J Neurophysiol 122: 1367–1372, 2019.
First published August 14, 2019; doi:10.1152/jn.00203.2019.

CASE STUDIES IN NEUROSCIENCE | *Nervous System Pathophysiology*

Case Studies in Neuroscience: Lack of inhibitory synaptic plasticity in the substantia nigra pars reticulata of a patient with lithium-induced tremor

Luka Milosevic,[1] Robert F. Dallapiazza,[2] Renato P. Munhoz,[3] Suneil K. Kalia,[2,4,5] Milos R. Popovic,[1,6] and William D. Hutchison[4,5,7]

[1]*Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, Ontario, Canada;* [2]*Division of Neurosurgery, Toronto Western Hospital – University Health Network, Toronto, Ontario, Canada;* [3]*Division of Neurology, University of Toronto, Toronto, Ontario, Canada;* [4]*Department of Surgery, University of Toronto, Toronto, Ontario, Canada;* [5]*Krembil Research Institute, Toronto, Ontario, Canada;* [6]*KITE, Toronto Rehabilitation Institute – University Health Network, Toronto, Ontario, Canada; and* [7]*Department of Physiology, University of Toronto, Toronto, Ontario, Canada*

Submitted 1 April 2019; accepted in final form 26 July 2019

Milosevic L, Dallapiazza RF, Munhoz RP, Kalia SK, Popovic MR, Hutchison WD. Case Studies in Neuroscience: Lack of inhibitory synaptic plasticity in the substantia nigra pars reticulata of a patient with lithium-induced tremor. *J Neurophysiol* 122: 1367–1372, 2019. First published August 14, 2019; doi:10.1152/jn.00203.2019.—Tremor is a well-known side effect from many psychiatric medications, including lithium and dopamine antagonists. In patients whose psychiatric symptoms are stabilized and only respond to certain medications, deep brain stimulation may offer relief of the consequent motor complications. We report the case of an elderly male with disabling tremor related to lithium therapy for bipolar affective disorder, who was subsequently treated with deep brain stimulation. In this patient, we obtained recordings from the substantia nigra pars reticulata and performed a high-frequency stimulation protocol that robustly elicits long-term potentiation (LTP)-like changes in patients with Parkinson's disease. We hypothesized that in this patient, who did not have Parkinson's disease, the levels of inhibitory plasticity would be much greater. However, we found an unanticipated lack of plasticity in the patient with lithium-induced tremor, compared with two de novo control patients with Parkinson's disease. This patient was successfully treated with deep brain stimulation in the vicinity of the ventral oral posterior nucleus, an area of the thalamus that receives inputs from the basal ganglia. We postulate that the lithium-induced blockade of LTP may bring about motor complications such as tremor while simultaneously contributing to the therapeutic mechanism for treating the symptoms of psychiatric disorders such as bipolar affective disorder.

NEW & NOTEWORTHY Use of a dual-microelectrode technique enabled us to compare long-term potentiation (LTP)-like changes in a patient with lithium-induced tremor to that of patients with Parkinson's disease. This study corroborated the findings in rodent brain slices that chronic lithium treatment may block LTP. Whereas a deficit in LTP may underlie the therapeutic mechanism for treating psychiatric disorders such as bipolar affective disorder, it may simultaneously contribute to consequent appearance of tremor.

basal ganglia; bipolar affective disorder; drug-induced tremor; lithium; synaptic plasticity

INTRODUCTION

Tremor is a well-known side effect from many psychiatric medications, including lithium and dopamine antagonists (Morgan and Sethi 2005). For many patients that develop tremor related to these medications, the simple solution is to lower dosages or change medications. However, this may not be an option for some patients whose psychiatric symptoms are stabilized and only respond to certain medications. Deep brain stimulation (DBS) of the thalamic ventral intermediate nucleus (Vim) and/or posterior subthalamic area (PSA) are highly efficacious treatments for patients with severe, medication-refractory essential tremor and tremor related to Parkinson's disease (Benabid et al. 1991; Blomstedt et al. 2010; Elble and Deuschl 2011; Milosevic et al. 2018b). Although there are fewer data regarding the effects of DBS for other tremor etiologies, there is some evidence that it can be useful in patients with drug-induced tremor who are unable to alter medications (Rodrigues et al. 2015). We report on a patient with lithium-induced tremor who was subsequently treated with DBS. In this patient, recordings were obtained from the substantia nigra pars reticulata (SNr), where a high-frequency stimulation (HFS) protocol was applied that normally elicits long-term potentiation (LTP)-like changes in patients with Parkinson's disease (Prescott et al. 2009). We took this as a unique opportunity to measure inhibitory plasticity in the SNr in a patient who did not have Parkinson's disease, hypothesizing that the levels of plasticity would be greater. However, we found an unexpected lack of SNr plasticity.

