Main text: 3496 words

Abstract: 246 words

Number of Figures: 1

Number of Table: 2

Manuscript

Impaired neuroplasticity in the prefrontal cortex in depression indexed through paired associative stimulation

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1002/da.22188](#).

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Conflicts of Interest

Y.N has received postdoctoral fellowship from the Centre for Addiction and Mental Health (CAMH) Foundation. R.Z has no conflicts of interest to declare. F.V.R has received research support from the Canadian Institutes of Health Research (CIHR), Brain Canada, Vancouver Coastal Health Research Institute and Michael Smith Foundation for Health Research. He receives in-kind equipment support from Magventure for an investigator-initiated study. J.D has received research support from CIHR, Brain Canada, the Canadian Biomarker Integration Network in Depression, the Ontario Brain Institute, the Klarman Family Foundation, the Edgstone Foundation, a travel stipend from Lundbeck and from ANT Neuro, and in-kind equipment support for an investigator-initiated trial from Magventure. F.F receives funding from NARSAD, Slaight Family Centre for Youth in Transition at the CAMH, Natural Sciences and Engineering Research Council of Canada (NSERC), the Ontario Brain Institute (OBI).

R.F.H.C was supported by the CIHR – Dystonia Medical Research Foundation Fellowship award. T.K.R received research support from Brain Canada, Brain and Behavior Research Foundation, Canada Foundation for Innovation, the CIHR, Ontario Ministry of Health and Long-Term Care, Ontario Ministry of Research and Innovation, the US National Institute of Health (NIH), and the W. Garfield Weston Foundation. Z.J.D has received research support

from the Ontario Mental Health (OMH) Foundation, the CIHR, the Brain and Behaviour Research Foundation (Formerly NARSAD), and the Temerty family and Grant family through the CAMH Foundation and the Campbell Institute. In the last 3 years, Z.J.D has received research and equipment in-kind support for an investigator-initiated study through Brainsway Inc and Magventure Inc. D.M.B has received research support from the CIHR, NIH, Weston Brain Institute, Brain Canada and the Temerty Family through the CAMH Foundation and the Campbell Research Institute. He receives research support and in-kind equipment support for an investigator-initiated study from Brainsway Ltd. and he is the site principal investigator for three sponsor-initiated studies for Brainsway Ltd. He receives in-kind equipment support from Magventure for an investigator-initiated study. He receives medication supplies for an investigator-initiated trial from Indivior.

Abstract

Background—Dysfunctional neuroplasticity may be one of the pathophysiological mechanisms underlying major depression. We have previously established methods to assess neuroplasticity from the dorsolateral prefrontal cortex (DLPFC) using a paired associative stimulation (PAS) paradigm, which pairs a preceding peripheral nerve stimulation with subsequent transcranial magnetic stimulation (TMS) combined with electroencephalography (EEG). We aimed to investigate neuroplasticity through the PAS paradigm in the DLPFC in patients with depression compared to healthy subjects.

Methods—Twenty-nine patients with depression and 28 healthy controls participated in this study. There were no significant age or sex differences between the two groups. All participants received PAS paradigm in the DLPFC. We analyzed PAS induced potentiation from the DLPFC in both groups calculating the power of TMS-evoked potentials (TEP). A 2-way ANOVA with PAS effect as a within-subject factor and diagnostic group as a between-subject factor was performed to examine the group differences in the PAS paradigm.

Results—DLPFC-PAS induced a significant potentiation at the stimulation site in both patients and healthy subjects (mean $\pm$ SD: 1.24 $\pm$ 0.33 [μ V] vs. 1.48 $\pm$ 0.28 [μ V])). However, when we compared PAS potentiation between patients and healthy subjects, there were significant main effects of PAS ($F_{1,53}=68.63$, $p<0.0001$) and PAS-by-diagnostic group interaction ($F_{1,53}=25.05$, $p<0.0001$). Post-hoc analysis demonstrated that patients had a significantly lower PAS potentiation compared to healthy subjects ($t_{55}=3.128$, $p=0.003$).

Conclusions—Our findings provide evidence for impaired neuroplasticity in DLPFC in patients with depression compared to healthy subjects. Such findings may ultimately help us understand the pathophysiology of MDD and mechanisms involved in its treatment.

Keywords: Depression; electrophysiology; EEG/Evoked Potentials; neurostimulation; neuroimaging

Abbreviations:

ACC: anterior cingulate cortex

ANOVA: analysis of variance

DLPFC: dorsolateral prefrontal cortex

DMPFC: dorsomedial prefrontal cortex

EEG: electroencephalography

HAM-D17: Hamilton Depression Rating Scale 17-Item

ICA: independent component analysis

ISI: inter-stimulus interval

LTP: long-term potentiation

MDD: Major depressive disorder

MEP: motor evoked potential

MI: modulation index

MNI: the Montreal Neurological Institute

MNS: median nerve stimulation

M1: primary motor cortex

MRI: magnetic resonance imaging

PAS: paired associative stimulation

RMT: resting motor threshold

rTMS: repetitive transcranial magnetic stimulation

SD: standard deviation

SSEP: somatosensory evoked potential

STDP: spike-timing-dependent plasticity

TEP: transcranial magnetic stimulation evoked potentials

TMS: transcranial magnetic stimulation

VMPFC: ventral medial prefrontal cortex

Introduction

Major depressive disorder (MDD) is the leading cause of years of life lived with disability across all ages worldwide (WHO, 2012). Recently, a *neuroplasticity hypothesis* of depression has been proposed that impairments of neural network plasticity (Price & Drevets, 2010) may represent a final common pathway underlying the pathophysiology of depression (Castren, 2013). Indeed, basic and clinical research have demonstrated that depression is

associated with reduced size of neuroanatomical structures that regulate mood and cognition such as the prefrontal cortex and the hippocampus, as well as decreased number and size of synapses in these areas, suggesting the impairment of structural neuroplasticity (Duman & Aghajanian, 2012; Garcia, 2002; Popoli, Gennarelli, & Racagni, 2002). Further, electrophysiological measures of neuroplasticity such as long-term potentiation (LTP) or LTP-like plasticity have been shown to be decreased in depression, suggesting the impairment of functional neuroplasticity in depression (Cooke & Bliss, 2006). Moreover, it has been demonstrated that patients with depression behaviorally have a significant deficit in declarative memory consolidation, suggesting decreased synaptic plasticity in a dorsal executive network that comprises the hippocampus, dorsolateral prefrontal cortex (DLPFC), dorsomedial prefrontal cortex (DMPFC), ventral medial prefrontal cortex (VMPFC), etc (Nissen et al., 2010; Sheline, Price, Yan, & Mintun, 2010). Thus, the *neuroplasticity hypothesis* of depression is emerging as a promising hypothesis that can comprehensively capture the underlying pathophysiology of the illness (Castren, 2005, 2013; Spedding, Neau, & Harsing, 2003).

