

Evaluating Alzheimer's Disease with the TMS-EEG Perturbation Complexity Index

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INTRODUCTION

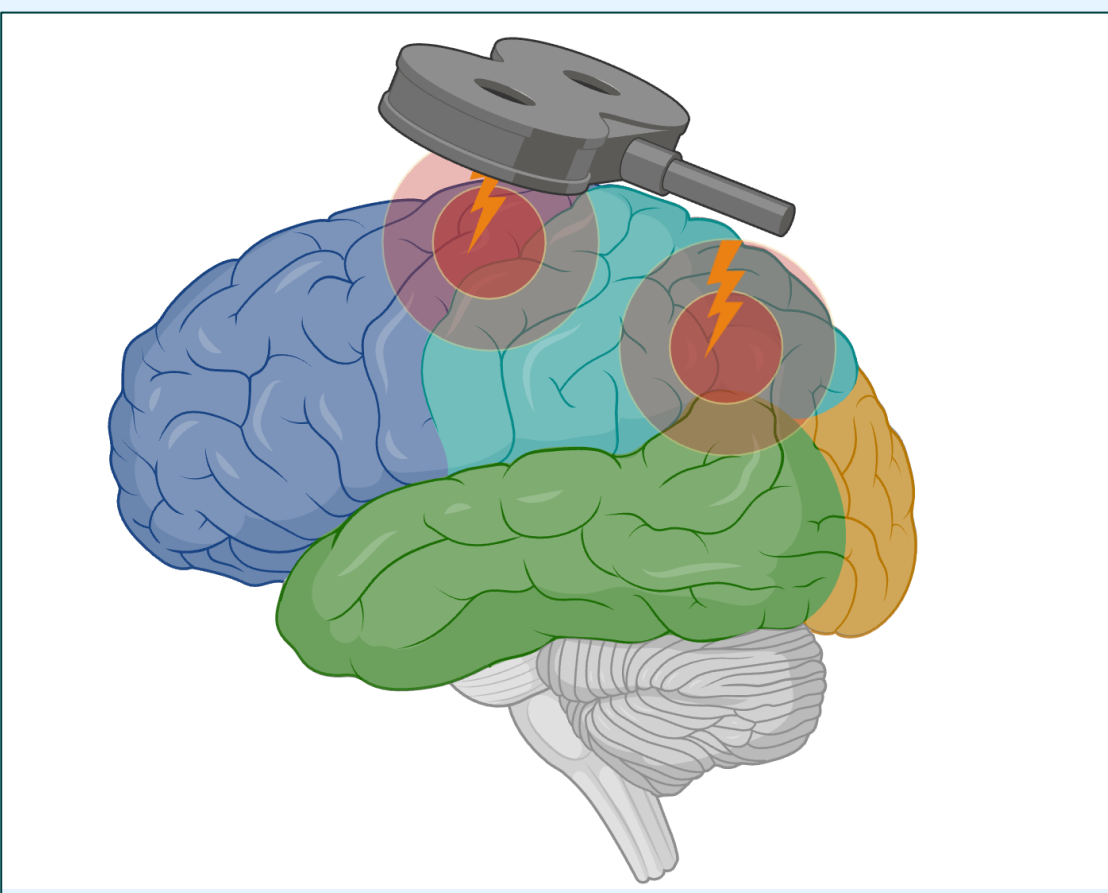
- Neurodegenerative diseases like Alzheimer's disease (AD) are characterized by progressive cognitive decline, including impairments in attention, working memory, and episodic memory; all conscious processes.
- Consciousness and memory are linked, particularly in cortical diseases like AD.¹ The Memory Theory of Consciousness (MToC) proposes that AD progressively disrupts conscious awareness as cortical damage accumulates, and that AD can be understood as a disorder of consciousness.¹ In advanced dementia, no reliable neurophysiological biomarker of conscious awareness exists.
- The Perturbational Complexity Index – State Transitions (PCIST) measures the complexity of the brain's response to transcranial magnetic stimulation (TMS) using electroencephalography (EEG) and is sensitive to levels of consciousness, including minimally conscious states.^{2,3,4}
- Prior work found PCIST values in three individuals with severe AD were at or below the hypothesized threshold for consciousness (~23 PCIST).^{5,6} Whether PCIST is sensitive to earlier AD stages, and whether values are systematically reduced across the AD continuum, remains an open question that this study addresses.

