Auditory Biomarker Identified for Early Cognitive Impairment

By Gavin M. Bidelman, PhD, and Claude Alain, PhD

"I can hear you, but I can't understand you." This is one of the most common reasons for older adults to consult an audiologist. Speech comprehension problems, especially in noisy environments, become increasingly common as we get older. Unfortunately, the cause(s) of reduced communication skills is not always easily determined. Contributing factors may include difficulty registering sound by the ear itself, as well as reduced information as an auditory signal is transmitted from the ear to brain areas that process and decode speech sounds. Understanding how aging affects listening skills is difficult because older adults often experience some form of reduced sensory input (i.e., presbycusis) in addition to other age-related changes in perceptual and cognitive functions. But independent of hearing loss, what happens to auditory function when our cognitive systems begin to fade?

MILD COGNITIVE IMPAIRMENT

With this question in mind, we have recently focused our attention on mild cognitive impairment (MCI), an intermediate phase in the progression of cognitive aging with an approximately 20 percent prevalence in adults aged 60 and older (*Clin Geriatr Med.* 2013;29[4]:753). MCI is an important stage to characterize because it shows a high rate (>40%) of conversion and is a key risk factor (x6) for developing more severe dementia and Alzheimer's disease (*Clin Geriatr Med.* 2013). Both of these account for around $240 million in annual health care costs in the United States alone (Alzheimer's Association, 2016).

While MCI may involve "memory hiccups" and other hallmarks of initial cognitive deficits, it is also associated with communication issues involving expressive and receptive language processing such as verbal fluency and reading comprehension (*Top Geriatr Rehabil.* 2014; 30[1]:18). Reduced communication abilities are thought to contribute to social isolation, confusion, and poorer quality of life in the elderly (*Otolaryngol Pol.* 2006;60[6]:883). Consequently, MCI is an

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ideal stage to monitor early cognitive decline and identify older adults at higher risk for developing dementia.

Gold standard diagnostics for MCI still rely heavily on large neuropsychological batteries that screen various cognitive domains (e.g., memory, attention, and reasoning). Unfortunately, clinical tests for cognitive impairment often have high variability and poor test-retest reliability and sensitivity (<50%), making it sometimes difficult to discriminate dementia from normal aging (*Exp Aging Res.* 2013;39[4]:382). Current neuroimaging diagnostics (e.g., MRI) are promising in defining the neurology of MCI but are not widely adopted clinically because they are costly, have numerous contraindications (e.g., metal, claustrophobia), and lack portability. Most of these physiological measures also characterize anatomical, volumetric, and metabolic abnormalities of the brain (e.g., cerebral spinal fluid, plaque) rather than functional changes that underlie human cognition or speech communication. To date, clinical interventions at early phases of cognitive decline (MCI-state) have produced mixed results (*N Engl J Med.*2005;352[23]:2379). Finding new biomarkers of MCI is paramount to providing access to interventions that may slow the progression to Alzheimer's disease.

Several questions remain unanswered regarding the links between cognitive aging and auditory function. Does cognitive decline affect listening skills above and beyond normal

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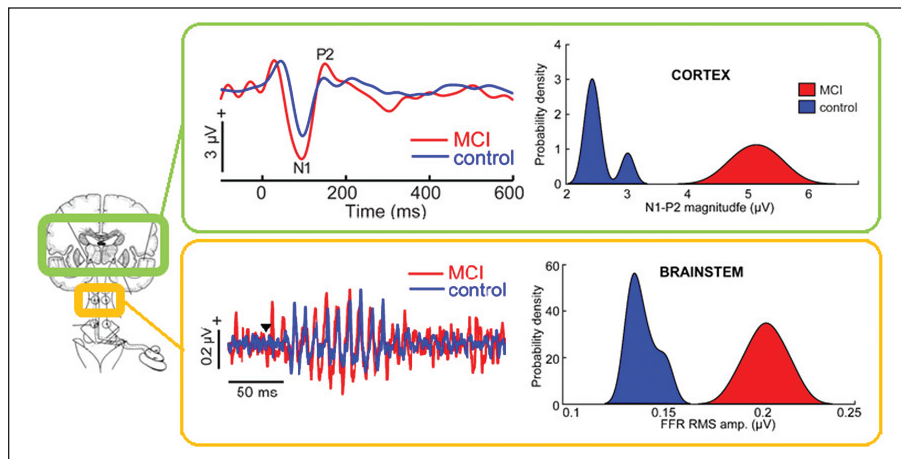
Figure 1: Older adults with MCI have hypersensitive (larger) neural responses to speech at both cortical (top) and subcortical (bottom) levels of the auditory system compared with age- and hearing-matched individuals with normal cognitive function.

aging? Are changes in basic speech and language function good predictors of declining mental faculties? We wondered if the brain's early auditory processing of speech could provide a new, entirely objective, and more sensitive measure of MCI. Our recent study aimed to address these questions and turn over a new leaf on MCI diagnostics through the lens of the auditory system (*J Neurosci.* 2017;37[13]:3610).