Functional neuroimaging studies have demonstrated that depression is associated with abnormal patterns of activity in prefrontal cortex, including the VMPFC and DLPFC (Downar, Blumberger, & Daskalakis, 2016; Ge et al., 2017; Koenigs et al., 2008). Furthermore, both the VMPFC and DLPFC are critical neural substrates for the pathogenesis of depression with distinct roles respectively (Koenigs & Grafman, 2009; Koenigs et al., 2008). Specifically, the VMPFC is a major component of affective regulation and processing in the limbic-prefrontal neurocircuitry, an area comprised of portions of anterior cingulate cortex (ACC) and medial orbitofrontal cortex, and this circuit is assumed to be impaired in MDD (Price & Drevets, 2012). In contrast, the DLPFC is primarily associated with cognitive and executive functions (Miller & Cohen, 2001), and further the DLPFC-mediated cognitive function is relevant to emotion (Eippert et al., 2007; Levesque et al., 2003; Ochsner, Bunge, Gross, & Gabrieli, 2002; Ochsner et al., 2004; Phan et al., 2005). In depression, hypoactivation of the DLPFC and dorsal ACC has been observed (Korgaonkar, Grieve, Etkin, Koslow, & Williams, 2013; Siegle, Thompson, Carter, Steinhauer, & Thase, 2007). Further, dysfunctional connectivities in fronto-striatal and limbic brain networks have been observed in depression (Greicius et al., 2007; Knutson, Bhanji, Cooney, Atlas, & Gotlib, 2008; Pezawas et al., 2005; Sheline et al.,

2009), which may also be associated with unique biotypes of depression (Williams, 2016).

Specifically, the cognitive control circuit consists of the DLPFC, ACC, dorsal parietal cortex, and precentral gyrus, which relates to support of higher cognitive functions such as working memory and selective attention (Cole & Schneider, 2007).

Recently, we have developed a method to index a degree of functional neuroplasticity from the DLPFC using a paired associative stimulation (PAS) paradigm (Rajji et al., 2013). This paradigm allows for the assessment of neurophysiological functioning within one of the major nodes of the cognitive control network (Alexopoulos et al., 2012). PAS is the TMS neurophysiology that can induce *in vivo* LTP-like potentiation in the human cortex (Stefan, Kunesch, Cohen, Benecke, & Classen, 2000). While a conventional PAS paradigm consists of repeated pairing of peripheral electrical afferent stimulation (e.g., median nerve stimulation: MNS) with TMS over the primary motor cortex (M1) (Stefan, Kunesch, Benecke, Cohen, & Classen, 2002; Stefan et al., 2000; Wolters et al., 2003), our group has demonstrated that PAS with TMS-EEG applied to the DLPFC instead of M1 elicits plastic effects in prefrontal cortex by indexing the TMS-evoked potential (TEP) (Rajji et al., 2013).

The physiological mechanism of the neuroplasticity induced by PAS is presumably based on a form of spike-timing-dependent plasticity (STDP) observed in pre-clinical (Markram, Lubke, Frotscher, & Sakmann, 1997) and human (Stefan et al., 2002; Stefan et al., 2000; Wolters et al., 2003) studies. In line with this, Rajji et al (2013) showed that the DLPFC-PAS exerts plastic effects at an inter-stimulus interval (ISI) of 25ms between afferent and cortical stimulation, but not at a control interval of 100ms (PAS-C). Further, γ power and θ -phase and γ -amplitude coupling after DLPFC-PAS were significantly higher than those of DLPFC-PAS-C. These findings may represent a neurophysiological endophenotype, reflecting the neuroplasticity of DLPFC in healthy participants. Thus, PAS administered to the DLPFC (DLPFC-PAS) may be a useful tool to evaluate functional neuroplasticity in the DLPFC in human participants (Loheswaran et al., 2017; Rajji et al., 2013).

Given the prominent role of the DLPFC in affective and cognitive symptoms of depression and the ability to probe neurophysiological function within this circuit, we aimed to explore PAS-induced potentiation, γ power, and θ - γ coupling in the DLPFC in patients with depression, compared to healthy controls. Thus, in the present study, we hypothesized that

patients with depression would have a lowered neuroplasticity as indexed by DLPFC-PAS, as well as γ power and θ - γ coupling, compared to healthy controls.

Materials and Methods

Participants

Twenty-nine patients with depression (16 female; 42.8 ± 10.0 years) and 28 healthy control participants (11 female; 38.5 ± 9.0 years) were examined in the present study. In the present study, we used a part of dataset for healthy controls from the different study using the same experimental setting, which has previously been published (Rajji et al., 2013). There were no significant age ($t_{55} = -1.690$, $p = 0.097$), or sex ($\chi^2_{57} = 1.442$, $p = 0.230$) differences between the two groups. PAS was administered to the DLPFC using combined TMS–EEG in all participants. Participants of both groups were eligible to participate in this study if they met the following

criteria: (i) aged 18-59; (ii) no history of neurological disorders including seizure, syncope or stroke; (iii) no current (past 6 months) alcohol or other drug abuse or dependence. For the healthy control participants, they also met the following criteria: vi) no history of neuropsychiatric disorders; (v) normal cognitive function; or vi) no prescription medications. For patients with depression, additional criteria were as follows: vii) diagnosis of major depressive episode as assessed by the HAM-D₁₇ score ≥ 18 ; (viii) no benzodiazepines more than *lorazepam* equivalent dose of 2 mg/day. The type and dose of psychiatric medications were kept unchanged at least one month before starting the study and during the study period. *Fluoxetine* equivalent doses were calculated according to the literature described by Hayasaka and colleagues (Hayasaka et al., 2015). Demographic and clinical data are shown in **Table 1**. All participants were screened with the Mini-International Neuropsychiatric Interview prior to study participation. The experiment was conducted in accordance with the Declaration of Helsinki and was reviewed and approved by the Ethics Committee of the Centre for Addiction and Mental Health. All participants provided written informed consent.

TMS procedure and electromyography measure

Monophasic TMS pulses were administered to the left M1 using a 70mm figure-of-eight coil (Magstim Company Ltd., UK). During the TMS testing, the participants sat in a chair with their eyes open and right hand relaxed throughout the study. First, the M1 hot spot for the right abductor pollicis brevis muscle to evoke the largest motor evoked potential (MEP) was determined. Second, the individual intensity of resting motor threshold (RMT) to induce more than 50 μ V MEP amplitude from the right abductor pollicis brevis muscle 5 times out of 10 trials was determined. Then, the individual intensity to induce 1mV peak-to-peak MEP amplitude of this muscle was determined in order to determine the intensity parameter of PAS paradigm.

Localization of DLPFC

The DLPFC stimulation site for TMS in patients with depression was localized using the modified BeamF3 method (Mir-Moghtadaei et al., 2015), which is the same method used clinically to determine the site for delivery of rTMS. This method uses a reverse co-registration from a stereotaxic coordinate on the standard Montreal neurological Institute (MNI-152) template brain, onto each individual's anatomical (MNI coordinates (x, y, z) =

(-38, 44, 26)) (Fox, Liu, & Pascual-Leone, 2013). In contrast, in healthy controls, MRI-guided localization method was used with the MRICro/reg software in the MINIBIRD system (Ascension Technologies, Burlington, VT) (Talairach coordinates (x, y, z) = (-50, 30, 36)) (Rajji et al., 2013). Although both targets for TMS are still within the DLPFC, there was an approximately 2 cm difference on average between the two groups.

