Appendix 1 to Lissemore JI, Mulsant BG, Rajji TK, et al. Cortical inhibition, facilitation and plasticity in late-life depression: effects of venlafaxine pharmacotherapy. *J Psychiatry Neurosci* 2020.

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Supplementary Information

1.0 Comparisons between Late-Life Depression Patients Post-Treatment and Healthy Controls

We previously identified reduced short-interval cortical inhibition (SICI) in late-life depression (LLD) patients as compared to healthy, younger controls, but not older, age-matched controls[1]. In order to assess whether TMS measures in LLD patients differed from control values following 12 weeks of venlafaxine treatment, we compared post-treatment TMS measures in LLD patients (n = 68, mean ± SD age = 66.8 ± 5.7 years, 41F / 27M) to baseline measures in younger healthy controls (n = 57, mean ± SD age = 36.4 ± 12.2 years, 29F / 28M) and age-matched healthy controls (n = 41, mean ± SD age = 69.0 ± 8.3 years, 23F / 18M). The sample of younger adults reported here is larger than published previously because a subset of participants was included in earlier analyses in order to match for age with another group[1].

Two-tailed independent t-tests were performed comparing LLD patients (n = 63) to either older or younger healthy controls for SICI, intracortical facilitation (ICF) and cortical silent period paradigms. Maximum paired associative stimulation (PAS)-induced plasticity was also compared between LLD patients (n = 51) and age-matched controls using an independent t-test. Comparisons were performed using post-venlafaxine data from the whole sample of LLD patients, and in the subset of treatment responders separately (SICI, ICF: n = 27; cortical silent period: n = 26; PAS: n = 21). Data distributions were checked using histograms, Q-Q plots, and the Shapiro-Wilk test. Positive skews in the data were corrected with a log transformation for SICI and PAS ratios, and a square root transformation for ICF ratios.

Consistent with our previously reported baseline findings[1], LLD patients showed significantly weaker inhibition in the SICI paradigm post-treatment compared to younger healthy controls (t_{118} = 4.53, p < 0.001). Post-treatment SICI was similarly weaker in the subset of LLD treatment responders compared to younger healthy controls (t_{82} = 3.31, p = 0.001). ICF and cortical silent period measures did not differ significantly between younger healthy controls and the whole sample of LLD patients or responders post-treatment (p > 0.07). In both the whole sample of patients and the treatment responder subgroup, no significant differences were observed between LLD patients post-treatment and age-matched healthy controls for any TMS measure (p > 0.16). Overall, these findings suggest that deficits in GABA-A receptor-mediated cortical inhibition previously identified in LLD patients as compared to younger, healthy adults persist following 12 weeks of venlafaxine treatment.

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2.0 Changes in Paired-Pulse Curves with Venlafaxine Treatment

A subset of patients (n = 20) underwent paired-pulse TMS with additional interstimulus intervals (ISIs) of 4ms (SICI), 15ms, and 20ms (ICF). We therefore explored treatment-related changes in the paired-pulse curves in these patients. We performed a 3 × 2 × 5 analysis of covariance (ANCOVA) with a within-subject factor of time (baseline, week 1 [n = 15], and week 12), a between-subject factor of treatment response (responders and non-responders), a within-subject factor of ISI (2, 4, 10, 15, 20ms), and a time-varying covariate of resting motor threshold.

As expected, there was a significant main effect of ISI ($F_{4,220} = 25.92$, $p < 0.001$), indicating that the different intervals between conditioning and test TMS pulses differentially modulated the amplitude of the motor evoked potential. We observed no significant main effect of time ($F_{2,233} = 0.77$, $p = 0.46$), or time × ISI interaction ($F_{8,220} = 0.76$, $p = 0.64$), suggesting no pharmacological modulation of the paired-pulse curves over time. Similarly, we observed no significant time × response or time × response × ISI interactions ($F_{2,231} = 0.21$, $p = 0.81$, $F_{8,220} = 0.17$, $p = 0.99$, respectively), suggesting no therapeutic response-dependent modulation of the paired-pulse curves during treatment. These findings are consistent with the primary findings, and suggest that the intracortical inhibition and facilitation findings were not likely specific to the 2ms and 10ms paired-pulse ISIs.

References.

1 Lissemore JI, Bhandari A, Mulsant BH *et al.* Reduced GABAergic cortical inhibition in aging and depression. *Neuropsychopharmacology* 2018;43(11):2277-84.