AIMS

- Explore differences in PCIST between healthy controls (HC) and early AD stages {mild cognitive impairment (MCI) and mild dementia}.

METHODS

- Data from 28 HC and 28 early AD collected from four TMS-EEG studies at BIDMC. Diagnoses of MCI or mild-to-moderate dementia confirmed by amyloid PET or CSF biomarkers.



- TMS was applied to the left motor cortex (L-M1) at the motor hotspot and left inferior parietal lobule-angular gyrus (L-IPL) using MRI-guided anatomical targeting.⁷

- Simultaneous EEG recording was performed using a 64-channel system.
- Custom Matlab scripts used to pre-process raw EEG data (baseline correction, filtering noise and ICA-based artifact removal) and calculate PCIST.³

	Healthy Controls (n = 27)			Amnesic MCI or mild dementia due to AD (n = 28)*		
	Mean (SD)	Min	Max	Mean (SD)	Min	Max
Age	72 (5.80)	65	89	71 (8.32)	55	84
Gender F/M	14(F)/13(M)			14(F)/14(M)		
CDR-SB	0.03 (0.133)	0.0	0.5	2.89 (1.48)	1.0	7.0
MoCA	26.96 (2.28)	20	30	19.71 (3.80)	9	24

Table 1: Demographic information separated by healthy controls and Alzheimer's disease (AD) subjects.

*AD subjects were determined to have amnesic MCI or mild dementia due to AD as described in the Methods. CDR-SB—Sum of Boxes—scored out of 18 (16–18 = severe). MoCA—scored out of 30 (<25 = impairment).