PAS measures

PAS was examined according to established methods (Classen et al., 2004; Stefan et al., 2000; Wolters et al., 2003); as previously extended to DLPFC (Rajji et al., 2013). Specifically, the ISI of PAS paradigm between right median nerve stimulation at wrist and TMS over the left DLPFC was set to 25ms. Conditioning stimulus of MNS intensity was set at 3 times the sensory threshold and test stimulus of TMS intensity was set at the intensity to evoke a 1mV peak-to-peak MEP amplitude when TMS alone was delivered to M1. Participants were instructed to keep count of the number of PNS in their mind during the PAS to maintain attention. PAS-induced potentiation was evaluated by overall TEP power changes before and after PAS paradigm. As the timing point of maximum potentiation after PAS (post_{max} TEP

power) varies among participants, we selected the maximum time point of TEP powers for each participant in the off-line analysis, following previously published methods (Loheswaran et al., 2017; Rajji et al., 2013).

EEG recording and pre-processing

TMS-EEG was acquired through a 64-channel Neuroscan Synamps 2 EEG system (Compumedics Neuroscan, Australia). All electrodes were referenced to an electrode located at the vertex. Recording electrodes impedance was kept lowered to $\leq 5k\Omega$ during experiment. EEG signals were recorded at DC with a sampling rate of 20kHz and an online lowpass filter of 200Hz was applied. All data were down-sampled to 1000Hz for off-line analyses.

EEG signal processing

EEG data were processed offline using the MATLAB software (R2014a, The MathWorks, MA, USA) in line with previously published methods (Rajji et al., 2013; Rajji et al., 2017). The continuous EEG data were epoched from -1000ms to 2000ms relative to the TMS pulse.

Baseline correction was conducted with respect to the pre-stimulus interval -50ms to -110ms. To avoid TMS artifacts, the epoched EEG data was re-segmented from 10ms to 2000ms post-TMS. Then, EEG data were visually inspected to exclude trials and channels that were highly contaminated with noise. As a result, more than 80% of trials and 95% of channels survived artifact rejection. Subsequently, independent component analysis (ICA) was applied to minimize and remove the typical TMS-related decay artifacts as well as eye- and muscle-related activity. The number of ICA components that were removed was no greater than 20% of original components individually. Subsequently, a Butterworth, zero-phase shift 1–55Hz band pass filter (24dB/Oct) and notch filter were applied. Finally, data was re-referenced to the average for further analyses.

DLPFC-PAS plastic effects on TEP power

For the TEP analysis of PAS, TEP power at baseline and Post 0, Post 15, and Post 30min were analyzed individually using the Hilbert transform method. Specifically, the influence of PAS paradigm on the individual TEP was computed for each time point (i.e., baseline, post 0, post 15, and post 30min) at the site of stimulation over the left DLPFC.

DLPFC-PAS plastic effects on neural oscillatory power

Frequency band power changes induced by PAS paradigm was calculated by the Hilbert transform method focused on the site of stimulation. Each frequency band was defined as follows: δ (1–3Hz); θ (4–7Hz); α (8–14Hz); β (14–30Hz); and γ (30–50Hz) and PAS potentiation was filtered into these five frequency bands. TEP potentiation by PAS within each frequency band between patients with depression and healthy controls was assessed by a 3-way analysis of variance (ANOVA) and post-hoc independent t -test for absolute δ – γ TEP changes with Bonferroni correction for each of the five frequency bands.

DLPFC-PAS mediated changes in θ -phase and γ -amplitude coupling

Following previously published methods (Axmacher et al., 2010; Rajji et al., 2013; Tort, Komorowski, Eichenbaum, & Kopell, 2010), we calculated the modulation index (MI) of θ – γ coupling as a relationship between the θ -phase and the γ -amplitude. EEG signal was first filtered into separate θ - and γ -waveforms with a zero-phase shift filter and then applied the

Hilbert transform. The γ -amplitudes corresponding to the ϑ -phase were sorted into six bins as follows: $[-180^{\circ}\sim-120^{\circ}]$, $[-120^{\circ}\sim-60^{\circ}]$, $[-60^{\circ}\sim0^{\circ}]$, $[0^{\circ}\sim60^{\circ}]$, $[60^{\circ}\sim120^{\circ}]$, $[120^{\circ}\sim180^{\circ}]$, and then they were averaged. To quantify coupling, an entropy-based MI was used (Tort et al, 2010). The relative amplitude distribution for each participant was calculated by dividing the amplitude of each phase by the sum of all amplitudes across bins. Here, lower entropy, corresponding to an increase of order, represents higher coupling (i.e., MI value). To assess whether there is any difference in the MI of ϑ - γ coupling induced by DLPFC-PAS, we performed a 2-way ANOVA for the MI values and post-hoc independent *t*-tests for absolute MI value changes by PAS between the two groups. The choice of the post-PAS time-point (i.e., Post 0, Post 15, or Post 30min) for each participant was determined based on the time-point of maximum potentiation of PAS.

Statistical analyses

The IBM SPSS Statistics 19 (Armonk, New York, USA) was used for statistical analysis. The following assessments were performed: 1) PAS effect on TEP power changes, 2) PAS effect on

each frequency band power modulation, and 3) PAS effect on ϑ -phase and γ -amplitude coupling of TEP, at the maximum overall TEP potentiation between patients and controls.

A 2-way ANOVA with a PAS effect (baseline TEP vs. post_{max} TEP) as a within-subject factor and a diagnostic group (patients vs. controls) as a between-subject factor was applied to TEP powers induced by PAS paradigm to examine the significant difference of PAS effect between the two group. When we observed a significant PAS effect-by-diagnostic group interaction, post-hoc analyses were performed. In addition, pre-PAS TEPs of both groups were compared with an independent t-test to examine the influence on PAS. Further, we applied a 3-way ANOVA for the δ - γ frequency band TEP power changes (2 levels: baseline TEP vs. post_{max} TEP; 5 levels: δ - γ bands) and a 2-way ANOVA for the MI of ϑ -phase and γ -amplitude coupling changes (baseline MI vs. post_{max} MI) by PAS paradigm between patients and controls. For the modulatory effects by PAS on the frequency band powers from δ to γ at the site of stimulation, Bonferroni correction was applied for the results of post-hoc independent *t*-tests (δ - γ : 5 frequency band TEP powers; $\alpha = 0.05/5$).

In patients group, medication effect on TEP metrics of PAS paradigm was examined using correlation analysis between daily *fluoxetine* equivalent dose and baseline TEP metrics

(baseline overall TEP power, δ - γ powers, and ϑ - γ coupling). Furthermore, we also examined the potential impact of depressive symptom severity as measured by the HAM-D₁₇ on TEP metrics of PAS.

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Results

Neuroplasticity as indexed by PAS-induced potentiation

Baseline neurophysiological data for both groups were not significantly different and are summarized in **Table 2**. When we compared the PAS potentiation of TEP power at the site of stimulation between patients and controls, there were significant main effects of PAS ($F_{1,53}=68.63$, $p<0.0001$) and PAS-by-diagnostic group interaction ($F_{1,53}=25.05$, $p<0.0001$). Post-hoc analyses demonstrated that patients had a significantly lower PAS potentiation compared to controls (mean $\pm$ standard deviation (SD): 1.24 ± 0.33 [μ V] vs. 1.48 ± 0.28 [μ V]; $t_{55}=3.128$, $p=0.003$) (see **Fig. 1 A**). There was no significant difference in baseline TEP before PAS in both groups ($t_{55}=1.734$, $p=0.088$). In contrast, spatial distributions of PAS-induced potentiation of patients and controls were basically similar, showing the left prefrontal area

dominant pattern (**Fig. 1 B**). In addition, although we observed significant PAS effects at the site of stimulation in both groups, the degree of PAS-induced potentiation on the topography appeared much less intense in patients compared to controls.