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Supplementary Table 1. Primary ANCOVA results in subgroups of interest. CSP = cortical silent period, SICI = short-interval cortical inhibition, ICF = intracortical facilitation, max PAS = maximum paired associative stimulation-induced potentiation. ATHF = Antidepressant Treatment History Form

	Time × Response Interaction	Main Effect of Time
Females only		
CSP (n = 39)	$F_{1,41} = 4.14$, $p = 0.05$	$F_{1,39} = 0.73$, $p = 0.40$
SICI (n = 40)	$F_{1,41} = 0.13$, $p = 0.72$	$F_{1,38} = 0.01$, $p = 0.92$
ICF (n = 40)	$F_{1,41} = 4.04$, $p = 0.05$	$F_{1,39} = 0.90$, $p = 0.35$
max PAS (n = 31)	$F_{1,31} = 3.62$, $p = 0.07$	$F_{1,30} = 0.002$, $p = 0.96$
Males only		
CSP (n = 24)	$F_{1,21} = 0.16$, $p = 0.70$	$F_{1,21} = 3.28$, $p = 0.08$
SICI (n = 23)	$F_{1,20} = 0.32$, $p = 0.58$	$F_{1,20} = 1.02$, $p = 0.32$
ICF (n = 23)	$F_{1,20} = 0.08$, $p = 0.78$	$F_{1,20} = 0.18$, $p = 0.68$
max PAS (n = 21)	$F_{1,19} = 0.29$, $p = 0.60$	$F_{1,20} = 1.35$, $p = 0.26$
Early-onset LLD only (onset < 60 years of age)		
CSP (n = 50)	$F_{1,49} = 0.63$, $p = 0.43$	$F_{1,50} = 0.20$, $p = 0.66$
SICI (n = 52)	$F_{1,52} = 0.11$, $p = 0.74$	$F_{1,52} = 0.38$, $p = 0.54$
ICF (n = 52)	$F_{1,52} = 1.26$, $p = 0.27$	$F_{1,52} = 0.003$, $p = 0.96$
max PAS (n = 41)	$F_{1,41} = 0.46$, $p = 0.50$	$F_{1,42} = 0.55$, $p = 0.46$
Late-onset LLD only (onset ≥ 60 years of age)		
CSP (n = 13)	$F_{1,11} = 0.42$, $p = 0.53$	$F_{1,11} = 0.27$, $p = 0.61$
SICI (n = 11)	$F_{1,8} = 0.07$, $p = 0.80$	$F_{1,9} = 1.35$, $p = 0.27$
ICF (n = 11)	$F_{1,8} = 1.99$, $p = 0.20$	$F_{1,8} = 0.13$, $p = 0.73$
max PAS (n = 10)	$F_{1,8} = 1.69$, $p = 0.23$	$F_{1,7} = 1.58$, $p = 0.25$
Prior adequate antidepressant trial (ATHF ≥ 3)		
CSP (n = 45)	$F_{1,43} = 1.06$, $p = 0.31$	$F_{1,42} = 0.21$, $p = 0.65$
SICI (n = 45)	$F_{1,44} = .002$, $p = 0.97$	$F_{1,43} = 0.48$, $p = 0.49$
ICF (n = 45)	$F_{1,44} = 3.47$, $p = 0.07$	$F_{1,43} = 0.28$, $p = 0.60$
max PAS (n = 37)	$F_{1,36} = 2.62$, $p = 0.11$	$F_{1,35} = 2.99$, $p = 0.09$
No prior adequate antidepressant trial (ATHF < 3)		
CSP (n = 18)	$F_{1,16} = 0.07$, $p = 0.79$	$F_{1,16} = 0.12$, $p = 0.73$
SICI (n = 18)	$F_{1,16} = 0.36$, $p = 0.55$	$F_{1,16} = 0.62$, $p = 0.44$
ICF (n = 18)	$F_{1,16} = 0.31$, $p = 0.59$	$F_{1,16} = 0.84$, $p = 0.37$
max PAS (n = 14)	$F_{1,11} = 0.04$, $p = 0.84$	$F_{1,12} = 0.16$, $p = 0.69$
Low venlafaxine final dose (< 225 mg/day)		
CSP (n = 18)	$F_{1,15} = 0.05$, $p = 0.82$	$F_{1,16} = 0.10$, $p = 0.76$
SICI (n = 18)	$F_{1,15} = 0.05$, $p = 0.83$	$F_{1,15} = 0.71$, $p = 0.41$
ICF (n = 18)	$F_{1,16} = 4.65$, $p = 0.05$	$F_{1,16} = 0.71$, $p = 0.41$
max PAS (n = 15)	$F_{1,12} = 0.0006$, $p = 0.99$	$F_{1,12} = 1.18$, $p = 0.30$

