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Case report

Repetitive transcranial magnetic stimulation for early-onset Alzheimer's disease – A case report

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ABSTRACT

Background: Early-onset Alzheimer's Disease (AD) is a rare form of AD defined as exhibiting signs and symptoms before age 65. Several studies have shown high frequency repetitive transcranial magnetic stimulation (rTMS) to be an effective treatment for individuals with mild cognitive impairment (MCI) and AD when applied to the left and/or right dorsolateral prefrontal cortex (DLPFC) with clear improvements found on standardized assessments of cognitive function.
Case report: Here, we present a case report of a 44-year-old patient with clinical and laboratory characteristics of definite early-onset AD.
Findings: rTMS led to marked cognitive improvements. We hope to inspire more clinical interest in exploring rTMS for treatment of dementia.

1. Introduction

Alzheimer's Disease (AD) is the most common form of dementia, characterized by progressive cognitive decline with deficits in learning and memory (Alcalá-Lozano et al., 2018). Early-onset AD is a rare form of AD defined as exhibiting signs and symptoms before age 65 whereas late-onset begins at or after age 65 (Kelley et al., 2008).

The efficacy of pharmacological treatment for both early and late-onset AD is significantly limited, creating a fundamental need for alternative treatments (Alcalá-Lozano et al., 2018). Non-invasive neuromodulation via external brain stimulation can enhance neuroplasticity with the potential for mitigating disease progression by strengthening synaptic activity and activating neuronal populations associated with memory and learning pathways (Antal et al., 2022; Weiler et al., 2020). Several studies have shown high frequency repetitive transcranial magnetic stimulation (rTMS) to be an effective treatment for individuals with mild cognitive impairment (MCI) and AD when applied to the left and/or right dorsolateral prefrontal cortex (DLPFC) with clear improvements found on standardized assessments of cognitive function (Devi et al., 2014; Zhao et al., 2016; Cotelli et al., 2011). Here, we present a case report of a 44-year-old patient with clinical and laboratory characteristics of definite early-onset AD who showed marked cognitive improvements following rTMS treatment.

The patient is a 44-year-old female who presented for evaluation and management of progressive cognitive decline and poor mood, starting most noticeably two years before presentation to our clinic. Primary symptoms included disorientation, short- and long-term memory loss, misplacing important objects, and deficits in executive function. Standard rating scales for mood disorders showed no clear signs of depressive illness including a PHQ-9 score of 2 and Burn's Depression Inventory score of 3. She had no impairments in basic activities of daily living (ADLs). Patient worked as an executive in a large organization for seven years before the onset of symptoms.

The initial presentation was remarkable for normal vitals, cranial nerves, and neuromuscular exam. The mental status exam was remarkable for normal orientation (x4), slight bradyphrenia, unable to spell 'WORLD' in reverse, and impaired recall: immediate: 1/3, delayed: 1/3 at 3, 5, and 7 min, unchanged with clues at all three time points. The patient's verbal responses were slow. Insight into cognitive symptoms appeared impaired.

In addition to bedside exam, NeuroTrax computer testing platform was used to assess several cognitive functions. NeuroTrax cognitive testing has high test–retest reliability and is a validated instrument as it differentiates cognitively healthy individuals from those with mild cognitive impairments (two standard deviations below the mean) (Dwolatzky et al., 2003). The norma-

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tive sample is standardized according to age and education (mean = 100, SD = 15). Patient scored more than two standard deviations below average on global cognition (60.8, $z = -2.61$), memory (37.2, $z = -4.19$), verbal functioning (25.0, $z = -5.0$), problem-solving (66.5, $z = -2.33$), and working memory (62.0, $z = -2.53$). She scored more than one standard deviation below average on executive functioning (77.4, $z = -1.5$), attention (76.4, $z = -1.58$), and visual-spatial processing (80.8, $z = -1.28$) (See Table 1).

The ApoE Alzheimer's Risk test detects the presence of the APOE4 variant (apolipoproteinE), which is a well-established genetic modifier strongly associated with an increased risk of early or late-onset AD (Schipper 2011). Patient underwent ApoE genotyping, revealing two copies of ApoE-E4 genotype present, consistent with the highest risk factor for dementia of Alzheimer's type (Schipper 2011). Cerebral spinal fluid (CSF) evaluation revealed elevated levels of P-tau and (110.8 pg/mL) total-tau (824 pg/mL) proteins, and reduced A-beta 42 (521.8 pg/mL) resulting in a A-beta 42 to T-tau index (ATI) of 0.43 – consistent with a diagnosis of AD (Weiler et al., 2020). (Reference range: 'not consistent with AD': P-Tau <54 pg/mL and ATI >1.2, 'borderline AD': P-Tau 54–68 pg/mL and/or ATI 0.8–1.2, 'consistent with AD': P-Tau >68 pg/mL and ATI <0.8) (Ferreira et al., 2014). The patient was diagnosed with early-onset AD due to combination of clinical signs and symptoms, severe deviation from normal performance on multiple cognitive domains on neurocognitive testing, and confirmatory CSF and genetic laboratory results.

Patient was treated with a trial of rivastigmine patch by her primary care physician, but discontinued use after increased fatigue and severe rash. Patient also underwent trials of oral memantine, pramipexole, and galantamine (anti-cholinesterase inhibitors and NMDA-receptor antagonists) and discontinued due to side effects including fatigue and skin rash.

