

Supplementary Material

Neural Mechanisms of Motor Dysfunction in Mild Cognitive Impairment and Alzheimer's Disease: A Systematic Review

PubMed Search Query

The search query was built by combining search queries for our population of interest, motor measures, and neuroimaging measures:

For Alzheimer's Disease and MCI:

MCI[Title/Abstract] OR "mild cognitive impairment"[Title/Abstract] OR alzheimer[Title/Abstract]

For motor measures:

"muscle strength"[Title/Abstract] OR "grip strength"[Title/Abstract] OR "isokinetic strength"[Title/Abstract] OR "vertical jump"[Title/Abstract] OR "motor speed"[Title/Abstract] OR "tapping speed"[Title/Abstract] OR "motor coordination"[Title/Abstract] OR dexterity[Title/Abstract] OR bimanual[Title/Abstract] OR "finger tapping"[Title/Abstract] OR "foot tapping"[Title/Abstract] OR "motor skill"[Title/Abstract] OR "motor function"[Title/Abstract] OR "motor performance"[Title/Abstract] OR "motor adaptation"[Title/Abstract] OR "purdue pegboard"[Title/Abstract] OR "grooved pegboard"[Title/Abstract] OR "archimedes spiral"[Title/Abstract] OR gait[Title/Abstract] OR walk[Title/Abstract] OR "timed up and go"[Title/Abstract] OR TUG [Title/Abstract] OR "walking while talking"[Title/Abstract] OR "dual task"[Title/Abstract] OR mobility[Title/Abstract] OR balance[Title/Abstract] OR Romberg[Title/Abstract] OR "sensory organization"[Title/Abstract] OR "sensory organisation"[Title/Abstract] OR vestibular[Title/Abstract] OR "motor sequence learning"[Title/Abstract] OR "motor learning"[Title/Abstract] OR "serial reaction time task"[Title/Abstract] OR stride[Title/Abstract]

For neuroimaging:

PET[Title/Abstract] OR "positron emission tomography"[Title/Abstract] OR "magnetic resonance imaging"[Title/Abstract] OR MRI[Title/Abstract] OR fMRI[Title/Abstract] OR fcMRI[Title/Abstract] OR "functional connectivity"[Title/Abstract] OR "diffusion weighted imaging"[Title/Abstract] OR DWI[Title/Abstract] OR "diffusion tensor imaging"[Title/Abstract] OR DTI[Title/Abstract] OR "near infrared spectroscopy"[Title/Abstract] OR NIRS [Title/Abstract] OR fNIRS [Title/Abstract] OR "brain structure" [Title/Abstract] OR "brain function" [Title/Abstract] OR "brain volume" [Title/Abstract] OR "volumetric" [Title/Abstract] OR "FLAIR" [Title/Abstract]

Additional terms for language and date range:

english[LA] AND ("1980/01/01"[Date - Create] : "3000"[Date - Create])

Combined PubMed query:

(MCI[Title/Abstract] OR "mild cognitive impairment"[Title/Abstract] OR alzheimer[Title/Abstract]) AND ("muscle strength"[Title/Abstract] OR "grip

strength"[Title/Abstract] OR "isokinetic strength"[Title/Abstract] OR "vertical jump"[Title/Abstract] OR "motor speed"[Title/Abstract] OR "tapping speed"[Title/Abstract] OR "motor coordination"[Title/Abstract] OR dexterity[Title/Abstract] OR bimanual[Title/Abstract] OR "finger tapping"[Title/Abstract] OR "foot tapping"[Title/Abstract] OR "motor skill"[Title/Abstract] OR "motor function"[Title/Abstract] OR "motor performance"[Title/Abstract] OR "motor adaptation"[Title/Abstract] OR "purdue pegboard"[Title/Abstract] OR "grooved pegboard"[Title/Abstract] OR "archimedes spiral"[Title/Abstract] OR gait[Title/Abstract] OR walk[Title/Abstract] OR "timed up and go"[Title/Abstract] OR TUG [Title/Abstract] OR "walking while talking"[Title/Abstract] OR "dual task"[Title/Abstract] OR mobility[Title/Abstract] OR balance[Title/Abstract] OR Romberg[Title/Abstract] OR "sensory organization"[Title/Abstract] OR "sensory organisation"[Title/Abstract] OR vestibular[Title/Abstract] OR "motor sequence learning"[Title/Abstract] OR "motor learning"[Title/Abstract] OR "serial reaction time task"[Title/Abstract] OR stride[Title/Abstract]) AND (PET[Title/Abstract] OR "positron emission tomography"[Title/Abstract] OR "magnetic resonance imaging"[Title/Abstract] OR MRI[Title/Abstract] OR fMRI[Title/Abstract] OR fcMRI[Title/Abstract] OR "functional connectivity"[Title/Abstract] OR "diffusion weighted imaging"[Title/Abstract] OR DWI[Title/Abstract] OR "diffusion tensor imaging"[Title/Abstract] OR DTI[Title/Abstract] OR "near infrared spectroscopy"[Title/Abstract] OR NIRS [Title/Abstract] OR fNIRS [Title/Abstract] OR "brain structure" [Title/Abstract] OR "brain function" [Title/Abstract] OR "brain volume" [Title/Abstract] OR "volumetric" [Title/Abstract] OR "FLAIR" [Title/Abstract]) AND english[LA] AND ("1980/01/01"[Date - Create] : "2021/08/26"[Date - Create])