Frequency modulatory effects of PAS

A 3-way ANOVA showed that there were significant main effects of PAS ($F_{1,55}=90.84$, $p<0.0001$) and frequency band ($F_{4,220}=64.12$, $p<0.0001$), as well as significant interactions in PAS-by-diagnostic group ($F_{1,55}=18.50$, $p<0.0001$), frequency band-by-diagnostic group ($F_{4,220}=14.69$, $p<0.0001$), PAS-by-frequency band ($F_{4,220}=46.02$, $p<0.0001$), and PAS-by-frequency band-by-diagnostic group ($F_{4,220}=13.54$, $p<0.0001$). Post-hoc independent t -tests indicated that there were significant differences in δ ($t_{55}=4.127$, $p<0.0001$: patients<controls), θ ($t_{55}=3.075$, $p=0.003$: patients<controls), and γ ($t_{55}=3.146$, $p=0.003$: patients<controls) band power changes induced by PAS between the two groups. These results suggest that patients with depression had impairments of PAS-induced potentiation, specifically in δ , θ , and γ frequency bands, compared to healthy controls. The results of each frequency band power change by PAS was depicted in **Fig. 1 C**.

Θ -phase and γ -amplitude modulations after PAS paradigm

A 2-way ANOVA demonstrated that there was a significant main effect of the MI of ϑ - γ coupling ($F_{1,55}=9.84$, $p=0.003$) and a significant interaction in MI of ϑ - γ coupling-by-diagnostic group ($F_{1,55}=16.39$, $p<0.0001$). Post-hoc independent t-test showed a significant difference of the MI of ϑ - γ coupling changes ($t_{55}=4.048$, $p<0.0001$: patients<controls) induced by PAS between patients and controls, suggesting that PAS-induced ϑ - γ coupling was significantly lower in patients with depression compared to healthy controls. The result of the MI of ϑ - γ coupling change by PAS was drawn in **Fig. 1 D**.

General antidepressant medication effects on EEG metrics of PAS

There were no correlations between individual daily *fluoxetine* equivalent doses and TEP outcomes of DLPFC-PAS (i.e., PAS-induced overall power potentiation, δ - γ bands power potentiation, and ϑ - γ coupling (MI)), suggesting that antidepressants had no significant impact on these PAS-induced metrics.

Impact of clinical severity on EEG metrics of PAS

We did not observe any correlations between depressive symptom severity as measured by the HAM-D₁₇ and TEP outcomes of the DLPFC-PAS, suggesting that clinical severity had no significant impact on these PAS-induced metrics as well.

Discussion

The present study is the first to demonstrate a reduced neuroplasticity in the DLPFC in patients with depression using the DLPFC-PAS paradigm with TMS-EEG, compared to healthy controls. Further, potentiation of γ , θ , and δ frequency bands as well as the MI of θ - γ coupling were significantly impaired in patients with depression, compared to healthy controls.

TMS paradigms such as the PAS protocol at ISI 25ms can induce LTP-like potentiation that is closely associated with neuroplasticity not only at synaptic level but also neuronal or network levels in human cortex (Hoogendam, Ramakers, & Di Lazzaro, 2010; Rajji et al., 2013). Thus, our findings of a significant difference of PAS-induced potentiation between patients with depression and healthy participants is consistent with the hypothesis that depression may be related to impaired capability to induce enough neuroplasticity in the prefrontal cortex to the level equivalent to healthy participants (Price & Drevets, 2010).

Among the spectral EEG power, γ oscillations are specifically theorized to provide a temporal framework for information processing in the cortex (Abbott & Nelson, 2000; Axmacher, Mormann, Fernandez, Elger, & Fell, 2006; Bosman, Lansink, & Pennartz, 2014; Weinberger, Miasnikov, Bieszczad, & Chen, 2013), which could contribute to cognitive functions (Abbott & Nelson, 2000; Fell & Axmacher, 2011). Further, impairment of γ activity may be associated with some neuropsychiatric disorders including depression (Noda et al., 2017; Pathak, Salami, Baillet, Li, & Butson, 2016). Moreover, δ power is significantly lower in depression compared to healthy controls (Pozzi, Golimstock, Petracchi, Garcia, & Starkstein, 1995), and δ power has been shown to be potentiated following high-frequency repetitive TMS (rTMS) of the left DLPFC in patients with depression (Noda et al., 2013; Spronk, Arns, Bootsma, van Ruth, & Fitzgerald, 2008; Valiulis et al., 2012). ϑ oscillations are also thought to contribute to learning and memory on longer range networks than γ activities (Buzsaki, 2002; Pignatelli, Beyeler, & Leinekugel, 2012). In addition, ϑ activity in human is often relevant to the δ band activity, which might be the counterpart of the ϑ activity in animal brain (Ekstrom et al., 2005; Watrous, Fried, & Ekstrom, 2011). rTMS treatment in depression

could induce an increase in θ power, which might be associated with clinical improvement (Noda et al., 2013; Valiulis et al., 2012). Thus, our findings showing that patients with depression had significantly lower γ , δ , and θ band power increases in the left DLPFC induced by the PAS paradigm are suggestive of neurophysiological dysfunctioning in depression compared to controls.

Oscillatory dynamics in the prefrontal cortex are implicated in a various cognitive processes (Fell et al., 2001). Specifically, the synchronization of γ band activities with the θ -phase oscillations (i.e., θ - γ coupling) in the brain may support long-term memory through the facilitation of neural communication and neuroplasticity (Axmacher et al., 2010; Fell & Axmacher, 2011; Park, Jhung, Lee, & An, 2013). Thus, our finding showing that patients with depression had a significantly lowered PAS-induced MI of θ - γ coupling compared to healthy participants provides compelling evidence that depression is associated with dysfunctional neuroplasticity in the prefrontal cortex (Cooke & Bliss, 2006; Price & Drevets, 2010). Furthermore, since the DLPFC plays an important role in cognitive domains such as working memory (Gevins, Smith, McEvoy, & Yu, 1997; Howard et al., 2003), executive function, and

social cognition (Uhlhaas & Singer, 2006), impaired neuroplasticity in the left DLPFC may represent a key pathophysiological mechanism in depression that may underlie the cognitive impairments (Castren, 2013; Price & Drevets, 2010).