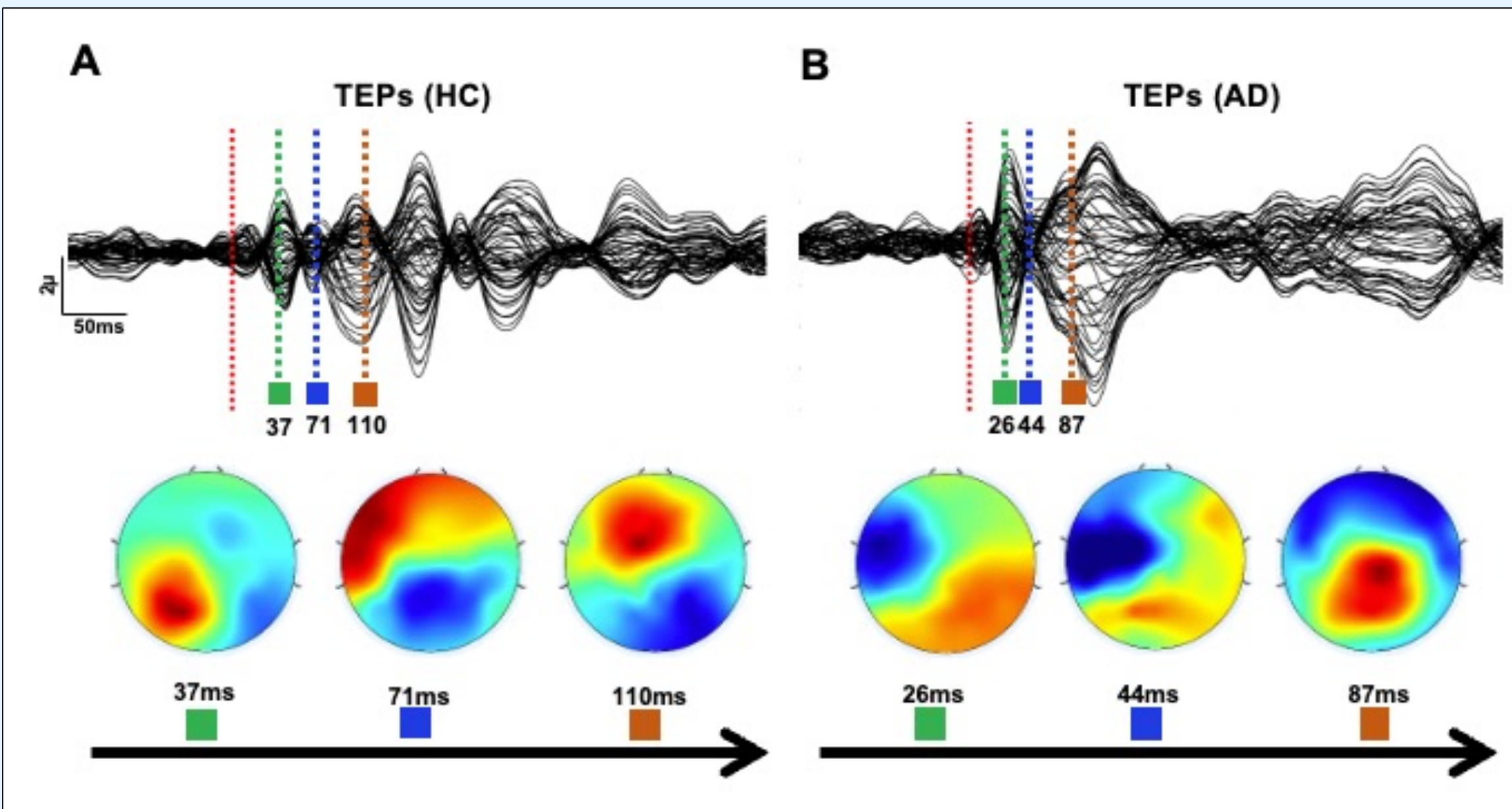


Figure 1: A and B: TMS evoked potentials (TEPs) from HC and AD representative subjects

Selected peaks (color vertical lines) demonstrated in the topographies are of selected time points.