Exclusion and Inclusion of Studies

We excluded articles based on information from the title, the abstract, and the entire manuscript. If key information in the title pointed out that the article was irrelevant, (e.g., because it indicated that this was an animal study) the article was excluded. If it was unclear from the title that the article was relevant or not, the abstract was read. If the abstract indicated that the article was irrelevant for this review, it was excluded. Otherwise, the full manuscript was read and reviewed for eligibility.

Excluded studies

Here, we list articles that might appear to meet the inclusion criteria, but which were excluded after review. For each study, we list the reason for exclusion.

- Lauretani, F., Ruffini, L., Sciarlattei, M., & Maggio, M. (2020). Relationship between comprehensive geriatric assessment and amyloid pet in older persons with mci. *BMC Geriatrics*, 20(1), 337. <http://dx.doi.org/10.1186/s12877-020-01746-x>

This study looks at differences in motor function between MCI due to AD and MCI not due to AD (based on amyloid deposition). However, the authors don't link the motor dysfunction to the amyloid metrics, but use amyloid deposition to build groups. So, it does not tell us how motor dysfunction in aMCI is related to brain metrics.

- Rajan, S., Brettschneider, J., & Collingwood, J. F. (2020). Regional segmentation strategy for DTI analysis of human corpus callosum indicates motor function deficit in mild cognitive impairment. *Journal of neuroscience methods*, 345, 108870. [http://dx.doi.org/S0165-0270\(20\)30293-4](http://dx.doi.org/S0165-0270(20)30293-4)

This study shows indirect proof for an association between changes in white matter microstructure in the corpus callosum that connects motor regions and gait + tremor. It was excluded because this association is not formally tested, only suggested based on motor findings and brain findings.

- Lu, K., Nicholas, J. M., Weston, P. S. J., Stout, J. C., O'Regan, A. M., James, S., Buchanan, S. M., ... (2021). Visuomotor integration deficits are common to familial and sporadic preclinical Alzheimer's disease. *Brain Communications*, 3(1), . <http://dx.doi.org/10.1093/braincomms/fcab003>

This study looks people at genetic risk for AD, but who don't have MCI or AD.

- Snir, J. A., Bartha, R., & Montero-Odasso, M. (2019). White matter integrity is associated with gait impairment and falls in mild cognitive impairment. results from the gait and brain study. *NeuroImage: Clinical*, 24(nil), 101975. <http://dx.doi.org/10.1016/j.nicl.2019.101975>

This study compares brain-behavioral correlations between MCI with fall history and without fall history. It is therefore not explaining motor problems in MCI, but brain relationships with falling *in* MCI.

- Kose, Y., Ikenaga, M., Yamada, Y., Morimura, K., Takeda, N., Ouma, S., Tsuboi, Y., (2016). Timed up and go test, atrophy of medial temporal areas and cognitive functions in community-dwelling older adults with normal cognition and mild cognitive impairment. *Experimental Gerontology*, 85(nil), 81–87. <http://dx.doi.org/10.1016/j.exger.2016.09.019>

The MCI and control group are combined and then split up into timed up-and-go performance groups. No association between motor function and atrophy is associated within MCI alone.

- Hawkins, K. M., Goyal, A. I., & Sergio, L. E. (2015). Diffusion tensor imaging correlates of cognitive-motor decline in normal aging and increased Alzheimer's disease risk. *Journal of Alzheimer's Disease*, 44(3), 867–878. <http://dx.doi.org/10.3233/jad-142079>

This study looks at the association between motor function and white matter measures in individuals who have a higher risk for AD, but who don't have a diagnosis of MCI or AD.

- Bracco, L., Bessi, V., Piccini, C., Mosconi, L., Pupi, A., & Sorbi, S. (2007). Metabolic correlates of executive dysfunction. *Journal of Neurology*, 254(8), 1052–1065. <http://dx.doi.org/10.1007/s00415-006-0488-1>

This study looks at the association between dual tasking load and metabolic rate in AD, but the dual task load is a measure of cognitive function performance affected by motor function, instead of looking at the load of cognitive function on motor performance.

