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A feasibility trial of conjoint magnetic seizure therapy and dialectical behavior therapy for suicidal patients with borderline personality disorder and treatment-resistant depression

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Non-invasive brain stimulation interventions for treating suicidal ideation in individuals with treatment-resistant depression offer the potential for new therapeutic options for patients with borderline personality disorder (BPD), a condition that responds poorly to antidepressant medications. Here we present a study to explore the application of magnetic seizure therapy (MST) in an open-label pilot trial of moderately to severely suicidal individuals with comorbid BPD and treatment-resistant depression conducted at the Centre for Addiction and Mental Health (Toronto, Canada). Using a non-randomized, case-control design, we investigated the feasibility and initial clinical effects of 5 weeks of conjoint MST and dialectical behaviour therapy (MST + DBT) compared with 5 weeks of DBT alone. Changes in primary symptom outcomes of suicidal ideation on the Modified Scale for Suicide Ideation and clinician-rated depression severity on the Hamilton Rating Scale for Depression – 24 were investigated using multilevel models. Additional outcomes included self-reported depression, BPD symptom severity and cognitive functioning. Out of 62 screened participants, $n = 21$ were enrolled, and $N = 19$ completed the intervention ($n = 9$ MST + DBT and $n = 10$ DBT only). The intervention was feasible to implement. Conjoint MST + DBT, but not DBT alone, led to a rapid, significant and clinically meaningful reduction in suicidal ideation at 5 weeks that was sustained at four-month follow-up. Conjoint MST + DBT was also associated with significant reductions in clinician-rated depression and BPD interpersonal symptom severity, but neither effect was sustained at four-month follow-up. There were no treatment-related effects on cognition. There were no treatment-related serious adverse events. These findings provide initial evidence to suggest that MST + DBT is a feasible intervention to reduce acute suicide risk in individuals with BPD and warrant further exploration in a sham-controlled randomized clinical trial.

Borderline personality disorder (BPD) is associated with an exceptionally high risk of suicide, with an average of more than three lifetime suicide attempts[1] and a completed suicide rate of 10% (ref. [2]). BPD and major depressive disorder (MDD) are frequently comorbid, which further elevates the risk of suicide[3]. At least one study showed that more severe baseline depression lowers the response to evidence-based psychotherapies for BPD, such as dialectical behaviour therapy (DBT)[4]. Further, available evidence does not generally support the use

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Table 1 | Participant demographics and clinical characteristics

	MST+DBT (*n*=9 women) mean (s.d.)	DBT only (*n*=10 women) mean (s.d.)	*t* value, *P* value
Age (years)	30.1 (9.4)	28.4 (7.9)	0.42, 0.68
Education (years)	14.30 (2.98)	14.3 (3.0)	0.00, 0.99
Length of current depressive episode (years)	12.9 (10.6)	5.6 (4.2)	1.93, 0.08
Number of lifetime depressive episodes	1.4 (0.5)	2.30 (0.94)	2.61, 0.02
Cumulative antidepressant resistance (current episode)	10.20 (1.81)	8.10 (4.04)	1.48, 0.16
Comorbidities (current)	PTSD (*n*=5) Bipolar disorder II (*n*=1)	PTSD (*n*=4)	—
Suicidal ideation (MSSI)	Base: 22.4 (7.5) Post: 9.1 (9.9) Follow-up: 14.3 (13.5)	Base: 15.4 (11.8) Post: 14.1 (12.2) Follow-up: 12.0 (10.7)	Base: 1.49, 0.16
Clinician-rated depression severity (HRSD-24)	Base: 35.60 (6.96) Post: 24.0 (10.1) Follow-up: 31.0 (11.5)	Base: 30.2 (10.0) Post: 26.0 (9.7) Follow-up: 27.0 (11)	Base: 1.30, 0.21
Self-reported depression severity (QIDS-SR)	Base: 21.3 (3.4) Post: 16.7 (6.2) Follow-up: 20.3 (5.9)	Base: 19 (4.6) Post: 18.2 (5.2) Follow-up: 17.8 (7.2)	Base: 1.26, 0.23
Total BPD symptom severity (ZAN-BPD)	Base: 15.89 (6.80) Post: 10.2 (7.4) Follow-up: 13.3 (6.8)	Base: 12.7 (3.6) Post: 12.5 (4.8) Follow-up: 13.3 (4.8)	Base: 1.18, 0.26