This study has some limitations. First, as patients with depression were taking antidepressant medication during the study, there may be some potential confounding effects on the PAS-induced potentiation, considering the fact that some antidepressants such as vortioxetine can enhance LTP in the rat hippocampus (Dale et al., 2014). However, there was no significant correlation between *fluoxetine* equivalent doses and PAS-induced TEP metrics. In addition, there is another evidence that citalopram has shown no significant positive impact on PAS using the ISI of 25ms in human M1 compared to placebo (Batsikadze, Paulus, Kuo, & Nitsche, 2013). Second, although we applied a standard PAS protocol using the ISI of 25ms to examine the neuroplasticity in the DLPFC (Classen et al., 2004; Stefan et al., 2000; Wolters et al., 2003), it might be possible to induce more robust PAS potentiation in the same region using a more optimal ISI. For M1-PAS, individually optimizing the ISI to the latency of the arrival of the N20 SSEP can enhance effects (Cash, Jegatheeswaran, Ni, &

Chen, 2017). Similarly, it has been postulated that the mechanism for DLPFC-PAS may relate to the SSEP N24 component which is observed at the F3 electrode (Noda et al., 2016), and plastic effects might be enhanced if the DLPFC-PAS ISI is individually optimized to this latency. Systematic analyses are needed using various ISIs to validate more reliable parameters of ISI. Thirdly, there may be some potential effects of auditory and visual input during the TMS-EEG experiment. However, since we compared pre and post PAS conditions that both had comparable auditory and visual components, and these furthermore removed by ICA, those confounding effects is unlikely to contribute to the changes observed following PAS. Fourthly, this study did not include the cognitive measures. The role of cognition in depression is increasingly recognized as an important mediator of response (Kaneriya et al., 2016; Pimontel et al., 2016). Future studies should consider assessing and evaluating the relationship between cognition and PAS neuroplasticity. Fifth, this study did not include the information on treatment response due to the cross-sectional nature of the study on TMS-EEG neurophysiology between the two groups. However, the relationships between baseline PAS-EEG and treatment response as well as PAS-EEG changes with treatment response should be assessed in future studies. Lastly, as mentioned in the Methods section,

since we applied the different forms of navigation to identify the DLPFC for both groups, it is possible that the differences observed may be related to possible difference in the site of stimulation between the patients and healthy participants, though both targets are within the DLPFC. Therefore, these findings will need replication in a sample of patients and healthy controls that have had TMS stimulation at the same site within the DLPFC in both groups.

In summary, this is the first study to compare PAS-induced potentiation in the DLPFC between patients with depression and healthy controls. We demonstrate that patients with depression may have impaired neuroplasticity in the prefrontal cortex. The reduced PAS-induced potentiation in depression was also characterized by specific frequency band (δ , θ , and γ bands) power reductions and phase-amplitude coupling (θ - γ coupling) depotentiation, suggesting that depression has an impaired functional neuroplasticity in the prefrontal cortex. Therefore, the DLPFC-PAS has the potential to be a useful diagnostic tools as a neurobiological indicator to assess the functional neuroplasticity of the prefrontal cortex non-invasively in patients with depression as well as other neuropsychiatric

disorders. Further, the DLPFC-PAS may also be used as a neurobiological indicator to assess the effect of antidepressant treatments.

Acknowledgments

This research was supported by the Temerty Centre for Therapeutic Brain Intervention, the Campbell Family Research Institute through the CAMH Foundation, the Canada Foundation for Innovation and Brain Canada. We gratefully thank all participants in the present study and we appreciate Ms. Shobha Mehta, Ms. Patricia Cui, and Ms. Mawahib Semeralul for their research assistance.

References

- Abbott, L. F., & Nelson, S. B. (2000). Synaptic plasticity: taming the beast. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. Review]. *Nat Neurosci*, 3 Suppl, 1178-1183. doi: 10.1038/81453
- Alexopoulos, G. S., Hoptman, M. J., Kanellopoulos, D., Murphy, C. F., Lim, K. O., & Gunning, F. M. (2012). Functional connectivity in the cognitive control network and the default mode network in late-life depression. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *J Affect Disord*, 139(1), 56-65. doi: 10.1016/j.jad.2011.12.002
- Axmacher, N., Henseler, M. M., Jensen, O., Weinreich, I., Elger, C. E., & Fell, J. (2010). Cross-frequency coupling supports multi-item working memory in the human hippocampus. [Research Support, Non-U.S. Gov't]. *Proc Natl Acad Sci U S A*, 107(7), 3228-3233. doi: 10.1073/pnas.0911531107
- Axmacher, N., Mormann, F., Fernandez, G., Elger, C. E., & Fell, J. (2006). Memory formation by neuronal synchronization. [Research Support, Non-U.S. Gov't Review]. *Brain Res Rev*, 52(1), 170-182. doi: 10.1016/j.brainresrev.2006.01.007
- Batsikadze, G., Paulus, W., Kuo, M. F., & Nitsche, M. A. (2013). Effect of serotonin on paired associative stimulation-induced plasticity in the human motor cortex. [Randomized Controlled Trial Research Support, Non-U.S. Gov't]. *Neuropsychopharmacology*, 38(11), 2260-2267. doi: 10.1038/npp.2013.127
- Bosman, C. A., Lansink, C. S., & Pennartz, C. M. (2014). Functions of gamma-band synchronization in cognition: from single circuits to functional diversity across cortical and subcortical systems. [Research Support, Non-U.S. Gov't Review]. *Eur J Neurosci*, 39(11), 1982-1999. doi: 10.1111/ejn.12606
- Buzsaki, G. (2002). Theta oscillations in the hippocampus. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. Review]. *Neuron*, 33(3), 325-340.

- Cash, R. F., Jegatheeswaran, G., Ni, Z., & Chen, R. (2017). Modulation of the Direction and Magnitude of Hebbian Plasticity in Human Motor Cortex by Stimulus Intensity and Concurrent Inhibition. *Brain Stimul*, 10(1), 83-90. doi: 10.1016/j.brs.2016.08.007
- Castren, E. (2005). Is mood chemistry? [Research Support, Non-U.S. Gov't Review]. *Nat Rev Neurosci*, 6(3), 241-246. doi: 10.1038/nrn1629
- Castren, E. (2013). Neuronal network plasticity and recovery from depression. [Research Support, Non-U.S. Gov't Review]. *JAMA Psychiatry*, 70(9), 983-989. doi: 10.1001/jamapsychiatry.2013.1
- Classen, J., Wolters, A., Stefan, K., Wycislo, M., Sandbrink, F., Schmidt, A., & Kunesch, E. (2004). Paired associative stimulation. [Review]. *Suppl Clin Neurophysiol*, 57, 563-569.
- Cole, M. W., & Schneider, W. (2007). The cognitive control network: Integrated cortical regions with dissociable functions. [Research Support, U.S. Gov't, Non-P.H.S.]. *Neuroimage*, 37(1), 343-360. doi: 10.1016/j.neuroimage.2007.03.071
- Cooke, S. F., & Bliss, T. V. (2006). Plasticity in the human central nervous system. [Review]. *Brain*, 129(Pt 7), 1659-1673. doi: 10.1093/brain/awl082
- Dale, E., Zhang, H., Leiser, S. C., Xiao, Y., Lu, D., Yang, C. R., . . . Sanchez, C. (2014). Vortioxetine disinhibits pyramidal cell function and enhances synaptic plasticity in the rat hippocampus. [Research Support, Non-U.S. Gov't]. *J Psychopharmacol*, 28(10), 891-902. doi: 10.1177/0269881114543719
- Downar, J., Blumberger, D. M., & Daskalakis, Z. J. (2016). The Neural Crossroads of Psychiatric Illness: An Emerging Target for Brain Stimulation. [Research Support, Non-U.S. Gov't Review]. *Trends Cogn Sci*, 20(2), 107-120. doi: 10.1016/j.tics.2015.10.007
- Duman, R. S., & Aghajanian, G. K. (2012). Synaptic dysfunction in depression: potential therapeutic targets. [Review]. *Science*, 338(6103), 68-72. doi: 10.1126/science.1222939