CASE REPORT

A left-handed man in his 70s with lithium-induced tremor was referred to the multidisciplinary movement disorders team at Toronto Western Hospital for evaluation and potential surgical treatment. His tremor was present at rest and with posture, and was most severe during handwriting activities. His tremor symptoms began after a previous hospitalization for depression and suicidal ideation. During this hospitalization he was tapered off clonazepam, which he had used for more than 20 yr, and he was started on lithium (300 mg twice a day) and

Address for reprint requests and other correspondence: W. D. Hutchison, MC12-417, 399 Bathurst St., Toronto, ON, Canada M5T 2S8 (e-mail: bill.hutchison@uhnresearch.ca).

olanzapine (2.5 mg twice a day) to treat bipolar affective disorder. His psychiatric history included bipolar affective disorder, posttraumatic stress disorder, anxiety, and depression with suicidal threats. He was diagnosed with lithium-induced tremor on the basis of clinical features (action/kinetic tremor) and temporal onset related to lithium treatment. He had no sensory loss and no other neurological symptoms to report. His tremor was not responsive to alcohol. Although olanzapine, at high doses, may lead to drug-induced parkinsonism (Rodrigues et al. 2015), the patient did not present with bradykinesia or any other symptoms of Parkinson's disease. He tried several medications for tremor, including propranolol, which did not help his symptoms. His mood and bipolar affective disorder were clinically stable on his medication regimen, and in consultation with his treating psychiatrist, it was deemed reasonable to continue lithium therapy. After a detailed multidisciplinary review, right-sided DBS surgery was offered as a treatment option for his left upper extremity tremor.

During DBS surgery, microelectrode recordings were performed in the patient with lithium-induced tremor, and data were compared with recordings from two patients with Parkinson's disease. The experiments conformed to the guidelines set by the Tri-Council Policy on Ethical Conduct for Research Involving Humans and were approved by the University Health Network Research Ethics Board, and each patient provided written, informed consent before taking part in the study. Techniques for electrophysiological identification of subthalamic nucleus (STN)/SNr (Hutchison et al. 1998) and thalamic subnuclei (Basha et al. 2014; Milosevic et al. 2018b) have been previously reported. For the patient with lithium-induced tremor, the surgical plan included three microelectrode mapping trajectories, targeting *1*) the subthalamic STN and/or PSA, where we also recorded from the SNr, *2*) the thalamic ventral oral posterior nucleus (Vop), and *3*) the Vim (Fig. 1). Each of the patients with Parkinson's disease underwent STN DBS surgery that only involved mapping of the STN/SNr while withdrawn from all antiparkinsonian medications (medication OFF).

SNr recording sites were confirmed on the basis of two criteria. *1*) Neuronal firing rates and patterns: SNr neurons fire at a much higher rate than STN neurons (SNr: 80–120 Hz vs. STN: 20–60 Hz) and exhibit much more regular firing patterns, whereas STN neurons exhibit irregular firing patterns (Hutchison et al. 1998). Recordings of single-neuron activity before the delivery of the stimulation protocol confirmed characteristic SNr neurons (Fig. 2, *bottom*). *2*) Presence of inhibitory focal evoked field potentials (fEPs): single pulses of stimulation in the SNr robustly elicit positive-going extracellular inhibitory fEPs (analogous to extracellular field inhibitory postsynaptic potentials, or IPSPs; Milosevic et al. 2018a, 2019; Prescott et al. 2009), whereas single pulses of stimulation in the STN do not (Milosevic et al. 2018a). The generation of these fEPs is most likely due to the large predominance (~90%) of GABAergic afferent innervation to the SNr (Bolam et al. 2000; Parent and Hazrati 1995), whereas the STN has a much more homogenous collateralization of incoming inhibitory and excitatory afferents. The overlap of these antagonistic responses (GABAergic and glutamatergic) likely shunts the explicit generation of either a field IPSP or excitatory postsynaptic potential (EPSP) in the STN (Kaneda and Kita 2005; Rodríguez-Moreno et al. 1997).

The SNr recording locations, where the synaptic plasticity stimulation protocol was delivered in each patient, did not differ substantially for the three patients included in this study (Fig. 1). The stimulation protocol (delivered only once in each patient) involved one baseline set of 1-Hz "test pulses" (100 μA, 150-μs pulse width, 10 s; 10 total pulses), followed by "standard HFS" (four 100-Hz trains, 2 s each, separated by 8 s), followed by another set of 1-Hz "test pulses" (10 total; Fig. 2, *middle*). We quantified changes in plasticity by the