Between-group differences were examined using a two-sample *t*-test (two-tailed). *P* values are uncorrected.

of medication to treat symptoms of BPD[5]. As such, although reducing suicide risk is a major area of focus in the clinical management of BPD, healthcare practitioners often have few treatment options for patients who remain at elevated risk for suicide following inadequate response to first-line interventions. Consequently, a concerningly high number of individuals with BPD repeatedly present to the emergency department and are subsequently hospitalized for suicide risk, which in the long term can increase the risk of suicide in BPD[6]. Taken together, there is an urgent need to identify additional safe and effective interventions to reduce suicide risk in BPD.

Non-invasive brain stimulation interventions to treat depression and reduce the associated risk of suicide offer the promise of new treatments for suicidal and depressed individuals with BPD, although few studies have investigated their safety and effectiveness in this population. For example, although electroconvulsive therapy (ECT) is the most well-researched and efficacious brain stimulation intervention for severe, treatment-resistant depression (TRD)[7], few trials have investigated the efficacy of ECT for MDD in BPD, and limited findings suggest that antidepressant responsiveness to ECT in BPD, and in BPD traits, ranges from slightly[8] to substantially[9] less robust compared with patients without BPD. Further, ECT carries well-documented cognitive adverse effects that include autobiographical memory impairment.

Magnetic seizure therapy (MST) is emerging as a safer alternative to ECT for the treatment of TRD[10] and associated suicidal ideation[11]. As in ECT, the hypothesized mechanism of action in MST is the induction of a seizure. However, MST uses magnetic fields to induce an electrical field, which results in focal stimulation. An MST-induced seizure produces effects in more superficial cortical areas, which may explain why patients experience fewer cognitive side effects[12]. A systematic review of eight MST trials found that a clinical response is achieved in 40–60% of participants with TRD[13], which is consistent with findings from a large clinical trial of MST for MDD[10]. Further, a recent pilot study comparing 100 Hz MST with ECT found no differences in antidepressant effectiveness between the two approaches[12]. Crucially, MST does not appear to be associated with the cognitive side effects observed after ECT[14], which is a pertinent advantage for individuals with BPD who show a range of cognitive deficits, including in episodic memory[15].

MST has yet to be investigated in BPD, although recent findings in BPD samples suggest that a related brain stimulation technique, repetitive transcranial magnetic stimulation (rTMS), may reduce levels of BPD severity and depression commonly observed in suicidal individuals with BPD[16–19]. In this Article, we present the results from an open-label clinical trial investigating the feasibility, and clinical and cognitive effects, of a 5-week course of conjoint MST plus DBT ($n = 9$) compared with DBT alone ($n = 10$) in suicidal patients with comorbid BPD and treatment-resistant depression. We hypothesized that treatment in the MST + DBT arm would result in substantial rates of response and remission on measures of suicidal ideation and depression. Moreover, we hypothesized that MST would have limited, if any, effects on performance on standard neuropsychological measures of attention, memory and executive functioning.

Results

Participant characteristics and medications are displayed in Tables 1 and 2, respectively. A Pearson correlation matrix of baseline symptom scores and demographics is presented in Supplementary Table 1.

A CONSORT flow diagram is displayed in Fig. 1. Our initial recruitment target was $N = 30$. Altogether, 21 out of 62 screened participants met eligibility criteria and provided written informed consent to participate. Due to the impact of COVID-19, additional recruitment beyond March 2020 was precluded. Our final sample size was $N = 19$ (9 MST + DBT and 10 DBT).

Symptom outcomes

Primary outcomes of suicidal ideation on the Modified Scale for Suicide Ideation (MSSI)[20] and clinician-rated depression on the Hamilton Rating Scale for Depression – 24 (HRSD-24)[21] and additional outcomes of self-reported depression on the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR)[22] and BPD symptom severity on the Zanarini Rating Scale for BPD (ZAN-BPD)[23] are displayed in Fig. 2. Individual symptom trajectories are shown in Fig. 3.

