence between distributed and often spatially remote neuronal units based on statistical parameters, such as covariance, spectral coherence, or phase-locking. (Since functional connectivity is a fundamentally statistical concept, it is often calculated between all elements of a system, regardless of whether these elements are connected by direct structural links.) Because these new methods of fMRI imaging can assess relationships between activity zones, they enable the construction of connectivity maps between regional sites. Pathological associations between brain regions that are so linked can be detected from variations in such maps.

Models of effective connectivity complement functional connectivity determinations through their assessment of the causal influences that system elements exert over one another, i.e., the directionality of influence. Inferences of causality assist in studies of the functional integration of neuronal populations and are used to interpret the mechanisms that underlie neuronal dynamics [21,22]. Various models have been employed for inferring effective connectivity from fMRI data, including structural equation modelling (SEM), multivariate autoregressive models (MAR), GRANGER, and dynamic causal modelling (DCM).

Among the most widely employed approaches for assessing effective connectivity, DCM for fMRI is based on an input-output model for a system of n interacting brain regions. In this method, the neuronal population activity of each region is represented by a single state variable, which is perturbed by controlled inputs. DCM models report the time series changes of a system state vector vis a vis the system's resting state, which are mathematically approximated using a Taylor series approximation for nonlinear functions that describe the system. Using these functional and dynamical approaches it is possible to explore the dynamic character of brain activity under normal and pathological conditions.

A consistent observation in such functional studies is that regions with similar functional properties, such as the left and right somato-motor cortices, exhibit coherent BOLD fluctuations even in the absence of movement under resting conditions [23]. Multiple other 'resting state' networks have also been observed, including visual auditory, language dorsal and ventral attention systems, corticothalamic circuits and a frontal opercular network. Given the success of resting state functional connectivity for probing the brain's functional architecture in normal subjects, these approaches have been increasingly applied towards understanding brain disease [24]. Much evidence indicates that the causal influences coupling neuronal populations change with context, as for example processing demands that may relate to task performance or stimulus properties. These techniques have therefore been used to determine how the networks undergo change with various task or other perturbation regimes [25] in disease states.

One of the most widely identified and frequently investigated resting state networks involves a set of regions that decrease activity during task performance, termed the default mode network (DMN) [24], which has been shown to be impaired in MCI and in Alzheimer's Disease (AD). The DMN is also involved in memory consolidation tasks. In AD, patients suffer from impaired DMN connectivity [26], which is correlated with a decreased FC in the DMN of AD patients relative to normal controls, especially between the posterior part of the cerebral cortex (Prec and PCC) and the anterior cingulate cortex (ACC) and medial prefrontal cortex (mPFC). The observed decline in FC in areas within the DMN has also been reported among MCI patients [27,28] suggesting that in at least one class of causal factors memory loss in MCI is also dispositional for AD.

On the other hand, while these procedures have successfully demonstrated their capacity for ascertaining causal linkages, the poor temporal resolution of the BOLD signal continues to incentivize ongoing research to develop approaches that can monitor neural activity at physiological time scales that directly correspond to the observations made at high spatial resolution [29]. A recent iteration on these attempts employs high strength magnetic fields to directly image neuronal activity, termed Direct Imaging of Neuronal Activity for functional MRI (DIANA-fMRI), with millisecond precision while retaining the original benefit of high spatial resolution. This novel approach has to date been used only in mice, where 9.4 T fields in conjunction with electrical whisker-pad stimulation directly captured the sequential propagation of activated nerve tracts along the thalamocortical pathway. If successful, DIANA-fMRI could open new avenues in brain science in which the flow of activity along neural networks is directly observed, a capability that would complement the current functional and effective connectivity methods.

## Biomarkers in MCI Prognosis

### Mild Cognitive Impairment in Relation to CSF and Plasma Biomarkers

MCI biomarkers have the potential to reveal underlying factors that are contributory in advance of clinical symptoms [30], since pathophysiological events are likely to precede clinically observable dysfunction. While biomarkers may be acquired from a spectrum of diagnostic indicators, including structural and functional neuroimaging, due to the ease with which bodily fluids can be obtained, molecular species obtained from such fluids have been the chief source used for biomarker identification and include cerebrospinal fluids or blood.

Among these, cerebrospinal fluid (CSF) Aβ1-42 and tau, have shown promising results in improving the prediction of which MCI subjects will develop AD. A combination of Aβ1–42 and Tau, for example, display a sensitivity as high as 95% and a specificity of 83% in detecting MCI subjects that went on to develop AD [31]. These biomarker measurements mainly reflect brain amyloidosis, apparent in CSF as Aβ42 and neurodegeneration as CSF tau [32,33]. These findings are consistent with blood plasma determinations where differential longitudinal changes in plasma Aβ levels are seen between cognitively stable individuals and those who go on to develop AD [31]. Lower ApoA1, ApoA2 and ApoH levels and a higher ApoB/ApoA1 ratios have also been associated with a higher risks of cognitive decline when measured over two years in cognitively normal individuals, with ApoA1 providing the most accurate predictor of decline.