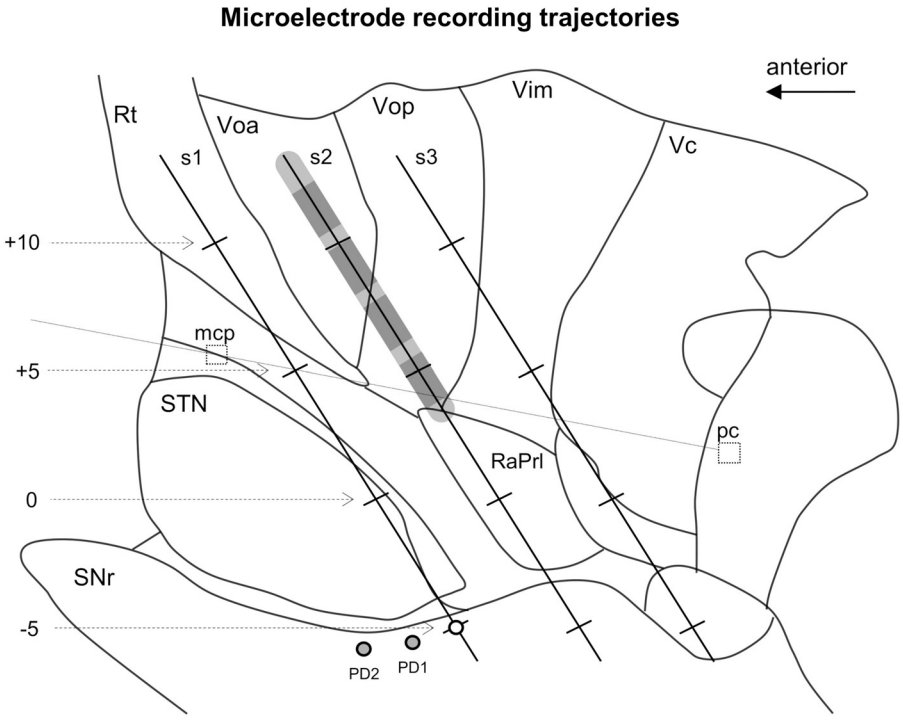

Fig. 1. Microelectrode trajectories. Corroborated neurophysiological results are superimposed on a 14.5-mm sagittal section, based on microelectrode recordings and effects from microstimulation. The synaptic plasticity stimulation protocol was delivered in the substantia nigra pars reticulata (SNr) of *section 1* (s1) at 5 mm below target (−5 mm; denoted by open circle). The deep brain stimulation macroelectrode was implanted in *section 2* (s2) due to maximal tremor-suppressing effects with microstimulation, with the bottom electrode contact positioned at the ventral thalamic border. The approximate locations of the SNr stimulation protocols for the 2 patients with Parkinson's disease (PD1 and PD2) are denoted by shaded circles. mcp, Mid-commissural point; pc, posterior commissure; RaPrl, prelemniscal radiations; Rt, reticular thalamic nucleus; STN, subthalamic nucleus; Vc, ventral caudal; Vim, ventral intermediate; Voa, ventral oral anterior; Vop, ventral oral posterior.

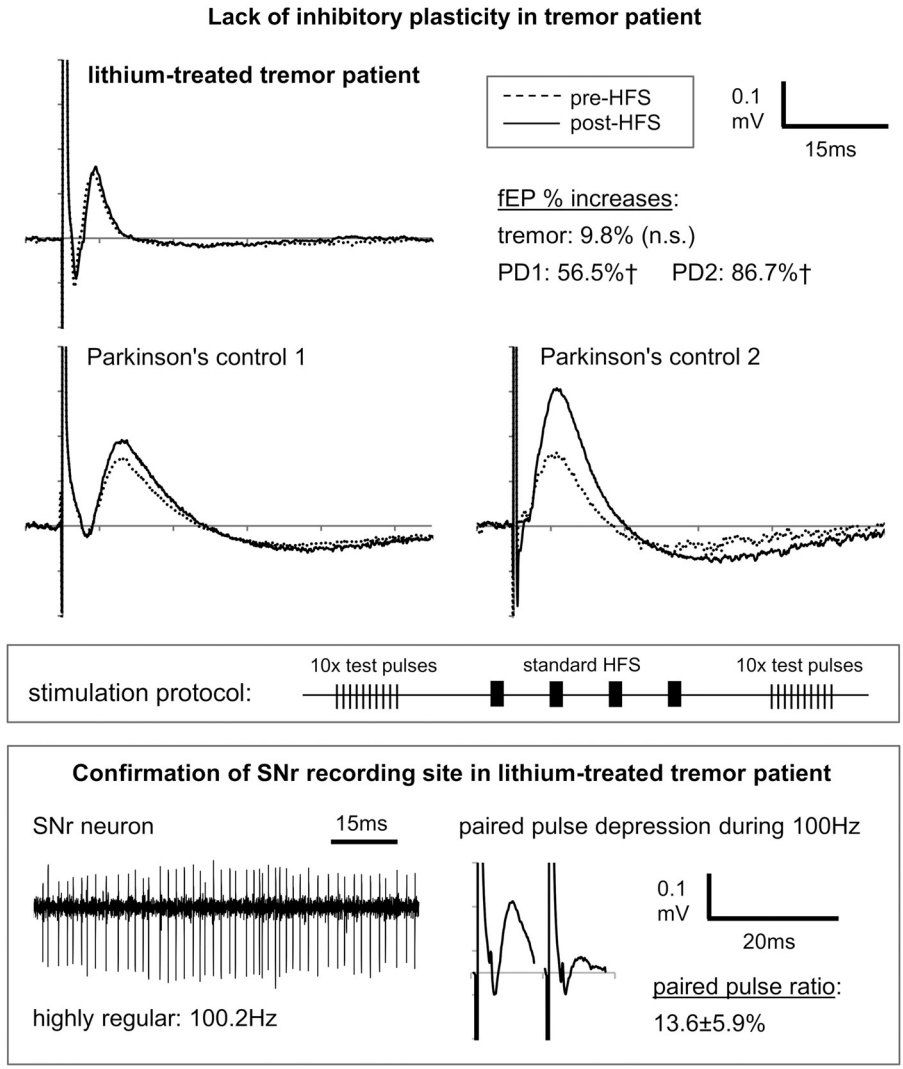

Fig. 2. Lack of inhibitory synaptic plasticity in patient with lithium-induced tremor. *Top*: significant increases in inhibitory focal evoked field potential (fEP) amplitudes after high-frequency stimulation (HFS) were measured in 2 patients with Parkinson's disease (PD1 and PD2), whereas there was a nonsignificant increase in fEP amplitude in the patient with lithium-induced tremor (†$P < 0.001$). Additionally, the fEPs of the lithium-treated tremor patient were of significantly ($P < 0.001$) shorter duration (6.6 ± 0.7 ms) compared with those of the 2 patients with Parkinson's disease (20.2 ± 1.7 ms). *Middle*: "standard HFS" microstimulation protocol. *Bottom*: in addition to the presence of stimulation-induced fEPs, confirmation of the substantia nigra pars reticulata (SNr) in the lithium-treated tremor patient was also based on characteristic firing rates and patterns (per Hutchison et al. 1998) of neurons encountered before delivery of the stimulation protocol. Additionally, robust paired-pulse depression of fEPs was observed during the 4 trains of HFS (in accordance with Milosevic et al. 2018a).

percentage change in fEP amplitude (peak to trough) before and after HFS (paired-sample *t* test, 2-tailed).

