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Assessment of Neuroplasticity in Late-Life Depression with Transcranial Magnetic Stimulation

Apoorva Bhandari¹, Jennifer I. Lissemore², Tarek K. Rajji^{1,2,3}, Benoit H. Mulsant^{2,3}, Robin F.H. Cash⁴, Yoshihiro Noda⁵, Reza Zomorodi^{1,3}, Jordan F. Karp^{6,7}, Eric J. Lenze⁸, Charles F. Reynolds III^{6,9}, Zafiris J. Daskalakis^{1,2,3}, and Daniel M. Blumberger^{1,2,3}

¹Temerty Centre for Therapeutic Brain Intervention, Centre for Addiction and Mental Health, Toronto, Ontario, M6J 1H4, Canada;

²Department of Psychiatry, University of Toronto, Toronto, Ontario, M5T 1R8, Canada;

³Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario, M5T 1R8, Canada

⁴Monash University, Alfred Psychiatry Research Centre, Melbourne, Australia

⁵Department of Psychiatry, Faculty of Medicine, Keio University, Japan

⁶Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA;

⁷VAPHS, Geriatric Research, Education, and Clinical Center;

⁸Healthy Mind Lab, Department of Psychiatry, Washington University School of Medicine, St Louis, MO, USA;

⁹Department of Psychiatry, Pittsburgh, PA, USA

Abstract

Background: Studies using Transcranial Magnetic Stimulation (TMS), a non-invasive method of brain stimulation, have implicated impaired neuroplasticity in the pathophysiology of depression in younger adults. The role of neuroplasticity in late-life depression (LLD) has not yet been explored using TMS.

Objective: This study aimed at evaluating motor cortical neuroplasticity using paired associative stimulation (PAS). Single-pulse TMS was used to induce motor-evoked potentials (MEP) in the contralateral hand muscle before and after PAS. The potentiation of MEP amplitudes after PAS was used as an indirect index of associative plasticity and long-term potentiation (LTP) (i.e. PAS-LTP).

Address for Correspondence: Daniel M. Blumberger, MD, MSc, FRCPC, Medical Head and Co-Director, Temerty Centre for Therapeutic Brain, Intervention Centre for Addiction and Mental Health, Associate Professor, Department of Psychiatry, University of Toronto 1001 Queen St. W. Unit 4, Room 115, Toronto, ON M6J, 1H4 Tel: 416-535-8501, Fax: 416-583-4613
daniel.blumberger@camh.ca.

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Results: 48 older adults with depression and 34 age-matched healthy controls (HC) were compared. PAS- LTP was successfully induced in 68.8% of older adults with depression and 47.1% of HC. At the group level, older adults with depression failed to show statistically significant induction of neuroplasticity, which was observed in HC. However, no significant differences were observed between the two groups for PAS-LTP.

Conclusion: Our results suggest that associative plasticity does not differ substantially between older adults with depression and age-matched HC. Continued research is needed to more comprehensively understand the role of neuroplasticity in the pathophysiology of LLD.

Keywords

Transcranial Magnetic Stimulation; Paired Associative Stimulation; Late-Life Depression; Aging; Neuroplasticity; Long-term Potentiation; N-Methyl-D-Aspartate

INTRODUCTION

Major depression in older adults –late-life depression (LLD)– is one of the most common neuropsychiatric disorders, affecting 10–20% of individuals over 65 years of age (Gottfries, 2001; Guerra et al., 2016). Individuals with LLD experience worse physical functioning, poorer quality of life, and heightened risk for neurocognitive impairment (Aizenstein et al., 2016).

The pathophysiological basis of LLD is complex and not yet fully understood. Neuroplasticity refers to the brain's dynamic ability to reorganize itself and form new neuronal connections in response to internal or external stimuli (Citri and Malenka, 2008). Synaptic plasticity is the fundamental mechanism underlying neuroplasticity, which involves the specific adaptation of synapses in response to a stimulus that in turn changes the way the synapse reacts to subsequent related stimuli (Citri and Malenka, 2008). This change in synaptic strength can either strengthen synaptic connections –long-term potentiation (LTP), or weaken synaptic connections –long-term depression (LTD) (Malenka and Bear, 2004).