Besides prognosis, biomarkers can also provide a differential diagnosis [34]. Nutritional insufficiencies leading to MCI that could serve as prospective biomarkers include elevated high-density lipoprotein (HDL), high folate, and low bilirubin levels. Low CSF S-adenosylmethionine (SAM) and high theobromine have been associated with a clinical progression to dementia, while cholesterol, iron, and 1,25(OH)2 vitamin D have been correlated with cognitive decline.

### Inflammation Markers

Another class of biomarkers for MCI includes those, which reveal inflammation processes that may potentially lead to MCI. Thymic output is known to decrease with age resulting in [35] a reduced ability to clear novel pathogens and an elevation in T-cell populations that are pro-inflammatory. Correspondingly, there is an increase in the cellular production of proinflammatory mediators, such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL)-6 and IL-1β in the serum of elderly individuals [36] that can cause brain tissue damage. Supporting this, correlations between inflammation and cognitive impairment have been reported in several human studies [37,38] suggesting a causative relationship leading to MCI. In a cohort of 1000 individuals [39] serum levels of TNF-α were correlated with a two-fold increase in the rate of cognitive decline over 6 months in nearly half of all study participants, whereas individuals with low serum levels of TNF-α showed no cognitive decline over the same period. In another study [40] a cohort of 3,000 White and African Americans having a mean age of 74 years were assessed for cognitive function and inflammatory factors. Individuals having the highest tertile of C-reactive protein (CRP) or IL-6 scored nearly two points lower on a Modified Mini-Mental State Examination. These scores declined further over the subsequent 2 years of study in comparison with those who had initially scored in the lowest tertile for CRP or IL-6.

## Micro RNA (miRNA) in the Diagnosis of MCI and AD

Micro RNAs (miRNA) are short (19–24 nucleotide long) non-coding RNAs that regulate gene expression and play a significant role in brain and neuronal development. Brain aging is known to be associated with altered miRNA expression, where miRNAs can modulate synaptic plasticity, inflammation, or lipid metabolism, which may be altered in association with cognitive decline [39] and could be involved in MCI related impairment. Various studies have identified miRNAs that are specifically altered in parallel with MCI symptoms [42]. The miR-132 and miR-134 families, for example, have been proposed as potential predictive markers for preclinical onset of MCI. Serum miRNAs like miR-93 and miR-146a are also elevated in MCI individuals, while miR-143 levels are reduced. Because the latter markers are downregulated in AD, miR-143 may be associated with the initiation events involved in AD-related neurodegeneration that begin during the MCI phase. Significantly, the miR-132 miRNAs are known to regulate the expression of different genes, including BDNF or SIRT1, that are likely to be associated with learning and memory. Accordingly, a combination of these miRNAs could have a higher predictive value for estimating the risk of MCI onset and its conversion to AD [43].

From a practical vantage, microRNA detection techniques enable rapid detection of large numbers of miRNA types through the use of high volume microarray technologies. Because these technologies are based on probe-target hybridization and fluorescence signal detection, they could provide quantitative estimates that enable assessment of the degree of impairment and its long-term prognosis.

## Biomarkers for Huntington's and Parkinson's Diseases [42-44]

MCI like cognitive dysfunction is known to manifest in both Huntington's and Parkinson's diseases (PD). Because the genetic cause in the case of HD is known there is both a clear biomarker and therapeutic target, mutant huntingtin protein (mHTT) [44]. This has been the basis for several promising therapeutic approaches specifically targeting Huntingtin DNA and RNA for the purpose of lowering the huntingtin protein. Recently, an anti-sense oligonucleotide (ASO) targeting huntingtin mRNA successfully reduced huntingtin protein levels for the first time in phase 1/2 trials of early HD patients [45]. Diagnostically, a combination of biomarkers may enhance therapeutic targeting since the neurofilament protein (Nfl) in both plasma and CSF is statistically better at discriminating between premanifest and manifest HD than CSF mHTT.

For Parkinson's disease, misfolded and aggregated a-synuclein is the major protein component of Lewy bodies and is regarded as a pathological hallmark of PD [46]. Post-translational modifications of a-synuclein protein, such as phosphorylation, ubiquitination, and oxidization, are contributory to protein misfolding. Since a-synuclein is both genetically and pathologically associated with PD and is detectable in biofluids, it has become widely-used for PD biomarker studies. Collectively various studies show that total CSF a-synuclein is significantly lower in PD patients than in patient controls. However, the diagnostic performance of oligomeric a-synuclein alone can be improved with use of the ratio of CSF oligomeric a-synuclein to total a- synuclein, together with phosphorylated a-synuclein and neurodegenerative biomarkers [46].

## Neurostimulation and MCI Management

The relatively high probability with which amnestic MCI evolves to dementia has strongly argued for therapeutic strategies that seek to restore memory. With this as a goal, a growing body of studies have turned to non-invasive forms of neurostimulation to assess their capacity for enhancing memory retention. These studies document positive effects of neurostimulation on memory restoration in several specific memory functions [47-49].