- Lopez, O. L., Becker, J. T., Jungreis, C. A., Rezek, D., Estol, C., Boiler, F., & DeKosky, S. T. (1995). Computed tomography–but not magnetic resonance imaging–identified periventricular white-matter lesions predict symptomatic cerebrovascular disease in probable Alzheimer’s disease. *Archives of Neurology*, 52(7), 659–664. <http://dx.doi.org/10.1001/archneur.1995.00540310029012>

This study does look at the association between impaired gait and white matter lesions, but it is not described how impaired gait was measured.

- Nestor, P. G., Parasuraman, R., Haxby, J. V., & Grady, C. L. (1991). Divided attention and metabolic brain dysfunction in mild dementia of the Alzheimer’s type. *Neuropsychologia*, 29(5), 379–387. [http://dx.doi.org/10.1016/0028-3932\(91\)90026-5](http://dx.doi.org/10.1016/0028-3932(91)90026-5)

The dual task under investigation is including an auditory and a visual reaction time task, which is not considered a motor task as we discuss in our review here.

Supplementary Table 1. Quality Assessment

Author	Year	Smallest experimental group size	Type of MCI or AD group	Study Design	Study Type
Beauchet O.	2015	43	undifferentiated MCI	Cross-sectional	A
Crockett R.	2019	19	undifferentiated MCI	Cross-sectional	A
Grijalva C.	2021	12	undifferentiated MCI	Cross-sectional	A
Holtzer R.	2020	11	undifferentiated MCI	Cross-sectional	A
Liu Y.	2021	20	undifferentiated MCI	Cross-sectional	A
Nadkarni N.	2009	42	AD	Cross-sectional	A
Nadkarni N.	2012	24	AD	Cross-sectional	A
Rosso A.	2017	35	undifferentiated MCI, unspecified AD	Prospective Cohort	A
Vidoni E.	2012	9	AD	Cross-sectional	A
Allali G.	2016	25	aMCI + naMCI	Cross-sectional	B
Allali G.	2019	41	aMCI + naMCI	Cross-sectional	B
Allali G.	2020	170	undifferentiated MCI	Cross-sectional	B
Ali P.	2021	30	aMCI	Cross-sectional	B
Almkvist O.	1992	50	AD	Cross-sectional	B
Annweiler C.	2013 S	20	undifferentiated MCI	Cross-sectional	C
Annweiler C.	2013 M	20	undifferentiated MCI	Cross-sectional	C
Beauchet O.	2019 A	42	aMCI + naMCI	Cross-sectional	C
Beauchet O.	2019 B	99	undifferentiated MCI	Cross-sectional	C
Beauchet O.	2020	170	undifferentiated MCI	Cross-sectional	B
Bennet D.	1992	106	AD	Cross-sectional	C
Camarda C.	2019	347	aMCI	Cross-sectional	C
Cosentino E.	2020	43	undifferentiated MCI	Cross-sectional	B
Crockett R.	2017	35	undifferentiated MCI	Cross-sectional	C
Doi T.	2017	270	aMCI + naMCI	Cross-sectional	C
Doi T.	2015	271	aMCI + naMCI	Cross-sectional	C
Hsu C.L.	2019	49	undifferentiated MCI	Cross-sectional	C
Lee Y.-W.	2017	107	AD	Cross-sectional	C
Makizako H.	2011	34	aMCI + naMCI	Cross-sectional	B
Mascalchi M.	2014	60	undifferentiated MCI	Cross-sectional	C
Moon Y.	2019	28	AD	Cross-sectional	C
Nilsson M.	2020	124	undifferentiated MCI	Cross-sectional	B
Olazarán J.	2013	53	AD	Cross-sectional	C
Onen F.	2004	23	undifferentiated MCI	Cross-sectional	C
Onen F.	2008	61	undifferentiated MCI	Cross-sectional	C
Reeves S.	2009	24	AD	Cross-sectional	C
Sakurai R.	2019	40	undifferentiated MCI	Prospective Cohort	C
Yoon D.	2018	21	undifferentiated MCI	Cross-sectional	C

Smallest experimental group: smallest group size for the experimental group (thus excluding a control group if present), yellow=<20; orange= 20-100; green>100. Type of MCI or AD: aMCI, amnesic mild cognitive impairment; naMCI, non-amnesic MCI; AD, Alzheimer's disease, orange = undifferentiated; green = specified. Study Type: A (green) Studies reporting brain by group interactions on motor performance. B and C (orange) Studies evaluating motor function in relation to neuroimaging outcome measures without healthy control comparison. Note: the letters for S, M, A, and B after the year for Annweiler 2013, and Beauchet 2019 indicate the first letter of the title of the manuscript to differentiate between these papers from the same first author and year.