MCI AND NEURAL PROCESSING OF SPEECH

In our study, older adults (age 52-86) were categorized as having MCI or of normal cognitive status (controls) based on their scores on the Montreal Cognitive Assessment (MOCA; *J Neurosci.* 2017; *J Am Geriatr Soc.* 2005;53[4];695). The MOCA is a freely available, normed behavioral screener that assesses several cognitive abilities (e.g., memory, attention) in about 10 minutes. The MOCA yields over 90 percent sensitivity/specificity in detecting MCI and Alzheimer's. Importantly, hearing acuity was normal across our listeners and matched between groups to rule out general effects of age-related hearing loss. Groups were also equated on other important demographic variables like education, musical training, and age, which are known to affect speech processing.

We then recorded speech-evoked brainstem and cortical EEG potentials as listeners performed a vowel identification task. This allowed us to look at how different levels of the auditory pathway encode acoustic signals and determine the earliest point at which MCI affects the neural representation of speech. Based on prior studies examining auditory evoked potentials in MCI, we expected that cortical responses would be abnormal in individuals presenting with low MOCA scores (*Brain.* 2007;130[Pt 3]:740).

In fact, we observed that MCI listeners' cortical activity to speech was roughly twice the amplitude of age- and hearing-matched control listeners, suggesting a hypersensitivity to acoustic stimuli (Fig. 1, top). However, altered cortical function was not entirely surprising in light of the known atrophy of

the cerebral cortex that occurs in early forms of dementia (*Neurology.* 2009;72[17]:1519).

More astonishing were brainstem responses. Subcortical activity showed a similar exaggeration of the speech signal and were again ~2x larger in MCI listeners (Fig. 1, bottom). We have not observed this type of brainstem overdrive in normal aging adults, suggesting that it is an added complication of MCI (*Neurobiol Aging.* 2014; 35[11]:2526). These global changes in neural excitability could be due to a reduction in neural inhibition that accompanies the normal aging process, which is presumably exacerbated in cases of cognitive impairments.

Notably, we did not find behavioral deficits in the MCI listeners' speech identification. This suggested that auditory neural responses to speech might provide a "pre-clinical" biomarker of early cognitive impairment before it manifests in behavioral speech assessments and noticeable communication deficits.

Using a linear discriminant analysis, we were also successful in correctly classifying individuals with MCI versus controls with over 80 percent accuracy using nothing but the amplitudes of their neural responses. Both cortical and brainstem speech potentials could distinguish cognitively normal listeners from MCI listeners, but brainstem turned out to be a more powerful measure in terms of predicting the severity of listeners' cognitive status (i.e., larger brainstem activity were associated with poorer MOCA scores).

These findings are exciting because they advanced the neurobiological understanding of MCI; we have now identified a subcortical biomarker in auditory-sensory processing. The brainstem response to speech arises as early as seven to 10 milliseconds after sound hits the ear from structures in the midbrain (*Hear Res.* 2015;323:68). Our findings challenge the notion that MCI is strictly the result of cortical dysfunction and implicate pathophysiological changes prior to conscious awareness, well below the cerebral cortex and in the upper brainstem.

CLINICAL OUTLOOK

Brainstem responses are easily recorded with single-channel evoked potential hardware commonly available in most audiology clinics. The MOCA is a free MCI screener conducted in less than 10 minutes. Declines in auditory and visual sensory processing are thought to accelerate cognitive aging and act as a catalyst for MCI (*Percept Psychophys.* 2013;75[3]:508). While neuropsychological testing is outside the typical audiologist's scope of practice, we hope that more widespread use of objective measures like brainstem or cortical speech-evoked potentials could aid in the identification and management of early cognitive impairments before they develop into more severe forms of dementia or Alzheimer's disease. **HJ**