HFS induced a nonsignificant enhancement of inhibitory synaptic plasticity in the patient with lithium-induced tremor (9.8%, $P = 0.06$), whereas the patients with Parkinson's disease (medication OFF) exhibited statistically significant enhancements of fEP amplitudes (56.5%, $P < 0.001$ and 86.7%, $P < 0.001$), consistent with our previous studies (Milosevic et al. 2018a, 2019; Prescott et al. 2009). These results are summarized in Fig. 2. In the medication-OFF condition, Prescott et al. (2009) reported an average increase in fEP amplitude of 29.3%, which is lower than that of the parkinsonian patients included in the present study. One reason for the disparity in fEP amplitudes after HFS in this study compared with prior work was methodological differences in measuring the fEP amplitude. In previous studies, we measured baseline to peak amplitudes; however, we have now changed to measure peak to trough amplitude (since both the peak and trough appear to extend beyond pre-HFS baseline levels). Furthermore, the patients with Parkinson's disease (PD1 and PD2) included in this study, who had far greater plasticity than the patient with lithium-induced tremor, possessed only mild tremor scores at most (average of rest, posture, and action tremor for upper extremities, lower extremities, and head, respectively: 0.67/4, 0.67/4, 0.67/4 for PD1; 0.67/4, 0/4, 0/4 for PD2) and mild motor symptom severity (Unified Parkinson's Disease Rating Scale Part III motor subscores of 32/108 for PD1 and 20/108 for PD2). The patient with less severe tremor and less severe motor symptoms was the patient with greater plasticity (PD2).

Although we have reported that fEPs are potentiated after HFS in patients with Parkinson's disease, we also have previously demonstrated that during HFS, fEPs in the SNr are rapidly attenuated with successive stimulation pulses, indicating synaptic depression (a phenomenon of short-term plasticity; Milosevic et al. 2018a). In the patient with lithium-induced tremor, although the enhancement of plasticity after HFS was lacking, synaptic depression during the four trains of 100-Hz stimulation was demonstrated. The average paired-pulse ratio between the first and second fEP during the 100-Hz stimulation trains (10-ms interstimulus intervals) was 13.6 ± 5.9% (Fig. 2, *bottom*), which conforms to our previous findings (Milosevic et al. 2018a).

The second trajectory (targeting Vop) was selected for DBS macroelectrode implantation due to maximal tremor suppressing effects intraoperatively (Fig. 1). The patient's preoperative score of 43 on The Essential Tremor Rating Assessment Scale

(TETRAS) was improved to 29 at 3 mo postoperatively with DBS-ON.

DISCUSSION

There is a total of five cortico-basal-ganglia loops that have been described anatomically; two are motor and oculomotor, and the remaining three are thought to be involved in cognition and mood (Alexander et al. 1991; Tekin and Cummings 2002). The dorsolateral-prefrontal circuit is involved executive function, the lateral-orbitofrontal circuit mediates socially critical restrain and empathy, and the anterior-cingulate-subcortical circuit subserves mood and motivation. Both of these last two circuits impinge on the SNr in the rostromedial and anterodorsal region, but the anterior-cingulate-subcortical circuit appears to most closely correspond to the region of SNr where we measured a lack of plasticity. There is evidence for a role of this region in disorders of mood, which comes from isolated observations of acute mood changes with stimulation at contacts in the ventral STN and dorsal SNr regions (Bejjani et al. 1999; Blomstedt et al. 2008; Huang et al. 2018; Krack et al. 2001; Okun et al. 2004). Additionally, the SNr has been postulated to be involved in cognition, thought to be largely mediated by dopaminergic neurons. Previous studies in patients undergoing STN DBS surgeries have provided evidence for the hypothetical role of the SNr (in the region immediately dorsal to the STN, as investigated here) in human reinforcement learning (Zaghloul et al. 2009) and novelty detection (Kamiński et al. 2018; Mikell et al. 2014). In terms of afferent innervation, this region of the SNr receives the majority of its inputs from the GABAergic direct pathway of the limbic striatum. As a whole, inhibitory striatonigral projections make up the majority (~90%) of the afferent innervation of the SNr (Bolam et al. 2000; Parent and Hazrati 1995).

We have demonstrated here that extracellular striatonigral inhibitory fEPs were not potentiated after HFS in a lithium-treated patient, whereas significant LTP-like effects occurred in patients with Parkinson's disease. Accordingly, lithium treatment has been shown to block long-term depression (LTD) in rat corticostriatal slices (Calabresi et al. 1993). In naive slices, EPSPs were depressed after tetanic stimulation (repetitive activation of corticostriatal glutamatergic inputs) but were not depressed following chronic lithium treatment. In addition to reduced EPSP amplitudes, EPSPs were also of shorter duration following chronic lithium treatment, which was also observed in our study. A more recent study in mouse hippocampal slices demonstrated that chronic lithium treatment reduced amplitudes of miniature EPSCs though brain-derived neurotrophic factor (BDNF)- and dynamin-dependent endocytosis of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-receptor subunits (Gideons et al. 2017). This reduced synaptic efficacy was postulated to contribute to the antimanic therapeutic mechanism of lithium treatment. Therefore, the first postulation that arises from our findings is that downregulated inhibitory LTP in the SNr may contribute (in part) to improved psychiatric symptoms, perhaps via the cortico-basal-ganglia loops involved in mood and motivation. Although little is known about both the pathophysiology of bipolar affective disorder and the mechanisms of action of mood stabilizing drugs, including lithium (Bachmann et al. 2005), there is converging evidence that bipolar affective disorder may arise from abnormalities in synaptic and neuronal plasticity cascades, leading to aberrant information processing (Einat and Manji 2006; Schloesser et al. 2008).