Normann and colleagues (2007) provided the first evidence for deficient LTP-like plasticity in depressed patients by assessing changes in visually-evoked potentials (VEP) – an index of LTP-like plasticity – in response to delivery of patterned visual stimuli. Depressed patients demonstrated significantly reduced VEP amplitudes compared to healthy controls (Normann et al., 2007). Since then, further studies have revealed reduced synaptic plasticity in the dorsal executive network reflected by assessing declarative memory consolidation (Nissen et al., 2010) and facilitation of synaptic plasticity in the ventral emotional network assessed by fear extinction (Kuhn et al., 2014) and acquisition (Nissen et al., 2010). However, these synaptic plasticity indices involve complex brain circuits, thus the localization of the mechanisms underlying altered synaptic plasticity are difficult to determine (Kuhn et al., 2016). To address this limitation, Player et al. (2014) showed enhanced motor cortical plasticity after a course of transcranial direct current stimulation treatment – a non-invasive form of brain stimulation that has been demonstrated to have therapeutic effects for depression (Kalu et al., 2012; Loo et al., 2012; Brunoni et al., 2013). However, this increase in plasticity did not correlate with the significant mood improvement observed.

Paired associative stimulation (PAS) combines transcranial magnetic stimulation (TMS) paradigm with peripheral nerve stimulation (PNS) to indirectly probe LTP-like plasticity in the human motor cortex (Stefan et al., 2000). PAS can be used to induce LTP-like plasticity (subsequently referred to as PAS-LTP) through the pairing of peripheral median nerve electrical stimulation with TMS to the contralateral motor cortex. This pairing allows for the synchronous arrival of the afferent (i.e., peripheral) stimulation and delivery of the electromagnetic stimulation to the motor cortex, activating pre- and post-synaptic neurons in a time-dependent manner to induce PAS-LTP (Stefan et al., 2002).

Two studies have used a PAS protocol to investigate synaptic plasticity in adults with depression. Player et al. (2013) conducted a study to examine PAS-LTP in depressed adults and found reduced PAS-LTP in the depressed group compared to healthy controls (HC). These findings were recently confirmed and extended by Kuhn et al. (2016) who also demonstrated reduced PAS-LTP in adults with MDD and provided the first evidence for restoration of PAS-LTP after remission. PAS-LTP has not been investigated in older adults with depression.

Disruption of mood-related brain circuitry has been implicated in LLD (Chen et al., 2009; Khundakar and Thomas, 2009). Structural neuroimaging studies have consistently demonstrated reduced volume of fronto-striatal-limbic regions in older depressed adults, particularly the prefrontal cortices and hippocampus (Disabato and Sheline, 2012; Taylor et al., 2014). Recent postmortem studies examining older depressed adults have reported reduced neuronal density in the orbitofrontal cortex (OFC) (Rajkowska et al., 2005) and caudate nucleus (Khundakar et al., 2011), and reduced neuronal volume in the dorsolateral prefrontal cortex (DLPFC) (Khundakar et al., 2009). These findings, taken together with evidence for the disruption of several key pathways fundamental to synaptic function and synaptogenesis including loss of neurotrophic support [e.g. brain-derived neurotrophic factor (BDNF)] (Diniz et al., 2014; Diniz et al., 2010), dysregulated glutamate metabolism (DeLorenzo et al., 2015; Sanacora et al., 2012), and elevation of proinflammatory cytokines (Alexopoulos and Morimoto, 2011), implicate impaired synaptic plasticity as a potential pathological process underlying the biological basis of LLD.

Thus, we conducted a study of PAS-LTP in a sample of older adults with depression. PAS-LTP was compared in older adults with depression and age-matched HC. We hypothesized that older adults with depression would display reduced PAS-LTP compared to age-matched HC.

