Neurophysiological biomarkers of Mild Cognitive Impairment (MCI) due to Alzheimer's disease: a TMS study

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Evolution of AD diagnostic criteria

Mayo Clinic criteria (Petersen et al. 1999)

Expanded Mayo Clinic Criteria (Winblad et al. 2004; Petersen et al 2004)

NIA-AA (Albert et al. 2011)

DSM-5 (American psichyatric association 2013)

NIA-AA Research Framework (Jack et al. 2018)

IWG criteria (Dubois et al. 2007) → *IWG revised criteria (Dubois et al. 2014)*

		Cognitive stage		
		Cognitively Unimpaired	**Mild Cognitive Impairment**	**Dementia**
Biomarker Profile	$A^-T^-(N)^-$	normal AD biomarkers, cognitively unimpaired	normal AD biomarkers with MCI	normal AD biomarkers with dementia
	$A^+T^-(N)^-$	Preclinical Alzheimer's pathologic change	Alzheimer's pathologic change with MCI	Alzheimer's pathologic change with dementia
	$A^+T^+(N)^-$	Preclinical Alzheimer's disease	Alzheimer's disease with MCI(Prodromal AD)	Alzheimer's disease with dementia
	$A^+T^+(N)^+$			
	$A^+T^-(N)^+$	Alzheimer's and concomitant suspected non Alzheimer's pathologic change, cognitively unimpaired	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with MCI	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with dementia
	$A^-T^+(N)^-$	non-Alzheimer's pathologic change, cognitively unimpaired	non-Alzheimer's pathologic change with MCI	non-Alzheimer's pathologic change with dementia
	$A^-T^-(N)^+$			
	$A^-T^+(N)^+$			

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease (Jack et al. 2018)

Short afferent inhibition (SAI):

- Performed delivering electrical stimulation to a peripheral nerve prior to a TMS pulse directed to the motor cortex at short ISI (20 to 50ms), reflecting the Ach inhibitory interneuron of the cortex (*Tokimura H. et al., J Physiol, 2000; Di Lazzaro V. et al., Exp. Brain Res, 2000*)

- Some studies have shown impairment of SAI in MCI patients (*Nardone et al., j. Neural Transm,2012; Benussi et al. Brain Stim, 2021*)

Intermittent theta burst stimulation

- Protocol of repetitive TMS characterized by very high frequency (50Hz) trains of stimuli delivered intermittently at theta frequency (5Hz) (*Di Lazzaro V. et al. J. Physiol, 2005*).

- Other studies shown an impairment in LTP induced by iTBS (*Di Lorenzo F. et al. Brain Stim, 2020; Colella D. et al. Clin Neurophysiol, 2021*).

	MCI due to AD (n = 4)	HC (n = 4)
Age at baseline (mean ± SD)	68 ± 2,1	65,2 ± 1,2
Female (TOT)	1	2
MMSE at baseline (mean ± SD)	22,2 ± 2,3	29,5 ± 0,5
MMSE T1 (mean ± SD)	21,7 ± 1,8	29,5 ± 0,5
CSF BETA-42 pg/mL (mean ± SD)	356,7 ± 79,4	-
CSF BETA-40 pg/mL (mean ± SD)	4945,2 ± 1960,8	-
TAU TOT pg/mL (mean ± SD)	440,375 ± 278,7	-
P-TAU pg/mL (mean ± SD)	106,95 ± 56,8	-

Inclusion criteria:

- Diagnosis of MCI due to AD (amnestic-MCI + alteration of Aβ and Tau) (PROAD) (*NIA-AA 2018*)
- No history of psychiatric disorders

Exclusion criteria:

- Evidence of secondary cause of dementia

CSF sampling:

- ABETA-42
- ABETA-40
- PTAU

Neuropsychological assessment:

- MMSE
- NPI

Neurophysiological assessment:

- MEP
- SICI
- ICF
- SAI 2-3
- iTBS

Baseline

Neuropsychological assessment and CSF sampling

T0

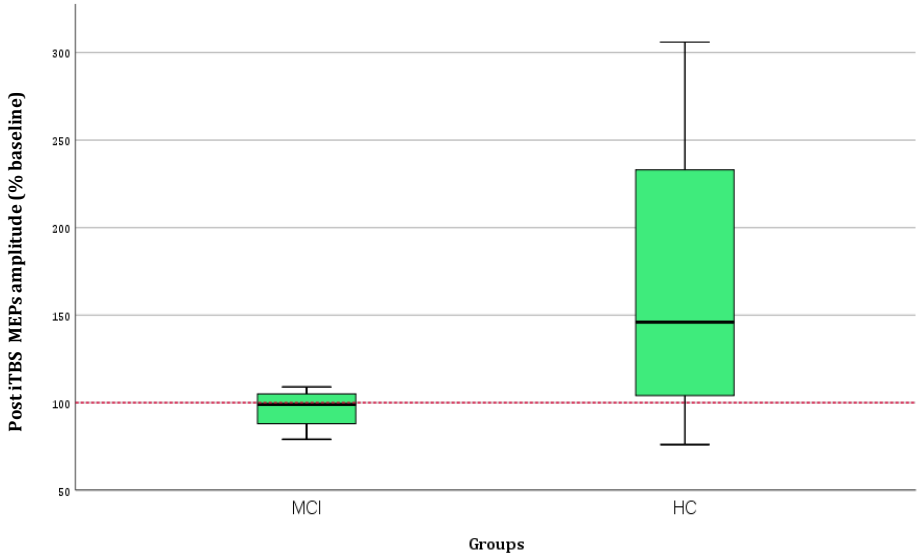
Neurophysiological assessment within 30 days