Moreover, we have previously demonstrated that patients with Parkinson's disease with lower levels of nigral LTP-like changes after HFS were associated with higher severity motor symptoms (Milosevic et al. 2019; Prescott et al. 2009), leading to the hypothesis that altered (reduced) plasticity in the basal ganglia output structures may contribute to motor symptoms of Parkinson's disease. These findings were replicated in the present study: the patient who presented with less severe tremor and motor scores demonstrated greater levels of plasticity. However, it is important to consider that both of these conditions (Parkinson's disease and lithium-induced tremor) are considered pathological states, and data from healthy control populations would be required to further confirm this hypothesis. Nevertheless, it is indeed suggested that downregulated synaptic efficacy of inhibitory striatonigral/striatopallidal projections brings about motor symptoms of Parkinson's disease (Albin et al. 1989; Alexander and Crutcher 1990; DeLong 1990; Surmeier et al. 2007). Thus we further postulate that lithium-induced blockade of inhibitory LTP may contribute to the extrapyramidal side effects (including but not limited to tremor) often observed with lithium therapy (Tyrer et al. 1980), via the cortico-basal-ganglia loops involved in motor function. Therefore, it is of particular interest that the trajectory targeting the Vop, which receives significant inputs from the basal ganglia output structures (the SNr and globus pallidus internus; Kultas-Ilinsky and Ilinsky 1991; Kuramoto et al. 2011), yielded the best tremor suppressing effects and was thus selected as the implantation site for the chronic DBS macroelectrode.

Lithium is most commonly thought to work through its inhibitory effects on the synthesis of inositol and subsequent effects on signal transduction (Berridge et al. 1989; Dixon et al. 1992, 1994; Gerasimenko et al. 2006; Lee et al. 1992; Lubrich et al. 1997; Salinas and Hall 1999), as well as its inhibitory effects on glycogen synthase kinase 3 (GSK-3; Klein and Melton 1996), an enzyme that is directly involved in gene transcription, cell structure, and synaptic plasticity (Machado-Vieira et al. 2009). It also has been suggested to be involved in dopamine-mediated regulation of corticostriatal plasticity (Calabresi et al. 2007). Lithium also inhibits neurotransmitters including dopamine (by altering the functionality of G protein-coupled receptor subunits) and glutamate (by downregulating *N*-methyl-D-aspartate receptors) and promotes GABA-mediated neurotransmission (by presynaptic facilitation of GABA release and postsynaptic upregulation of $GABA_B$ receptors) (Malhi et al. 2013). Indeed, bipolar affective disorder has been associated with reduced GABAergic neurotransmission (Brambilla et al. 2003). It is possible that by blocking dopaminergic neurotransmission, lithium may reverse/block inhibitory LTP-like changes in the SNr, which have previously been demonstrated to be dopamine-sensitive (Floran et al. 1990; Milosevic et al. 2019; Prescott et al. 2009). Although we cannot specifically comment on changes to levels of neurotransmission that are inherent to bipolar affective disorder or are a consequence of lithium therapy, this work demonstrates for the first time in humans that modulation of synaptic efficacy in the basal ganglia was lacking in a patient with lithium-induced tremor.

Although the tremor etiology of the patient we report on is consistent lithium-induced tremor rather than resulting from olanzapine-related parkinsonism, a limitation of this study is the inability to parse out specifically whether the absent SNr plasticity was the result of lithium therapy or was due to the involvement of olanzapine (despite low doses). Although there have been notions that atypical neuroleptics (including olanzapine and haloperidol) may have modulatory effects on synaptic plasticity (Duman 2002), the described effects have been variable or marginal (Centonze et al. 2004; Dzyubenko et al. 2017; Hammonds and Shim 2009; Shim et al. 2012). Furthermore, there have been notions that lithium may have neuroprotective effects through upregulation of various neurotrophic and transcription factors including BDNF and CREB (Hammonds and Shim 2009; Manji et al. 2000; Nibuya et al. 1996). One study in hippocampal rat brain slices suggested that lithium administration enhanced glutamatergic LTP independently of hippocampal neurogenesis (Son et al. 2003), whereas our study demonstrates reduced/absent inhibitory LTP in the basal ganglia.

Given the inability to obtain data from healthy control populations, the conclusions of this study rely on previous animal literature as well as direct comparisons between two pathological patient populations. As such, further studies are warranted regarding the role of lithium in the modulation of synaptic plasticity, its therapeutic mechanisms of action, and mechanisms related to consequent generation of motor complications.

ACKNOWLEDGMENTS

We thank the patients for participation in the study.

GRANTS

This work was supported in part by Natural Sciences and Engineering Research Council: Discovery Grant RGPIN-2016-06358 (to M. R. Popovic) and the Dystonia Medical Research Foundation (to W. D. Hutchison).