- Eippert, F., Veit, R., Weiskopf, N., Erb, M., Birbaumer, N., & Anders, S. (2007). Regulation of emotional responses elicited by threat-related stimuli. [Research Support, Non-U.S. Gov't]. *Hum Brain Mapp*, 28(5), 409-423. doi: 10.1002/hbm.20291
- Ekstrom, A. D., Caplan, J. B., Ho, E., Shattuck, K., Fried, I., & Kahana, M. J. (2005). Human hippocampal theta activity during virtual navigation. *Hippocampus*, 15(7), 881-889. doi: 10.1002/hipo.20109
- Fell, J., & Axmacher, N. (2011). The role of phase synchronization in memory processes. [Research Support, Non-U.S. Gov't Review]. *Nat Rev Neurosci*, 12(2), 105-118. doi: 10.1038/nrn2979
- Fell, J., Klaver, P., Lehnertz, K., Grunwald, T., Schaller, C., Elger, C. E., & Fernandez, G. (2001). Human memory formation is accompanied by rhinal-hippocampal coupling and decoupling. [Research Support, Non-U.S. Gov't]. *Nat Neurosci*, 4(12), 1259-1264. doi: 10.1038/nn759
- Fox, M. D., Liu, H., & Pascual-Leone, A. (2013). Identification of reproducible individualized targets for treatment of depression with TMS based on intrinsic connectivity. [Research Support, N.I.H., Extramural]. *Neuroimage*, 66, 151-160. doi: 10.1016/j.neuroimage.2012.10.082
- Garcia, R. (2002). Stress, synaptic plasticity, and psychopathology. [Review]. *Rev Neurosci*, 13(3), 195-208.
- Ge, R., Blumberger, D. M., Downar, J., Daskalakis, Z. J., Dipinto, A. A., Tham, J. C. W., . . . Vila-Rodriguez, F. (2017). Abnormal functional connectivity within resting-state networks is related to rTMS-based therapy effects of treatment resistant depression: A pilot study. *J Affect Disord*, 218, 75-81. doi: 10.1016/j.jad.2017.04.060
- Gevins, A., Smith, M. E., McEvoy, L., & Yu, D. (1997). High-resolution EEG mapping of cortical activation related to working memory: effects of task difficulty, type of processing, and practice. [Research Support, U.S. Gov't, Non-P.H.S. Research Support, U.S. Gov't, P.H.S.]. *Cereb Cortex*, 7(4), 374-385.

- Greicius, M. D., Flores, B. H., Menon, V., Glover, G. H., Solvason, H. B., Kenna, H., . . . Schatzberg, A. F. (2007). Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Biol Psychiatry*, 62(5), 429-437. doi: 10.1016/j.biopsych.2006.09.020
- Hayasaka, Y., Purgato, M., Magni, L. R., Ogawa, Y., Takeshima, N., Cipriani, A., . . . Furukawa, T. A. (2015). Dose equivalents of antidepressants: Evidence-based recommendations from randomized controlled trials. [Research Support, Non-U.S. Gov't]. *J Affect Disord*, 180, 179-184. doi: 10.1016/j.jad.2015.03.021
- Hoogendam, J. M., Ramakers, G. M., & Di Lazzaro, V. (2010). Physiology of repetitive transcranial magnetic stimulation of the human brain. [Review]. *Brain Stimul*, 3(2), 95-118. doi: 10.1016/j.brs.2009.10.005
- Howard, M. W., Rizzuto, D. S., Caplan, J. B., Madsen, J. R., Lisman, J., Aschenbrenner-Scheibe, R., . . . Kahana, M. J. (2003). Gamma oscillations correlate with working memory load in humans. [Case Reports Research Support, U.S. Gov't, P.H.S.]. *Cereb Cortex*, 13(12), 1369-1374.
- Kaneriya, S. H., Robbins-Welty, G. A., Smagula, S. F., Karp, J. F., Butters, M. A., Lenze, E. J., . . . Reynolds, C. F., 3rd. (2016). Predictors and Moderators of Remission With Aripiprazole Augmentation in Treatment-Resistant Late-Life Depression: An Analysis of the IRL-GRey Randomized Clinical Trial. [Multicenter Study Randomized Controlled Trial Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *JAMA Psychiatry*, 73(4), 329-336. doi: 10.1001/jamapsychiatry.2015.3447
- Knutson, B., Bhanji, J. P., Cooney, R. E., Atlas, L. Y., & Gotlib, I. H. (2008). Neural responses to monetary incentives in major depression. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Biol Psychiatry*, 63(7), 686-692. doi: 10.1016/j.biopsych.2007.07.023

- Koenigs, M., & Grafman, J. (2009). The functional neuroanatomy of depression: distinct roles for ventromedial and dorsolateral prefrontal cortex. [Research Support, N.I.H., Intramural Review]. *Behav Brain Res*, 201(2), 239-243. doi: 10.1016/j.bbr.2009.03.004
- Koenigs, M., Huey, E. D., Calamia, M., Raymont, V., Tranel, D., & Grafman, J. (2008). Distinct regions of prefrontal cortex mediate resistance and vulnerability to depression. [Comparative Study Research Support, N.I.H., Extramural Research Support, N.I.H., Intramural Research Support, U.S. Gov't, Non-P.H.S.]. *J Neurosci*, 28(47), 12341-12348. doi: 10.1523/JNEUROSCI.2324-08.2008
- Korgaonkar, M. S., Grieve, S. M., Etkin, A., Koslow, S. H., & Williams, L. M. (2013). Using standardized fMRI protocols to identify patterns of prefrontal circuit dysregulation that are common and specific to cognitive and emotional tasks in major depressive disorder: first wave results from the iSPOT-D study. [Research Support, Non-U.S. Gov't]. *Neuropsychopharmacology*, 38(5), 863-871. doi: 10.1038/npp.2012.252
- Levesque, J., Eugene, F., Joanette, Y., Paquette, V., Mensour, B., Beaudoin, G., . . . Beaudregard, M. (2003). Neural circuitry underlying voluntary suppression of sadness. [Research Support, Non-U.S. Gov't]. *Biol Psychiatry*, 53(6), 502-510.
- Loheswaran, G., Barr, M. S., Zomorodi, R., Rajji, T. K., Blumberger, D. M., Foll, B. L., & Daskalakis, Z. J. (2017). Impairment of Neuroplasticity in the Dorsolateral Prefrontal Cortex by Alcohol. *Sci Rep*, 7(1), 5276. doi: 10.1038/s41598-017-04764-9
- Markram, H., Lubke, J., Frotscher, M., & Sakmann, B. (1997). Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. [Research Support, Non-U.S. Gov't]. *Science*, 275(5297), 213-215.
- Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. Review]. *Annu Rev Neurosci*, 24, 167-202. doi: 10.1146/annurev.neuro.24.1.167