METHODS

Study Participants

Older adults with depression were recruited among participants in two clinical treatment studies at the Centre for Addiction and Mental Health (CAMH, Toronto, Ontario) prior to initiating treatment. A total of 56 older adults with depression were recruited from the two clinical trials and 38 age and sexmatched HC were recruited using registries and community advertisements. Based on the effect size of the Player et al. (2013) study (Cohen's $d = 0.67$)

with power ($1 - \beta$) set at 0.80 and $\alpha = 0.05$, two-tailed a sample size of 72 total subjects (36 LLD and 36 HC) was required.

Older adults with depression were ≥ 60 years of age and met diagnostic criteria for MDD (single or recurrent) based on the Structural Clinical Interview for the DSM-IV (SCID-IV) (First et al., 2002). They had Montgomery-Asberg Depression Rating Scale (MADRS) scores ≥ 15 (Montgomery and Asberg, 1979) and the Mini-Mental State Examination (MMSE) scores ≥ 25 (Folstein et al., 1975). Comorbidity was assessed using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) (Linn et al., 1968). Patients were excluded if they: (i) presented with a comorbid Axis I disorder –with the exception of an anxiety disorder; (ii) had an unstable medical illness; or (iii) were taking an anticonvulsant. Benzodiazepine use was permitted; however, the dose could not exceed 2 mg/day of lorazepam or equivalent. Prior treatment resistance was assessed using the Antidepressant Treatment History Form (ATHF).

All HC presented with: (i) no prior history of psychiatric illness or any psychiatric comorbidities as assessed by the Mini International Neuropsychiatric Interview Version 6.0 (MINI 6.0); (ii) tested negative for any substances on the MedTOX urine toxicology screen (MEDTOX® Diagnostics, Inc., Burlington, NC, USA); and (iii) passed a TMS safety screen.

The study was approved by the CAMH Research Ethics Board and performed in accordance with the Declaration of Helsinki. All participants provided written informed consent.

PAS Procedure

For electromyography (EMG) recordings, disposable 9mm surface electrodes were positioned over the right abductor pollicis brevis (APB) muscle belly (active electrode) and the interphalangeal joint of the thumb (reference electrode). The ground electrode was placed at the proximal end of the right forearm on the inside of the elbow joint. Participants were asked to relax their right hand throughout the protocol and EMG recordings were monitored in real time to confirm APB muscle relaxation. The EMG signal was amplified, filtered (band pass 2–2.5 kHz) and digitized at 5 kHz.

A 7-cm figure-of-eight coil with two Magstim 200 stimulators was used to deliver monophasic TMS pulses to the left motor cortex. The resting motor threshold (RMT) was defined as the minimal output intensity that evoked a $\geq 50\mu\text{V}$ motor-evoked potential (MEP) in 5 out of 10 consecutive trials in a relaxed muscle (Rossini et al., 1994). The TMS intensity required to evoke MEPs with a peak-to-peak amplitude of $\sim 1\text{mV}$ (0.5 – 1.5mV) in the relaxed APB muscle was then identified for use as the test stimulus (TS) intensity in the PAS protocol (Rossini et al., 1994).

The PAS protocol was administered using standard procedures (see *Stefan et al., 2000; Rajji et al., 2011*). In brief, PAS was administered by delivering 180 single-pulse TMS stimuli to the left motor cortex, preceded by peripheral electrical nerve stimulation to the right median nerve by 25ms. Electrical median nerve stimulation was delivered at 300% of the participant's sensory threshold (i.e., the minimum detectable peripheral nerve stimulus). To account for attention effects, participants were instructed to count the electrical stimuli felt at

the wrist and intermittently asked to report their count of the stimuli. Their reported count was recorded alongside the actual count (Stefan et al., 2004). The absolute difference between the participant's count and the actual count (count difference) was used as an index of attention during the PAS protocol.