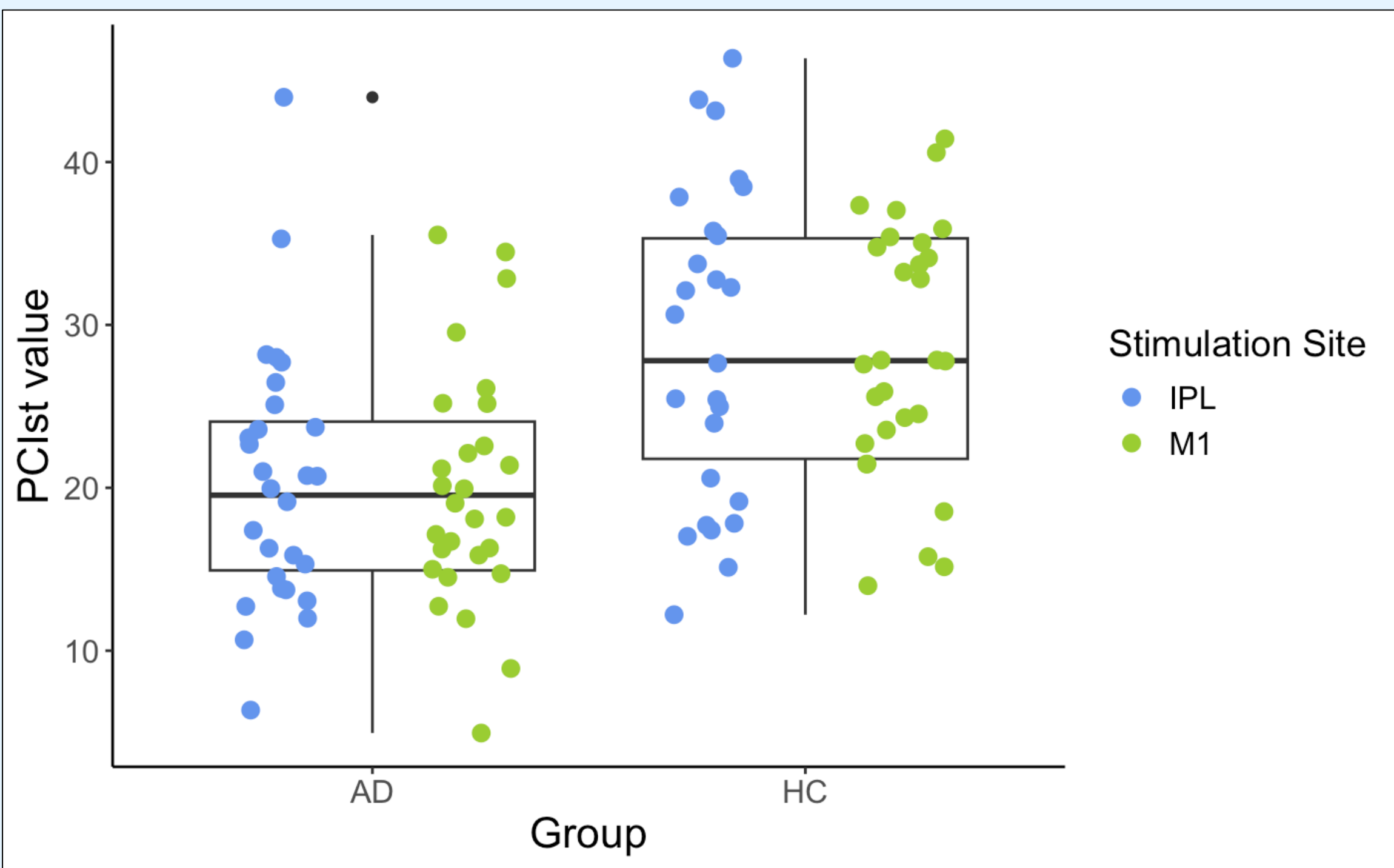


Figure 2: Mean PCIst value of both the AD and HC group by stimulation sites.

*AD at IPL (M = 20.39, SD = 7.97), AD at M1 (M = 19.88, SD = 7.29)
Healthy control at IPL (M = 28.69, SD = 9.75), Healthy control at M1 (M = 28.41, SD = 7.71).

RESULTS

- Individuals with AD showed significantly lower PCIST values compared to healthy controls (AD: M = 20.1, SD = 7.57; HC: M = 28.2, SD = 8.68; F(1,51) = 22.45, p < .001, $\eta^2 = .31$), indicating reduced cortical complexity in AD (Figure 2). No significant PCIST value difference was found between L-IPL and L-M1 stimulation sites, suggesting similar cortical complexity response in both regions (See Figure 3).
- No significant difference was found between L-IPL and L-M1 stimulation sites, and there was no group $\times$ site interaction, indicating that reduced cortical complexity in AD was consistent across both regions (Figure 3). Group differences remained significant after controlling for stimulation intensity, resting motor threshold, and scalp-to-cortex distance, including a trending difference at IPL consistent with parietal atrophy, confirming that findings reflect true neural differences rather than anatomical confounds.
- Two-stage Lasso regression found no significant cognitive or neurophysiological predictors of PCIST beyond group membership, supporting PCIST as an independent marker of cortical integrity in AD.

CONCLUSION

PCIST was significantly reduced in MCI and mild AD compared to healthy controls across both stimulation sites, suggesting global disruption. Reductions were independent of standard cognitive measures, indicating PCIST captures cortical dysfunction beyond cognition. These results support PCIST as a promising neurophysiological marker of cortical integrity and consciousness in AD, consistent with MToC.

FUTURE DIRECTIONS

- Examine PCIST in relation to resting-state cortical slowing and DMN disruption
- Investigate associations between PCIST and amyloid/tau burden
- Track PCIST longitudinally to assess sensitivity to disease progression and treatment response
- Extend PCIST to other cortical dementias

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