Following a discussion of risks and benefits, the husband and patient agreed with trial of neuromodulation using rTMS at our center. Written signed consent was obtained for treatment and publication of this case report. The Motor Threshold (MT) was determined as the intensity required to activate the contralateral Abductor Policis Brevis (APB) consistently for at least 50% of trials at the same intensity per visual guidance. Patient underwent daily MRI-navigated rTMS sessions. The stimulation parameters were chosen based, in part, on current trial evidence for early-onset dementia (Ahmed et al., 2012, Devi et al., 2014, Cotelli et al., 2011). All stimulations were performed using a figure-of-eight coil using the CloudTMS Machine (Neurosoft Ltd, Russia). Cortical targets included left/right DLPFC (10 Hz, 26 intertrain interval, 120% MT, 40 pulses in train, 50 trains, 2000 total pulses) for 19 sessions. Stimulation targets were identified and labeled using MRI navigation software (Neural Navigator, Brain Science tools B.V., 2022. Version 3.0 Build Release238, Netherlands).

Following 19 sessions of rTMS, the patient showed significant improvement in five cognitive domains on NeuroTrax. She demonstrated improvement in memory by 22%, executive functioning by 32.4%, attention by 13.2%, verbal functioning by 148%, and working

Table 1
NeuroTrax Index Scores and Z-scores at baseline and after rTMS.

	Baseline		After TMS #19			
	Index Score	**Z-Score**	**Index Score**	**Z-Score**	**% Change Index Score**	**Z-score Change**
Global Cognitive Score	**60.8**	**−2.61**	**71.8**	**−1.93**	**18.1%**	**0.68**
Memory	**37.2**	**−4.19**	**45.4**	**−3.64**	**22%**	**0.55**
Verbal Memory: Total Accuracy	25.0		54.0			
Delayed Verbal Memory: Accuracy	25.5		34.7			
Non-Verbal Memory: Total Accuracy	63.2		57.6			
Delayed non-verbal Memory: Accuracy	35.3		35.3			
Executive Functioning	**77.4**	**−1.50**	**102.5**	**0.16**	**32.4%**	**1.36**
Go-No-Go: Composite Score	64.4		89.3			
Catch Game: Total Score	99.4		115.8			
Stroop Interference: Composite Score, Level 3	68.4		DI			
Attention	**76.3**	**−1.58**	**86.4**	**−0.91**	**13.2%**	**0.67**
Go-No-Go: Response Time	71.7		91.6			
Go-No-Go: Response Time Std Dev	62.7		85.6			
Stroop Interference: Response Time, Level 2	94.3		82.0			
Visual Spacial Processing	**80.8**	**−1.28**	**65.7**	**−2.29**	**−18.2%**	**1.01**
Visual Spatial Processing: Accuracy	80.8		65.7			
Verbal Function	**25.0**	**−5.00**	**62.0**	**−2.53**	**148%**	**2.47**
Verbal Function: Rhyming, Accuracy	25.0		66.5			
Problem Solving	**66.5**	**−2.33**	**66.5**	**−2.23**	**0%**	**0**
Problem Solving: Accuracy	66.5		66.5			
Working Memory	**62.0**	**−2.53**	**73.8**	**1.76**	**19%**	**0.77**
Go-No-Go: Composite Score	64.4		89.3			
Verbal Memory: Accuracy, Repetition 1	42.7		58.4			
Non-Verbal Memory: Accuracy, Repetition 1	79.0		DI			

DI - Data Insufficient for a Score.
'Composite Score' is computed from Accuracy and Response Time. Response Time and Response Time Std Dev computed for correct responses. All scores were normalized for age and educational level and fit to an IQ-style scale. Z-scores (were calculated for a mean score 100 and SD 15. Raw outcome parameter data is normalized according to age- and education-specific normative data. Normalized scores are then scaled to a standard scale with mean of 100 and standard deviation (SD) of 15. Groups of normalized parameters that measure similar cognitive functions are then averaged to produce **Index Scores** (indicated in bold), each reflecting performance in a particular cognitive domain (area). A Global Cognitive Score is computed as the average of all index scores computed for a given administration and serves as a measure of overall battery performance (indicated in bold). Normative data are generated from cognitively healthy individuals in controlled research studies (current sample size: n = 1569.

memory by 19% when compared to baseline scores (See Table 1). There was no change in problem-solving ability and a slight decrease in visual-spatial processing. The patient did not report any adverse events from TMS stimulation during treatment.

To our knowledge, this is the first known case report of applying TMS stimulation on a clinically and laboratory-confirmed patient with early-onset AD. Stimulation of the DLPFC at 20 Hz was selected based on current randomized clinical trials (RCT) of applying TMS for late-onset AD (Alcalá-Lozano et al., 2018; Weiler et al., 2020; Ahmed et al., 2012; Devi et al., 2014; Zhao et al., 2016; Cotelli et al.,2011), showing significant improvements in cognition maintained for 3 or more months (Ahmed et al.,2012). Other studies have shown long-lasting improvements in memory (Zhao et al., 2016) and verbal functioning, specifically in sentence comprehension, noun/verb identification (Cotelli et al., 2011), and nonverbal and verbal agility in patients with late-onset AD (Zhao et al., 2016). We hope this case report will inspire further robust clinical research towards identifying TMS protocols for the treatment of early-onset AD.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: First Author, Ali Elahi, is 100% owner of Neurospa Brain Rejuvenation Centers, Inc, a medical corporation in California. Second Author, Tiffany Frechette, is a part-time employee at Neurospa Brain Rejuvenation Center, Inc., a medical corporation in California. There are no other financial relationships that would be considered a 'conflict of interest' between the authors and any other entity or organization.

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