MEPs were collected prior to the PAS intervention (Baseline) and at four time points after PAS (post 1: 0 min, post 2: 15 min, post 3: 30 min, and post 4: 60 min). Each testing block (post 1–4) consisted of 20 MEPs delivered at 0.1Hz for a total duration of 3 minutes.

Data Analysis

All data are reported as mean $\pm$ standard deviation (SD) unless otherwise stated. For each participant, the mean of the 20 MEP amplitudes was calculated for each time point (Baseline and Post 1–4); post-PAS MEP values were normalized by dividing them by the participant's baseline MEP value. To compare MEP potentiation following PAS, the normalized post-PAS MEP amplitude values were averaged across all post-stimulation time points (PAS-LTP_{avg}) (Player et al., 2013). Given the inter-individual variance of post-PAS timing for maximum MEP potentiation, we selected the maximum MEP ratio for each participant (PAS-LTP_{max}) after PAS for analyses.

All statistical analyses were done using the Statistical Package for the Social Sciences (SPSS), version 24.0. To attain normal distributions all TMS-EMG data were log-transformed. Data points 3 standard deviations from the mean were classified as outliers and were removed from further analyses (Field, 2009). Data from 2 LLD participants were removed due to outliers. In addition, data from 10 participants (6 with LLD and 4 HC) were removed from the analyses due to faulty data recording.

Demographic and clinical characteristics and baseline pre-PAS parameters were compared between older adults with depression and HC using independent samples t-tests for continuous variables and Chi-Square (χ^2) tests for categorical variables. The significance level for all analyses was set to an α level of 0.05 (two-tailed).

Effect of PAS on MEP amplitude—The Shapiro-Wilk test, histograms, Q-Q plots and box plots were used to explore normality of this multivariate dataset. Repeated measures analysis of variance (RM-ANOVA) was performed for normalized MEP values, with group (LLD *vs* HC) and time (Baseline, Post 0– 60 min) as the between and within-subjects factors, respectively.

To assess overall plasticity induction after PAS administration, separate one-sample t- tests were performed for each group to compare PAS-LTP_{avg} (i.e., average of post-PAS MEP/pre-PAS MEP) to a test value of 1. Then, t-tests for independent samples were conducted to compare average (PAS-LTP_{AVG}) and maximum (PAS-LTP_{MAX}) MEP potentiation between the two groups (LLD *vs* HC).

Cluster analyses—Due to the high inter-individual variability in response to PAS, we used the SPSS K- Means cluster analysis to distinguish “PAS responders” (i.e., participants that showed the expected response; LLD-R *or* HC-R) and “PAS non-responders” (i.e.,

participants who did not show the expected response; LLD-NR *or* HC-NR). This analysis used MEP amplitudes for each time point (post 1–4), normalized to baseline.

Due to the differences in sample size (33 LLD-R *vs* 16 HC-R) and data not meeting the normality assumptions, Mann-Whitney U Tests were performed to compare the average (PASLTP_{avg}) and maximum (PAS-LTP_{max}) MEP potentiation of both groups of responders.

Correlation analyses—Correlations between TMS measures and demographic or clinical variables were assessed in the whole sample with Pearson or Spearman correlation analyses depending on the distributions of the measures of interest. Correlations were analyzed within groups only if the relationship in the whole sample reached significance.

Sensitivity Analyses—Sensitivity analyses were performed to assess the robustness of our findings in the presence or absence of several factors which may influence PAS-LTP induction: (i) antidepressant or benzodiazepine/sedative use, (ii) treatment resistance, and (iii) late (≥ 60) or early (< 60) onset of depressive symptoms (*see* Supplementary Information).

RESULTS

Table 1 summarizes the demographic and clinical characteristics across groups. Older adults with depression and HC did not differ in age, sex, or education. Furthermore, no significant differences were observed for the pre-PAS parameters between the two groups (*see* Table 2).