- Mir-Moghtadaei, A., Caballero, R., Fried, P., Fox, M. D., Lee, K., Giacobbe, P., . . . Downar, J. (2015). Concordance Between BeamF3 and MRI-neuronavigated Target Sites for Repetitive Transcranial Magnetic Stimulation of the Left Dorsolateral Prefrontal Cortex. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Brain Stimul*, 8(5), 965-973. doi: 10.1016/j.brs.2015.05.008
- Nissen, C., Holz, J., Blechert, J., Feige, B., Riemann, D., Voderholzer, U., & Normann, C. (2010). Learning as a model for neural plasticity in major depression. [Research Support, Non-U.S. Gov't]. *Biol Psychiatry*, 68(6), 544-552. doi: 10.1016/j.biopsych.2010.05.026
- Noda, Y., Cash, R. F., Zomorodi, R., Dominguez, L. G., Farzan, F., Rajji, T. K., . . . Blumberger, D. M. (2016). A combined TMS-EEG study of short-latency afferent inhibition in the motor and dorsolateral prefrontal cortex. *J Neurophysiol*, 116(3), 938-948. doi: 10.1152/jn.00260.2016
- Noda, Y., Nakamura, M., Saeki, T., Inoue, M., Iwanari, H., & Kasai, K. (2013). Potentiation of quantitative electroencephalograms following prefrontal repetitive transcranial magnetic stimulation in patients with major depression. [Research Support, Non-U.S. Gov't]. *Neurosci Res*, 77(1-2), 70-77. doi: 10.1016/j.neures.2013.06.002
- Noda, Y., Zomorodi, R., Saeki, T., Rajji, T. K., Blumberger, D. M., Daskalakis, Z. J., & Nakamura, M. (2017). Resting-state EEG gamma power and theta-gamma coupling enhancement following high-frequency left dorsolateral prefrontal rTMS in patients with depression. *Clin Neurophysiol*, 128(3), 424-432. doi: 10.1016/j.clinph.2016.12.023
- Ochsner, K. N., Bunge, S. A., Gross, J. J., & Gabrieli, J. D. (2002). Rethinking feelings: an fMRI study of the cognitive regulation of emotion. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S. Research Support, U.S. Gov't, P.H.S.]. *J Cogn Neurosci*, 14(8), 1215-1229. doi: 10.1162/089892902760807212
- Ochsner, K. N., Ray, R. D., Cooper, J. C., Robertson, E. R., Chopra, S., Gabrieli, J. D., & Gross, J. J. (2004). For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. [Research Support, Non-U.S. Gov't Research Support,

- U.S. Gov't, Non-P.H.S. Research Support, U.S. Gov't, P.H.S.]. *Neuroimage*, 23(2), 483-499. doi: 10.1016/j.neuroimage.2004.06.030
- Park, J. Y., Jhung, K., Lee, J., & An, S. K. (2013). Theta-gamma coupling during a working memory task as compared to a simple vigilance task. [Comparative Study Research Support, Non-U.S. Gov't]. *Neurosci Lett*, 532, 39-43. doi: 10.1016/j.neulet.2012.10.061
- Pathak, Y., Salami, O., Baillet, S., Li, Z., & Butson, C. R. (2016). Longitudinal Changes in Depressive Circuitry in Response to Neuromodulation Therapy. *Front Neural Circuits*, 10, 50. doi: 10.3389/fncir.2016.00050
- Pezawas, L., Meyer-Lindenberg, A., Drabant, E. M., Verchinski, B. A., Munoz, K. E., Kolachana, B. S., . . . Weinberger, D. R. (2005). 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. [Research Support, N.I.H., Intramural]. *Nat Neurosci*, 8(6), 828-834. doi: 10.1038/nn1463
- Phan, K. L., Fitzgerald, D. A., Nathan, P. J., Moore, G. J., Uhde, T. W., & Tancer, M. E. (2005). Neural substrates for voluntary suppression of negative affect: a functional magnetic resonance imaging study. [Comparative Study Research Support, Non-U.S. Gov't]. *Biol Psychiatry*, 57(3), 210-219. doi: 10.1016/j.biopsych.2004.10.030
- Pignatelli, M., Beyeler, A., & Leinekugel, X. (2012). Neural circuits underlying the generation of theta oscillations. [Research Support, Non-U.S. Gov't Review]. *J Physiol Paris*, 106(3-4), 81-92. doi: 10.1016/j.jphysparis.2011.09.007
- Pimontel, M. A., Rindskopf, D., Rutherford, B. R., Brown, P. J., Roose, S. P., & Sneed, J. R. (2016). A Meta-Analysis of Executive Dysfunction and Antidepressant Treatment Response in Late-Life Depression. [Meta-Analysis Review]. *Am J Geriatr Psychiatry*, 24(1), 31-41. doi: 10.1016/j.jagp.2015.05.010
- Popoli, M., Gennarelli, M., & Racagni, G. (2002). Modulation of synaptic plasticity by stress and antidepressants. [Research Support, Non-U.S. Gov't Review]. *Bipolar Disord*, 4(3), 166-182.

- Pozzi, D., Golimstock, A., Petracchi, M., Garcia, H., & Starkstein, S. (1995). Quantified electroencephalographic changes in depressed patients with and without dementia. [Research Support, Non-U.S. Gov't]. *Biol Psychiatry*, 38(10), 677-683. doi: 10.1016/0006-3223(94)00371-8
- Price, J. L., & Drevets, W. C. (2010). Neurocircuitry of mood disorders. [Research Support, N.I.H., Extramural Review]. *Neuropsychopharmacology*, 35(1), 192-216. doi: 10.1038/npp.2009.104
- Price, J. L., & Drevets, W. C. (2012). Neural circuits underlying the pathophysiology of mood disorders. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review]. *Trends Cogn Sci*, 16(1), 61-71. doi: 10.1016/j.tics.2011.12.011
- Rajji, T. K., Sun, Y., Zomorodi-Moghaddam, R., Farzan, F., Blumberger, D. M., Mulsant, B. H., . . . Daskalakis, Z. J. (2013). PAS-induced potentiation of cortical-evoked activity in the dorsolateral prefrontal cortex. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Neuropsychopharmacology*, 38(12), 2545-2552. doi: 10.1038/npp.2013.161
- Rajji, T. K., Zomorodi, R., Barr, M. S., Blumberger, D. M., Mulsant, B. H., & Daskalakis, Z. J. (2017). Ordering Information in Working Memory and Modulation of Gamma by Theta Oscillations in Humans. *Cereb Cortex*, 27(2), 1482-1490. doi: 10.1093/cercor/bhv326
- Sheline, Y. I., Barch, D. M., Price, J. L., Rundle, M. M., Vaishnavi, S. N., Snyder, A. Z., . . . Raichle, M. E. (2009). The default mode network and self-referential processes in depression. [Research Support, N.I.H., Extramural]. *Proc Natl Acad Sci U S A*, 106(6), 1942-1947. doi: 10.1073/pnas.0812686106
- Sheline, Y. I., Price, J. L., Yan, Z., & Mintun, M. A. (2010). Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. [Research Support, N.I.H., Extramural]. *Proc Natl Acad Sci U S A*, 107(24), 11020-11025. doi: 10.1073/pnas.1000446107