Neurostimulation interventions rely on their ability to induce long lasting neuroplastic change in the brain, including the strengthening or weakening of synaptic strength together with corresponding micro-anatomical changes such as increases in dendritic spines or axonal sprouting. Transcranial magnetic stimulation (TMS), the most widely used form of non-invasive neurostimulation, typically delivers very brief, high-intensity magnetic pulses, which can be adapted to a wide variety of stimulation paradigms. Current regimes have evolved from early studies demonstrating that a short burst of rapid rTMS increased excitability in the brain [50] while later studies showed that low-frequency repetitive TMS reduced the brain's excitability [51]. These complementary results revealed that by modulating stimulation frequency it was possible to yield different plastic outcomes. Building on these differences neurostimulation therapies have since extended their stimulation protocols to treat a wide range of therapeutic conditions, including depression, stroke, movement disorders, epilepsy, and pain.

## Positive Effects of Neurostimulation on Associative and Episodic Memory

Current investigations into neurostimulation protocols for memory enhancement increasingly rely on a growing body of findings on the structural and functional connectivity of memory processes. These findings show that memory processes are distributed among a cluster of functionally connected brain regions, which include the perirhinal cortex (PRC), entorhinal cortex, and parahippocampal cortex, collectively known as the medial temporal lobe (MTL) [20], with the hippocampus as an integrating hub. Together these regions have been termed the hippocampal cortical network (HCN), which is now known to support episodic memory [52,53]. In amnestic MCI, a frequent observation made in neuroimaging studies is atrophy of the hippocampus, consistent with a primary role for the hippocampus in spatial and episodic memory. Episodic memory is also disrupted by lesions affecting key HCN components [54] and their connections. Such lesions alter fMRI measures of connectivity among the HCN network in correspondence with a variety of amnestic states [55]. Accordingly, neurostimulation studies seeking to improve memory have frequently targeted this brain network.

A growing body of evidence reveals that the connectivity between brain regions of the HCN network relies on oscillatory activity associated with the theta-frequency band. Human intracranial recordings notably display an increase in phase synchronization at theta band frequencies (4–8-Hz) at rest [56], during memory formation, and during memory retrieval. Moreover, invasive electrical stimulation induces long-term potentiation in the hippocampus preferentially at theta-frequencies, increasing interregional connectivity throughout the HCN network [57]. This has led to stimulation protocols that have emphasized the use of theta burst stimulation to restore functional connectivity within the network.

Using these protocols, improvements in episodic memory are observed that generally parallel corresponding increases in hippocampal fMRI connectivity of the HCN network. Furthermore, only with the theta burst paradigm can differences in stimulation effects on hippocampal connectivity that are related to memory retrieval be identified. Together these findings suggest that fMRI connectivity measures of HCN synchrony are causally related to episodic memory and indicates the potential of the theta burst protocol for restoration of episodic memory retrieval [49].

## Recruitment of Supplementary Areas to Preserve Cognitive Functioning

An alternative approach to the use of theta stimulation to improve memory functions and interregional functional connectivity is the leveraging of the well-known phenomenon of over recruitment of distributed, bilateral prefrontal cortical regions, known to occur in older adults. Age-related increases in contralateral recruitment have been frequently observed across a variety of studies that employ

different stimuli and cognitive tasks, including episodic semantic retrieval, attention, motor coordination, and working memory [58].

Recruitment can be monitored by assessing whether the strength of connections within a cluster of nodes termed modules changes during task based performance [59], where network modularity is defined by the presence of particular groups of nodes that connect more intimately with each other than with other nodes in the network. Once the modular network has been identified, the extent of local or global network activity can be assessed quantitatively using within-module degree (WMD) and between-module degree (BMD) parameters that assess the recruitment of distant brain communities.

Using rTMS it has been found that 5 Hz stimulation to a memory-specific target is associated with greater within-module connectivity (WMD) during successful encoding, while 1 Hz stimulation induces a more distributed pattern of connectivity with other modules (BMD) [60]. Significantly, stimulation-induced reductions in local activity after 1 Hz rTMS—but not 5Hz rTMS—generate increased connectivity between the left PFC and other ipsilateral and contralateral modules in prefrontal and parietal regions an effect specific to successfully encoded trials. This result suggests the presence of a highly responsive global network that is able to shift connectivity patterns in response to the disruption of local resources by relying on a more distributed pattern of connectivity.

## Conclusion

The presumption that MCI is solely a prodromal phase of AD is now generally disregarded and there is a growing consensus that MCI constitutes a distinct medical entity having a wide etiological range. This etiological diversity is the basis for a broad set of MCI outcomes that extend beyond dementia. While several of these are progressive, like AD, many other cases exist for which there is a high probability of arresting or even reversing symptomatic progression. The possibility of reversion as well as the need for early AD diagnosis motivates the current breadth of investigations into the identification and management of the causal factors giving rise to MCI.

These studies have achieved notable success in diagnostic and therapeutic power, benefitting from improved understanding of the functional architecture of brain activity, greater predictive accuracy of biomarker combinations, and non-invasive neurostimulatory methods that narrowly channel modulatory effects within a personalized format. Coupled with large scale molecular batteries that considerably improve statistical correlations, the identification of various etiological factors is providing a surer basis for the choice of therapies needed to address MCI prior to substantial and irreversible cognitive loss.

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