Effect of PAS on MEP amplitude

The 2×5 RM-ANOVA comparing older adults with depression and HC across all time points (Baseline, Post 1–4) revealed no significant effect of time ($F(3.47, 277.17) = 2.10, p = 0.09$), or time $\times$ group interaction ($F(3.47, 277.17) = 1.227, p = 0.30$) (*see* Figure 1,3,4).

Older adults with depression did not display overall MEP potentiation ($t(47) = 1.206, p = 0.23$), whereas, the overall MEP potentiation for age-matched HC was significantly different from 1 ($t(33) = 2.231, p = 0.033$). The two groups did not differ significantly in terms of average ($t(79.78) = -1.058, p = 0.262$) and maximum ($t(79.76) = -1.279, p = 0.204$) MEP potentiation. No differences in attention during PAS were observed between the two groups; ($t(72) = -0.043, p = 0.97$).

Cluster analysis

The cluster analyses revealed two clusters of participants in each group: a cluster of 33 (68.8%) older adults with depression and a cluster of 16 (47.1%) HC, both showing the expected response to PAS (i.e., facilitated MEP amplitude) referred to as “PAS responders (R)” and a cluster showing no facilitation in MEP amplitude, referred to as “PAS non-responders (NR)”. A total of 48 older adults with depression and 34 HC were included in the cluster analyses. 68.8% ($n = 33$) of depressed older adults and 47.1% ($n = 16$) of HC responded as expected to the PAS protocol; *see* Figure 2.

For responders, we observed no statistically significant difference between depressed older adults and HC for both average (LLD-R mean rank= 23.42, HC-R mean rank= 28.25; $U=212$, $p=0.267$) and maximum (LLD-R mean rank= 24.20, HC-R mean rank= 26.66; $U=237.5$, $p=0.571$) MEP potentiation.

Correlation Analyses

A weak negative correlation was observed between age and RMT across groups suggesting increased cortical excitability with advancing age; Spearman's rho (r_s) = -0.262 , $p=0.011$. This correlation remained significant in the healthy control group ($r_s = -0.405$, $p=0.012$), but not in older adults with depression ($r_s = -0.147$, $p=0.283$). No other significant correlations between demographic or clinical characteristics and TMS measures were observed.

Sensitivity Analyses

We observed no significant influence of antidepressant or benzodiazepine/sedative use, treatment resistance, and late (≥ 60) or early (< 60) onset of depressive symptoms on PAS-LTP induction (see *Supplementary Information*).

DISCUSSION

To our knowledge, this is the first TMS study to evaluate neuroplasticity in older adults with depression using PAS. We did not observe in older adults with depression the induction of plasticity observed in HC. However, no significant differences in overall plasticity were observed between older adults with depression and age-matched controls.

In both groups, cluster analyses revealed a cluster of participants in whom PAS-induced LTPlike plasticity ("PAS responders") and participants in whom PAS did not induce LTP-like plasticity ("PAS non-responders"): The PAS protocol successfully induced LTP-like plasticity in about twothirds of older adults with depression and half of the HC sample. These results confirm the considerable inter-individual variability in response to PAS (Muller-Dahlhaus et al., 2008; Stefan et al., 2000). We further assessed differences in both average and maximum plasticity in responders only and found no significant differences between groups.

Player et al. (2013) provided the first objective demonstration of impaired neuroplasticity in depression using PAS. However, while Player et al. observed a total absence of MEP potentiation (normalized to baseline) in younger adults with MDD across all post-stimulation time points, we observed a small, albeit non-significant, MEP potentiation across all time points in our older adults with depression. Furthermore, while Player et al. (2013) reported a significant difference for mean MEP amplitude facilitation between younger depressed and healthy adults, we found no such difference between older adults with depression and age-matched HC.