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High venlafaxine final dose (≥ 225 mg/day)		
CSP (n = 45)	$F_{1,45} = 1.56$, $p = 0.22$	$F_{1,43} = 1.02$, $p = 0.32$
SICI (n = 45)	$F_{1,44} = 0.03$, $p = 0.86$	$F_{1,43} = 1.66$, $p = 0.20$
ICF (n = 45)	$F_{1,44} = 0.25$, $p = 0.62$	$F_{1,43} = 0.20$, $p = 0.65$
max PAS (n = 36)	$F_{1,37} = 1.92$, $p = 0.17$	$F_{1,35} = 1.33$, $p = 0.26$

Supplementary Table 2. Primary ANCOVA results excluding patients who were left-handed or missing handedness data, concurrently using any dose of benzodiazepine or another antidepressant at any point in the study, or diagnosed with a comorbid anxiety disorder. CSP = cortical silent period, SICI = short-interval cortical inhibition, ICF = intracortical facilitation, max PAS = maximum paired associative stimulation-induced potentiation.

	Time × Response Interaction	**Main Effect of Time**
Right-handed only		
CSP (n = 49)	$F_{1,48} = 0.46$, $p = 0.50$	$F_{1,48} = 0.30$, $p = 0.59$
SICI (n = 48)	$F_{1,47} = 0.43$, $p = 0.51$	$F_{1,46} = 0.08$, $p = 0.77$
ICF (n = 48)	$F_{1,47} = 2.30$, $p = 0.14$	$F_{1,47} = 0.11$, $p = 0.74$
max PAS (n = 38)	$F_{1,36} = 0.65$, $p = 0.43$	$F_{1,37} = 0.80$, $p = 0.38$
No concurrent benzodiazepine or zopiclone use		
CSP (n = 34)	$F_{1,32} = 1.30$, $p = 0.26$	$F_{1,32} = 0.03$, $p = 0.87$
SICI (n = 34)	$F_{1,33} = 0.007$, $p = 0.93$	$F_{1,32} = 1.37$, $p = 0.25$
ICF (n = 34)	$F_{1,33} = 1.95$, $p = 0.17$	$F_{1,32} = 0.10$, $p = 0.76$
max PAS (n = 27)	$F_{1,25} = 2.61$, $p = 0.12$	$F_{1,25} = 2.25$, $p = 0.15$
No trazodone use or low cross-titration dose of another antidepressant at baseline		
CSP (n = 35)	$F_{1,33} = 0.22$, $p = 0.64$	$F_{1,33} = 5.29$, $p = 0.028$
SICI (n = 36)	$F_{1,35} = 1.04$, $p = 0.32$	$F_{1,35} = 0.03$, $p = 0.87$
ICF (n = 36)	$F_{1,35} = 2.37$, $p = 0.13$	$F_{1,35} = 0.05$, $p = 0.83$
max PAS (n = 28)	$F_{1,26} = 0.008$, $p = 0.93$	$F_{1,27} = 1.83$, $p = 0.19$
No comorbid anxiety diagnosis		
CSP (n = 40)	$F_{1,38} = 0.0008$, $p = 0.98$	$F_{1,36} = 0.79$, $p = 0.38$
SICI (n = 40)	$F_{1,39} = 0.17$, $p = 0.68$	$F_{1,39} = 0.01$, $p = 0.91$
ICF (n = 40)	$F_{1,39} = 1.41$, $p = 0.24$	$F_{1,38} = 0.20$, $p = 0.66$
max PAS (n = 35)	$F_{1,34} = 0.87$, $p = 0.36$	$F_{1,33} = 1.48$, $p = 0.23$

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Supplementary Table 3. Primary ANCOVA results excluding patients with SICI ratios > 1 (showing facilitation rather than inhibition), ICF ratios < 1 (showing inhibition rather than facilitation), or maximum PAS ratios < 1 (showing inhibition rather than facilitation). SICI = short-interval cortical inhibition, ICF = intracortical facilitation, max PAS = maximum paired associative stimulation-induced potentiation.

	Time × Response Interaction	**Main Effect of Time**
SICI responders only		
SICI (n = 48)	$F_{1,47} = 0.58$, $p = 0.45$	$F_{1,46} = 0.02$, $p = 0.89$
ICF responders only		
ICF (n = 53)	$F_{1,52} = 3.98$, $p = 0.051$	$F_{1,51} = 0.006$, $p = 0.94$
PAS responders only		
max PAS (n = 36)	$F_{1,35} = 2.00$, $p = 0.17$	$F_{1,35} = 1.57$, $p = 0.22$