- Siegle, G. J., Thompson, W., Carter, C. S., Steinhauer, S. R., & Thase, M. E. (2007). Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: related and independent features. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S.]. *Biol Psychiatry*, 61(2), 198-209. doi: 10.1016/j.biopsych.2006.05.048
- Spedding, M., Neau, I., & Harsing, L. (2003). Brain plasticity and pathology in psychiatric disease: sites of action for potential therapy. [Review]. *Curr Opin Pharmacol*, 3(1), 33-40.
- Spronk, D., Arns, M., Bootsma, A., van Ruth, R., & Fitzgerald, P. B. (2008). Long-term effects of left frontal rTMS on EEG and ERPs in patients with depression. [Research Support, Non-U.S. Gov't]. *Clin EEG Neurosci*, 39(3), 118-124.
- Stefan, K., Kunesch, E., Benecke, R., Cohen, L. G., & Classen, J. (2002). Mechanisms of enhancement of human motor cortex excitability induced by interventional paired associative stimulation. [Clinical Trial Controlled Clinical Trial Research Support, Non-U.S. Gov't]. *J Physiol*, 543(Pt 2), 699-708.
- Stefan, K., Kunesch, E., Cohen, L. G., Benecke, R., & Classen, J. (2000). Induction of plasticity in the human motor cortex by paired associative stimulation. [Research Support, Non-U.S. Gov't]. *Brain*, 123 Pt 3, 572-584.
- Tort, A. B., Komorowski, R., Eichenbaum, H., & Kopell, N. (2010). Measuring phase-amplitude coupling between neuronal oscillations of different frequencies. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S.]. *J Neurophysiol*, 104(2), 1195-1210. doi: 10.1152/jn.00106.2010
- Uhlhaas, P. J., & Singer, W. (2006). Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. [Research Support, Non-U.S. Gov't Review]. *Neuron*, 52(1), 155-168. doi: 10.1016/j.neuron.2006.09.020

- Valiulis, V., Gerulskis, G., Dapsys, K., Vistartaite, G., Siurkute, A., & Maciulis, V. (2012). Electrophysiological differences between high and low frequency rTMS protocols in depression treatment. *Acta Neurobiol Exp (Wars)*, 72(3), 283-295.
- Watrous, A. J., Fried, I., & Ekstrom, A. D. (2011). Behavioral correlates of human hippocampal delta and theta oscillations during navigation. [Clinical Trial]. *J Neurophysiol*, 105(4), 1747-1755. doi: 10.1152/jn.00921.2010
- Weinberger, N. M., Miasnikov, A. A., Bieszczad, K. M., & Chen, J. C. (2013). Gamma band plasticity in sensory cortex is a signature of the strongest memory rather than memory of the training stimulus. [Research Support, N.I.H., Extramural]. *Neurobiol Learn Mem*, 104, 49-63. doi: 10.1016/j.nlm.2013.05.001
- WHO. (2012, April 2016). Depression Fact sheet, from <http://www.who.int/mediacentre/factsheets/fs369/en/>
- Williams, L. M. (2016). Precision psychiatry: a neural circuit taxonomy for depression and anxiety. [Review]. *Lancet Psychiatry*, 3(5), 472-480. doi: 10.1016/S2215-0366(15)00579-9
- Wolters, A., Sandbrink, F., Schlottmann, A., Kunesch, E., Stefan, K., Cohen, L. G., . . . Classen, J. (2003). A temporally asymmetric Hebbian rule governing plasticity in the human motor cortex. [Clinical Trial Randomized Controlled Trial]. *J Neurophysiol*, 89(5), 2339-2345. doi: 10.1152/jn.00900.2002

Figure Legends

Figure 1. A. TEP traces in the PAS paradigm in patients with depression. PAS induced a significant potentiation in patients with depression (mean $\pm$ SD: patients: 1.24 ± 0.33 [μ V] vs. controls: 1.48 ± 0.28 [μ V]). However, compared to healthy controls, degree of potentiation was significantly lower in patients group ($t_{55} = 3.128$, $p = 0.003$; patients < controls). **B. Topographies demonstrating the PAS-induced potentiation between patients with depression and healthy controls.** In patients group, a degree of PAS-induced potentiation over the left frontal area was much lighter than healthy controls. **C. Bar graphs showing cross-sectional differences of frequency bands modulation by the DLPFC-PAS paradigm between patients and controls.** There were significant differences in δ ($t_{55} = 4.127$, $p < 0.0001$: patients < controls), ϑ ($t_{55} = 3.075$, $p = 0.003$: patients < controls), and γ ($t_{55} = 3.146$, $p = 0.003$: patients < controls) band power changes induced by the DLPFC-PAS paradigm between the two groups. **D. Bar graph demonstrating a cross-sectional difference of the MI of ϑ - γ coupling changes by PAS paradigm between patients and controls.** There was a significant difference of the MI of ϑ - γ coupling changes ($t_{55} = 4.048$, p

< 0.0001: patients < controls) between the two groups, suggesting that PAS-induced θ - γ coupling was significantly lower in patients with depression compared to healthy controls.

Tables

Table 1. Demographic and clinical data for patients with depression and healthy controls.

Mean ($\pm$ SD)	Patients (N = 29)	Controls (N = 28)
Age	42.8 $\pm$ 10.0	38.5 $\pm$ 9.0
Male: Female	13 : 16	17 : 11
HAM-D ₁₇	20.7 $\pm$ 4.1	--
Fluoxetine Equivalent Does (mg/day)	51.2 $\pm$ 42.1	--

SD: standard deviation, HAM-D₁₇: the Hamilton Rating Scale for Depression

Table 2. Baseline neurophysiological data for patients with depression and healthy controls

Mean ($\pm$ SD)	Patients (N = 29)	Controls (N = 28)	Statistics
RMT (%)	48.2 $\pm$ 8.4	44.3 $\pm$ 10.5	$t_{55} = -1.564$, $p = 0.123$
Intensity to evoke a 1mV peak-to-peak MEP amplitude (%)	58.8 $\pm$ 9.7	55.0 $\pm$ 13.5	$t_{55} = -1.249$, $p = 0.217$
3 times the sensory threshold [mA]	6.9 $\pm$ 0.9	6.4 $\pm$ 1.3	$t_{55} = -1.945$, $p = 0.057$
PNS counts (180 pulses in total)	178.8 $\pm$ 2.9	180.3 $\pm$ 4.1	$t_{55} = 1.621$, $p = 0.111$

RMT: resting motor threshold, MEP: motor-evoked potential, PNS: peripheral nerve stimulation

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Title:

Impaired neuroplasticity in the prefrontal cortex in depression indexed through paired associative stimulation

Date:

2018-05-01

Citation:

Noda, Y., Zomorodi, R., Vila-Rodriguez, F., Downar, J., Farzan, F., Cash, R. F. H., Rajji, T. K., Daskalakis, Z. J. & Blumberger, D. M. (2018). Impaired neuroplasticity in the prefrontal cortex in depression indexed through paired associative stimulation. *DEPRESSION AND ANXIETY*, 35 (5), pp.448-456. <https://doi.org/10.1002/da.22738>.

Persistent Link:

<http://hdl.handle.net/11343/284994>