Similarly, when we examined the time course of excitability changes post-PAS, we found no significant differences between groups. In contrast, Kuhn et al. (2016) observed a significant difference in PAS-induced plasticity between younger depressed adults and HC (Kuhn et al.,

2016). This may be partly explained by the higher percentage of depressed adults on antidepressant medication in the study by Kuhn et al. (2016) (26/27) compared to our sample (16/48), as some antidepressants are known to facilitate synaptic plasticity (Castren, 2004). Additionally, Kuhn et al.'s (2016) sample may be different from ours: they included younger adults with short MDD episodes of which only 56% were recurrent; by contrast, 39 of 48 (81%) of our older adults with depression presented with recurrent episodes and their duration was longer. The relationship among age, depression characteristics (e.g. episode duration or recurrence), and neuroplasticity requires further investigation.

There is growing evidence for a robust, heterogeneous influence of normative aging on numerous genes and biological pathways that overlap with those implicated in the neurobiology of depression (McKinney and Sibille, 2013). In this study we were not able to distinguish the neurophysiological profile of LLD from that of normative aging. Our results suggest a potential dampening effect of age on neuroplasticity which may have blunted the difference between MDD and HC seen in younger samples.

Our results should be considered in light of several limitations. Translation of our motor cortical PAS-LTP findings to other brain regions more central to depression pathology is limited because of variances in (i) cortical architecture, (ii) receptor density, and (iii) neurotransmitter distribution between brain regions (Cash, R.F. et al., 2017). Future studies could assess PAS-LTP directly in the dorsolateral prefrontal cortex (DLPFC) using TMS in combination with electroencephalography (EEG) (Rajji et al., 2013). A recent study by Noda et al. (2018) found impaired neuroplasticity in the DLPFC of younger depressed patients compared to healthy controls using TMS-EEG (Noda et al., 2018). Additionally, while we evaluated older adults with depression at a single time point to control for symptom state and medication status, future studies would benefit from evaluating PAS-LTP before and after therapeutic treatment to examine the correlation between cortical plasticity and therapeutic response.

We attempted to match 2 depressed for each healthy subject on age and sex. However, the matching was compromised by several participants who had contaminated or unusable data. Nevertheless, an independent samples t-test for age between groups (LLD vs HC) did not demonstrate any statistical difference in age between groups.

We were not able to differentiate between the effects of normative aging and LLD on PAS-induced LTP because of the absence of a young healthy control sample. During this study a third of the older adults with depression were on antidepressant medications and comparatively less were on benzodiazepines/sedatives. Previous studies have shown that antidepressants can facilitate neuroplasticity (Batsikadze et al., 2013; Normann et al., 2007). However, our sensitivity analyses showed no PAS-LTP differences in older adults with depression either on or off antidepressants or benzodiazepines/sedatives (see Supplementary Information). Furthermore, discrepancies between our study and previous studies (Kuhn et al., 2016; Player et al., 2013) may be explained by a potential impact of depressive symptom severity. For this study, our older adults with depression were required to have at least mild depression (MADRS ≤ 15), whereas in previous studies the participants had moderate

depression. However, the vast majority of our depressed participants (n=44) had a MADRS score = 20.

Additionally, prior studies only included right handed subjects as assessed according to the Edinburgh Handedness Inventory (Kuhn et al., 2016; Player et al., 2013). However, in our study handedness was assessed for participants who were subsequently randomized after baseline assessments (n=68) using the Hand Dominance Questionnaire. Of the 68 participants, the majority (n=62) were right handed with 6 participants being left handed.

Lastly, nerve conduction times may be slower in older adults (Doherty et al., 1993; Dorfman and Bosley, 1979; Mesrati and Vecchierini, 2004). This could mean that the standard timing of PAS (25ms) may no longer elicit associative plasticity effects in the expected manner; this warrants further research. However, in this study we used standard PAS methodology (Stefan et al., 2000) and testing conditions were identical across both groups (Cash, R.F.H. et al., 2017).