DISCLOSURES

S.K.K., and W.D.H. have received honoraria, travel funds, and/or grant support from Medtronic. M.R.P. is a shareholder in MyndTec Inc. and an advisor to Myant Inc. L.M., R.F.D., R.P.M., have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

L.M., R.F.D., R.P.M., S.K.K., M.R.P., and W.D.H. conceived and designed research; L.M. and W.D.H. performed experiments; L.M. analyzed data; L.M. and W.D.H. interpreted results of experiments; L.M. prepared figures; L.M., R.F.D., and W.D.H. drafted manuscript; R.F.D., R.P.M., S.K.K., M.R.P., and W.D.H. edited and revised manuscript; R.F.D., R.P.M., S.K.K., M.R.P., and W.D.H. approved final version of manuscript.

REFERENCES

Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. *Trends Neurosci* 12: 366–375, 1989. doi:10.1016/0166-2236(89)90074-X.

Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends Neurosci* 13: 266–271, 1990. doi:10.1016/0166-2236(90)90107-L.

Alexander GE, Crutcher MD, DeLong MR. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. In: *Progress in Brain Research. The Prefrontal–Its Structure, Function and Cortex Pathology*, edited by Uylings HB, Van Eden CG, De Bruin JP, Corner MA, Feenstra MG. Amsterdam: Elsevier, 1991, vol. 85, p. 119–146.

Bachmann RF, Schloesser RJ, Gould TD, Manji HK. Mood stabilizers target cellular plasticity and resilience cascades: implications for the development of novel therapeutics. *Mol Neurobiol* 32: 173–202, 2005. doi:10.1385/MN:32:2:173.

Basha D, Dostrovsky JO, Lopez Rios AL, Hodaie M, Lozano AM, Hutchison WD. Beta oscillatory neurons in the motor thalamus of movement disorder and pain patients. *Exp Neurol* 261: 782–790, 2014. doi:10.1016/j.expneurol.2014.08.024.

Bejjani BP, Damier P, Arnulf I, Thivard L, Bonnet AM, Dormont D, Cornu P, Pidoux B, Samson Y, Agid Y. Transient acute depression induced by high-frequency deep-brain stimulation. *N Engl J Med* 340: 1476–1480, 1999. doi:10.1056/NEJM199905133401905.

Benabid AL, Pollak P, Gervason C, Hoffmann D, Gao DM, Hommel M, Perret JE, de Rougemont J. Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. *Lancet* 337: 403–406, 1991. doi:10.1016/0140-6736(91)91175-T.

Berridge MJ, Downes CP, Hanley MR. Neural and developmental actions of lithium: a unifying hypothesis. *Cell* 59: 411–419, 1989. doi:10.1016/0092-8674(89)90026-3.

Blomstedt P, Hariz MI, Lees A, Silberstein P, Limousin P, Yelnik J, Agid Y. Acute severe depression induced by intraoperative stimulation of the substantia nigra: a case report. *Parkinsonism Relat Disord* 14: 253–256, 2008. doi:10.1016/j.parkreldis.2007.04.005.

Blomstedt P, Sandvik U, Tisch S. Deep brain stimulation in the posterior subthalamic area in the treatment of essential tremor. *Mov Disord* 25: 1350–1356, 2010. doi:10.1002/mds.22758.

Bolam JP, Hanley JJ, Booth PA, Bevan MD. Synaptic organisation of the basal ganglia. *J Anat* 196: 527–542, 2000. doi:10.1046/j.1469-7580.2000.19640527.x.

Brambilla P, Perez J, Barale F, Schettini G, Soares JC. GABAergic dysfunction in mood disorders. *Mol Psychiatry* 8: 721–737, 2003. doi:10.1038/sj.mp.4001362.

Calabresi P, Picconi B, Tozzi A, Di Filippo M. Dopamine-mediated regulation of corticostriatal synaptic plasticity. *Trends Neurosci* 30: 211–219, 2007. doi:10.1016/j.tins.2007.03.001.

Calabresi P, Pisani A, Mercuri NB, Bernardi G. Lithium treatment blocks long-term synaptic depression in the striatum. *Neuron* 10: 955–962, 1993. doi:10.1016/0896-6273(93)90210-I.

Centonze D, Usiello A, Costa C, Picconi B, Erbs E, Bernardi G, Borrelli E, Calabresi P. Chronic haloperidol promotes corticostriatal long-term potentiation by targeting dopamine D2L receptors. *J Neurosci* 24: 8214–8222, 2004. doi:10.1523/JNEUROSCI.1274-04.2004.

DeLong MR. Primate models of movement disorders of basal ganglia origin. *Trends Neurosci* 13: 281–285 1990. doi:10.1016/0166-2236(90)90110-V.

Dixon JF, Lee CH, Los GV, Hokin LE. Lithium enhances accumulation of [^{3}H]inositol radioactivity and mass of second messenger inositol 1,4,5-trisphosphate in monkey cerebral cortex slices. *J Neurochem* 59: 2332–2335, 1992. doi:10.1111/j.1471-4159.1992.tb10129.x.

Dixon JF, Los GV, Hokin LE. Lithium stimulates glutamate "release" and inositol 1,4,5-trisphosphate accumulation via activation of the *N*-methyl-D-aspartate receptor in monkey and mouse cerebral cortex slices. *Proc Natl Acad Sci USA* 91: 8358–8362, 1994. doi:10.1073/pnas.91.18.8358.

Duman RS. Synaptic plasticity and mood disorders. *Mol Psychiatry* 7, *Suppl* 1: S29–S34, 2002. doi:10.1038/sj.mp.4001016.