T1

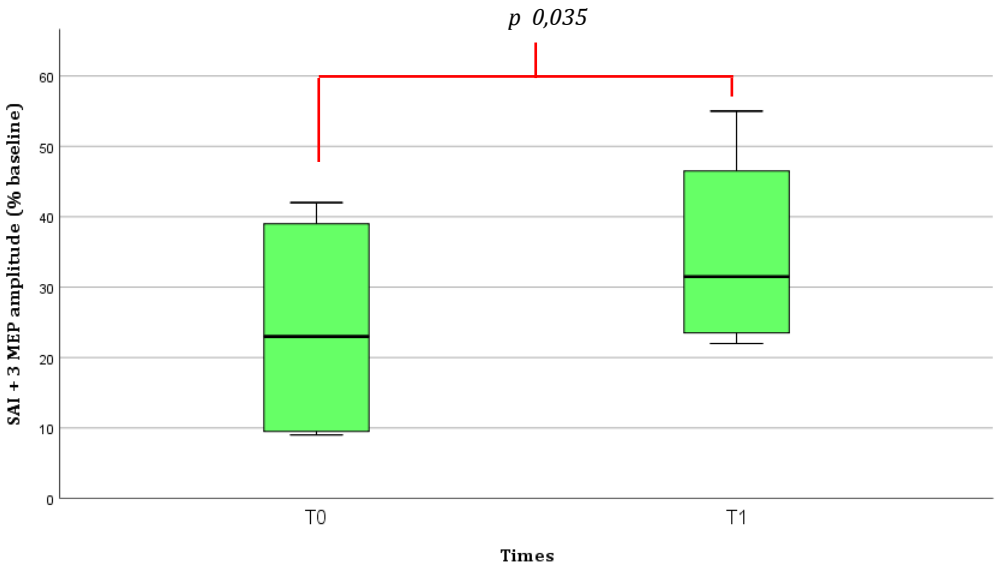
Neurophysiological/Neuropsychological assessment after 180 days

	MCI due to AD (n = 4)				Healty Controls (n = 4)	
	T0		T1		T0	
		p value		*p value*		*P value*
SAI + 2 ms (% mean ± SD)	26 ± 16	*0,02*	30 ± 16	*0,02*	38 ± 23	*0,02*
SAI + 3 ms (% mean ± SD)	24 ± 17	*0,02*	35 ± 15	*<0,01*	52 ± 17	*<0,01*
SICI (% mean ± SD)	35 ± 15	*0,04*	35 ± 21	*0,05*	45 ± 24	*0,04*
ICF (% mean ± SD)	139 ± 43	*0,24*	167 ± 38	*0,10*	159 ± 89	*0,17*
MEP post-iTBS (% mean ± SD)	97 ± 13	*0,44*	94 ± 37	*0,46*	168 ± 98	*0,22*
MEP baseline mV (mean ± SD)	1146 ± 494	-	1099 ± 435	-	471 ± 89	-

	MCI due to AD (n = 4)	Healty Controls (n = 4)	
	T0	T0	
			P value
SAI + 2 ms (% mean ± SD)	26 ± 16	38 ± 23	*0,19*
SAI + 3 ms (% mean ± SD)	24 ± 17	52 ± 17	*0,09*
SICI (% mean ± SD)	35 ± 15	45 ± 24	*0,35*
ICF (% mean ± SD)	139 ± 43	159 ± 89	*0,17*
MEP post-iTBS (% mean ± SD)	97 ± 13	168 ± 98	*0,5*
MEP baseline mV (mean ± SD)	1146 ± 494	471 ± 89	*0,06*



	MCI due to AD (n = 4)		
	T0	T1	
			P value
SAI + 2 ms (% mean ± SD)	26 ± 16	30 ± 16	*0,69*
SAI + 3 ms (% mean ± SD)	24 ± 17	35 ± 15	*0,03*
SICI (% mean ± SD)	35 ± 15	35 ± 21	*0,57*
ICF (% mean ± SD)	139 ± 43	167 ± 38	*0,23*
MEP post-iTBS (% mean ± SD)	97 ± 13	94 ± 37	*0,86*
MEP baseline mV (mean ± SD)	1146 ± 494	1099 ± 89	*0,89*



Conclusions:

- ICF and LTP induced by iTBS is altered in patients with MCI due to AD
- SAI might be preserved in the initial phase
- The neurophysiological parameters remains stable over time with the exception of SAI + 3in our cohort
- More studies are warranted for the validation of TMS measures as biomarkers of MCI due to AD

Limitation:

- Sample size
- Short follow Up

Thank You!

Dr. Alessandro Cruciani