In conclusion, our study is the first TMS study to evaluate neuroplasticity in older adults with depression using PAS. We did not observe a significant induction of plasticity in older adults with depression that was seen in HC. However, no significant differences in plasticity were found between older adults with depression and age-matched HC. In this study we were not able to differentiate between the changes associated with normative aging and LLD. Further research including both younger and older adults is needed to disambiguate the contribution of aging in determining the role of neuroplasticity in the pathophysiology of LLD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Group data (mean $\pm$ standard error) displaying the time course of motor-evoked potential (MEP) amplitude potentiation after paired associative stimulation (PAS) in older depressed adults (blue circles) and age-matched healthy controls (orange circles). LLD= Late-Life Depression; HC= Healthy Control.

Figure 2.

Group data (mean $\pm$ standard error) displaying the time course of motor-evoked potential (MEP) amplitude potentiation after paired associative stimulation (PAS) in older depressed adult PAS responders (blue circles) and age-matched healthy control responders (orange circles). MEP amplitudes shown were normalized to baseline values for each participant. LLD= Late-Life Depression; HC= Healthy Control.

Figure 3.

Group data (mean $\pm$ standard error) displaying the time course of motor-evoked potential (MEP) amplitude potentiation after paired associative stimulation (PAS) in older depressed adult PAS responders (blue circles) and non-responders (red circles). MEP amplitudes shown were normalized to baseline values for each participant. LLD-R = Late-Life Depression Responders; LLD-NR = Late-Life Depression Non-Responders.

Figure 4.

Group data (mean $\pm$ standard error) displaying the time course of motor-evoked potential (MEP) amplitude potentiation after paired associative stimulation (PAS) in older healthy adult PAS responders (blue circles) and non-responders (red circles). MEP amplitudes shown were normalized to baseline values for each participant. HC-R = Healthy Control Responders; HC-NR = Healthy Control Non-Responders.

Table 1:

Demographic and Clinical Characteristics of Participants

	LLD (<i>n</i> =48)	HC (<i>n</i> =34)	Statistic	p-value
Demographic characteristics				
Age (years; range)	67.9±6.9; 60–92	69.10±8.88; 60–91	$t(59.95) = -0.554$	0.58
Sex	19M/29F	14M/20F	$\chi(1) = 0.021$	0.89
Education (years)	15.1±2.8	15.52±2.34	$t(80) = -0.769$	0.44
Clinical characteristics				
MADRS	25.9±4.9	-	-	-
MMSE	29.0±1.1	-	-	-
CIRS-G	6.6±3.0	-	-	-
Age of Onset				
60 years (n, %)	9 (19%)	-	-	-
< 60 years (n, %)	39 (81%)	-	-	-
Treatment Resistant (n, %)	34 (71%)	-	-	-
Medication use (n, %)				
Antidepressants	17 (35%)	-	-	-
Benzodiazepines/sedatives	11 (23%)	-	-	-

Abbreviations: LLD = Late-Life Depression; HC = Healthy Control; MADRS = Montgomery-Asberg depression rating scale; MMSE = Mini-Mental State Examination; CIRS-G = Cumulative Illness Rating Scale for Geriatrics.

*Treatment resistance defined as having failed an antidepressant trial with a score ≥ 3 on the Antidepressant Treatment History Form (ATHF) during the current episode.

Table 2.

Pre-PAS Parameters

	LLD (<i>n</i>=48)	HC (<i>n</i>=34)	Statistic	p-value
RMT (%MSO)	48.2±9.5	48.6±7.3	t(80) = -0.362	0.719
TS intensity (%MSO)	61.±12.54	63.2±12.9	t(80) = -0.696	0.489
Pre-PAS mean MEP amplitude (mV)	0.94±0.28	0.88±0.23	t(80) = 0.790	0.432

Abbreviations: LLD= Late-Life Depression; HC= Healthy Control; PAS = Paired Associative Stimulation; RMT= Resting Motor Threshold; %MSO = Percentage Maximum Stimulator Output; TS intensity = Test stimulus intensity = intensity required to elicit 1mV peak-to-peak motor-evoked potential (MEP) amplitude.