Dzyubenko E, Juckel G, Faissner A. The antipsychotic drugs olanzapine and haloperidol modify network connectivity and spontaneous activity of neural networks in vitro. *Sci Rep* 7: 11609, 2017. doi:10.1038/s41598-017-11944-0.

Einat H, Manji HK. Cellular plasticity cascades: genes-to-behavior pathways in animal models of bipolar disorder. *Biol Psychiatry* 59: 1160–1171, 2006. doi:10.1016/j.biopsych.2005.11.004.

Elble R, Deuschl G. Milestones in tremor research. *Mov Disord* 26: 1096–1105, 2011. doi:10.1002/mds.23579.

Floran B, Aceves J, Sierra A, Martinez-Fong D. Activation of D1 dopamine receptors stimulates the release of GABA in the basal ganglia of the rat. *Neurosci Lett* 116: 136–140, 1990. doi:10.1016/0304-3940(90)90399-T.

Gerasimenko JV, Flowerdew SE, Voronina SG, Sukhomlin TK, Tepikin AV, Petersen OH, Gerasimenko OV. Bile acids induce Ca^{2+} release from both the endoplasmic reticulum and acidic intracellular calcium stores through activation of inositol trisphosphate receptors and ryanodine receptors. *J Biol Chem* 281: 40154–40163, 2006. doi:10.1074/jbc.M606402200.

Gideons ES, Lin PY, Mahgoub M, Kavalali ET, Monteggia LM. Chronic lithium treatment elicits its antimanic effects via BDNF-TrkB dependent synaptic downscaling. *eLife* 6: e25480, 2017. doi:10.7554/eLife.25480.

Hammonds MD, Shim SS. Effects of 4-week treatment with lithium and olanzapine on levels of brain-derived neurotrophic factor, B-cell CLL/lymphoma 2 and phosphorylated cyclic adenosine monophosphate response element-binding protein in the sub-regions of the hippocampus. *Basic Clin Pharmacol Toxicol* 105: 113–119, 2009. doi:10.1111/j.1742-7843.2009.00416.x.

Huang Y, Aronson JP, Pilitsis JG, Gee L, Durphy J, Molho ES, Ramirez-Zamora A. Anatomical correlates of uncontrollable laughter with unilateral subthalamic deep brain stimulation in Parkinson's disease. *Front Neurol* 9: 341, 2018. doi:10.3389/fneur.2018.00341.

Hutchison WD, Allan RJ, Opitz H, Levy R, Dostrovsky JO, Lang AE, Lozano AM. Neurophysiological identification of the subthalamic nucleus in surgery for Parkinson's disease. *Ann Neurol* 44: 622–628, 1998. doi:10.1002/ana.410440407.

Kamiński J, Mamelak AN, Birch K, Mosher CP, Tagliati M, Rutishauser U. Novelty-sensitive dopaminergic neurons in the human substantia nigra predict success of declarative memory formation. *Curr Biol* 28: 1333–1343.e4, 2018. doi:10.1016/j.cub.2018.03.024.

Kaneda K, Kita H. Synaptically released GABA activates both pre- and postsynaptic GABA(B) receptors in the rat globus pallidus. *J Neurophysiol* 94: 1104–1114, 2005. doi:10.1152/jn.00255.2005.

Klein PS, Melton DA. A molecular mechanism for the effect of lithium on development. *Proc Natl Acad Sci USA* 93: 8455–8459 1996. doi:10.1073/pnas.93.16.8455.

Krack P, Kumar R, Ardouin C, Dowsey PL, McVicker JM, Benabid AL, Pollak P. Mirthful laughter induced by subthalamic nucleus stimulation. *Mov Disord* 16: 867–875, 2001. doi:10.1002/mds.1174.

Kultas-Ilinsky K, Ilinsky IA. Fine structure of the ventral lateral nucleus (VL) of the Macaca mulatta thalamus: cell types and synaptology. *J Comp Neurol* 314: 319–349, 1991. doi:10.1002/cne.903140209.

Kuramoto E, Fujiyama F, Nakamura KC, Tanaka Y, Hioki H, Kaneko T. Complementary distribution of glutamatergic cerebellar and GABAergic basal ganglia afferents to the rat motor thalamic nuclei. *Eur J Neurosci* 33: 95–109, 2011. doi:10.1111/j.1460-9568.2010.07481.x.

Lee CH, Dixon JF, Reichman M, Moummi C, Los G, Hokin LE. Li^+ increases accumulation of inositol 1,4,5-trisphosphate and inositol 1,3,4,5-tetrakisphosphate in cholinergically stimulated brain cortex slices in guinea pig, mouse and rat. The increases require inositol supplementation in mouse and rat but not in guinea pig. *Biochem J* 282: 377–385, 1992. doi:10.1042/bj2820377.

Lubrich B, Patishi Y, Kofman O, Agam G, Berger M, Belmaker RH, van Calker D. Lithium-induced inositol depletion in rat brain after chronic treatment is restricted to the hypothalamus. *Mol Psychiatry* 2: 407–412, 1997. doi:10.1038/sj.mp.4000267.

Machado-Vieira R, Manji HK, Zarate CA Jr. The role of lithium in the treatment of bipolar disorder: convergent evidence for neurotrophic effects as a unifying hypothesis. *Bipolar Disord* 11, *Suppl* 2: 92–109, 2009. doi:10.1111/j.1399-5618.2009.00714.x.

Malhi GS, Tanious M, Das P, Coulston CM, Berk M. Potential mechanisms of action of lithium in bipolar disorder. Current understanding. *CNS Drugs* 27: 135–153, 2013. doi:10.1007/s40263-013-0039-0.

