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Assessment of neuroplasticity in late-life depression with transcranial magnetic stimulation

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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).
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.

1. 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 et al. (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

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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 circuity 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 post-mortem 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., 2010, 2014), dysregulated glutamate metabolism (DeLorenzo et al., 2015; Sanacora et al., 2012), and elevation of pro-inflammatory 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.

2. Methods

2.1. 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 sex-matched 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 – β) set at 0.80 and α = 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.

2.2. PAS procedure

For electromyography (EMG) recordings, disposable 9 mm 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 ≥50 μV 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 ~1 mV (0.5–1.5 mV) 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 25 ms. 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 0.1 Hz for a total duration of 3 min.