Manji HK, Moore GJ, Chen G. Clinical and preclinical evidence for the neurotrophic effects of mood stabilizers: implications for the pathophysiology and treatment of manic-depressive illness. *Biol Psychiatry* 48: 740–754, 2000. doi:10.1016/S0006-3223(00)00979-3.

Mikell CB, Sheehy JP, Youngerman BE, McGovern RA, Wojtasiewicz TJ, Chan AK, Pullman SL, Yu Q, Goodman RR, Schevon CA, McKhann GM 2nd. Features and timing of the response of single neurons to novelty in the substantia nigra. *Brain Res* 1542: 79–84, 2014. doi:10.1016/j.brainres.2013.10.033.

Milosevic L, Gramer R, Kim TH, Algarni M, Fasano A, Kalia SK, Hodaie M, Lozano AM, Popovic MR, Hutchison WD. Modulation of inhibitory plasticity in basal ganglia output nuclei of patients with Parkinson's disease. *Neurobiol Dis* 124: 46–56, 2019. doi:10.1016/j.nbd.2018.10.020.

Milosevic L, Kalia SK, Hodaie M, Lozano AM, Fasano A, Popovic MR, Hutchison WD. Neuronal inhibition and synaptic plasticity of basal ganglia neurons in Parkinson's disease. *Brain* 141: 177–190, 2018a. doi:10.1093/brain/awx296.

Milosevic L, Kalia SK, Hodaie M, Lozano AM, Popovic MR, Hutchison WD. Physiological mechanisms of thalamic ventral intermediate nucleus stimulation for tremor suppression. *Brain* 141: 2142–2155, 2018b. doi:10.1093/brain/awy139.

Morgan JC, Sethi KD. Drug-induced tremors. *Lancet Neurol* 4: 866–876, 2005. doi:10.1016/S1474-4422(05)70250-7.

Nibuya M, Nestler EJ, Duman RS. Chronic antidepressant administration increases the expression of cAMP response element binding protein (CREB) in rat hippocampus. *J Neurosci* 16: 2365–2372, 1996. doi:10.1523/JNEUROSCI.16-07-02365.1996.

Okun MS, Raju DV, Walter BL, Juncos JL, DeLong MR, Heilman K, McDonald WM, Vitek JL. Pseudobulbar crying induced by stimulation in the region of the subthalamic nucleus. *J Neurol Neurosurg Psychiatry* 75: 921–923, 2004. doi:10.1136/jnnp.2003.016485.

Parent A, Hazrati LN. Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry. *Brain Res Brain Res Rev* 20: 128–154, 1995. doi:10.1016/0165-0173(94)00008-D.

Prescott IA, Dostrovsky JO, Moro E, Hodaie M, Lozano AM, Hutchison WD. Levodopa enhances synaptic plasticity in the substantia nigra pars reticulata of Parkinson's disease patients. *Brain* 132: 309–318, 2009. doi:10.1093/brain/awn322.

Rodrigues B, Patil PG, Chou KL. Thalamic deep brain stimulation for drug-induced tremor. *Parkinsonism Relat Disord* 21: 1369–1370, 2015. doi:10.1016/j.parkreldis.2015.08.033.

Rodríguez-Moreno A, Herreras O, Lerma J. Kainate receptors presynaptically downregulate GABAergic inhibition in the rat hippocampus. *Neuron* 19: 893–901, 1997. doi:10.1016/S0896-6273(00)80970-8.

Salinas PC, Hall AC. Lithium and synaptic plasticity. *Bipolar Disord* 1: 87–90, 1999. doi:10.1034/j.1399-5618.1999.010205.x.

Schloesser RJ, Huang J, Klein PS, Manji HK. Cellular plasticity cascades in the pathophysiology and treatment of bipolar disorder. *Neuropsychopharmacology* 33: 110–133, 2008. doi:10.1038/sj.npp.1301575.

Shim SS, Hammonds MD, Tatsuoka C, Feng IJ. Effects of 4-weeks of treatment with lithium and olanzapine on long-term potentiation in hippocampal area CA1. *Neurosci Lett* 524: 5–9, 2012. doi:10.1016/j.neulet.2012.06.047.

Son H, Yu IT, Hwang SJ, Kim JS, Lee SH, Lee YS, Kaang BK. Lithium enhances long-term potentiation independently of hippocampal neurogenesis in the rat dentate gyrus. *J Neurochem* 85: 872–881, 2003. doi:10.1046/j.1471-4159.2003.01725.x.

Surmeier DJ, Ding J, Day M, Wang Z, Shen W. D1 and D2 dopamine-receptor modulation of striatal glutamatergic signaling in striatal medium spiny neurons. *Trends Neurosci* 30: 228–235, 2007. doi:10.1016/j.tins.2007.03.008.

Tekin S, Cummings JL. Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. *J Psychosom Res* 53: 647–654, 2002. doi:10.1016/S0022-3999(02)00428-2.

Tyrer P, Alexander MS, Regan A, Lee I. An extrapyramidal syndrome after lithium therapy. *Br J Psychiatry* 136: 191–194, 1980. doi:10.1192/bjp.136.2.191.

Zaghloul KA, Blanco JA, Weidemann CT, McGill K, Jaggi JL, Baltuch GH, Kahana MJ. Human substantia nigra neurons encode unexpected financial rewards. *Science* 323: 1496–1499, 2009. doi:10.1126/science.1167342.