Suicidal ideation

At post-treatment, only the MST + DBT arm showed improvements in suicidal ideation, as indicated by a significant interaction effect (beta (β) = −12.03 [95% confidence interval (CI): −19.24, −4.82]; standard error (SE) = 3.75; $t[31] = -3.21$; $P < 0.01$). Post hoc tests showed that improvements in MST + DBT at post-treatment ($\beta = 13.33$; SE = 2.72; $t(31) = 4.90$; $P < 0.001$) were sustained at follow-up ($\beta = 7.74$; SE = 2.84; $t(31) = 2.73$; $P = 0.03$). Within the DBT-only condition, no pairwise contrasts reached

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Table 2 | Medications by type taken during the active treatment course, during pre-treatment only and from post-treatment to follow-up

	Taken during treatment			Taken pre-treatment only (screen to baseline)		Taken post-treatment to follow-up	
Medication type	**MST+DBT**	**DBT only**	**Total *N*=(19)**	**MST+DBT**	**DBT only**	**MST+DBT**	**DBT only**
SSRI		Escitalopram (*n*=1) Paroxetine (*n*=1)	*N*=2				
SNRI	Duloxetine (*n*=2) Venlafaxine (*n*=1) Levomilnacipran (*n*=1)	Duloxetine (*n*=1) Venlafaxine (*n*=2)	*N*=3				
SARIs		Trazodone (*n*=1)	*N*=1		Trazodone (*n*=1)		
TCAs	Mirtazapine (*n*=2)					Mirtazapine (*n*=1)	
Aminoketone	Bupropion (*n*=1)						
Antipsychotic	Quetiapine (*n*=1) Risperidone (*n*=1) Levomepromazine (*n*=1)	Quetiapine (*n*=1)	*N*=1	Lurasidone (*n*=1) Loxapine (*n*=1)			
Benzodiazepine	Clonazepam (*n*=2) Lorazepam (*n*=1)				Lorazepam (*n*=1)	Lorazepam (*n*=1)	
Sedative/hypnotic				Zopiclone (*n*=1)		Zolpidem (*n*=1)	
Anti-convulsant		Lamotrigine (*n*=1)	*N*=1	Apo lithium carbonate (*n*=1) Gabapentin (*n*=1)		Gabapentin (*n*=1)	
Alpha blocker	Prasozin (*n*=1)						Prasozin (*n*=1)
Beta blocker	Propranolol (*n*=1)						
Opiate antagonist	Naltrexone (*n*=1)						
Other	*n*=5	*n*=4	*N*=9		*n*=1	*n*=2	

statistical significance ($P > 0.05$), although a modest improvement from baseline to follow-up was observed ($\beta = 6.51$; SE = 2.80; $t(31) = 2.32$; $P = 0.07$). There were no interaction effects between baseline BPD symptom severity and the effects of time or condition ($P < 0.05$) and no three-way interaction effects among BPD symptom severity, time and condition ($P < 0.05$).

Depression

At post-treatment, only the MST + DBT arm showed improvements in clinician-rated HRSD-24 depression, as indicated by a marginal interaction effect ($\beta = -7.32$ [95% CI: −14.10, −0.54]; SE = 3.53; $t[31] = -2.08$; $P = 0.05$). Post hoc tests showed significant improvements in MST + DBT at post-treatment ($\beta = 11.22$; SE = 2.56; $t(31) = 4.39$; $P < 0.001$), which were not sustained at follow-up ($\beta = 4.90$; SE = 2.67; $t(31) = 1.84$; $P = 0.17$). Within the DBT-only condition, no pairwise contrasts for HRSD-24 depression reached statistical significance ($P > 0.05$). There were no interaction effects between baseline BPD symptom severity and the effects of time or condition ($P < 0.05$) and no three-way interaction effects among BPD symptom severity, time and condition ($P < 0.05$).

In terms of self-reported depressive symptoms on the QIDS-SR, no significant time, condition or interaction effects were found ($P > 0.05$).

BPD symptom severity

ZAN-BPD total symptom severity. At post-treatment, only the MST + DBT arm showed an improvement in total BPD symptom severity, as indicated by a marginal but non-significant interaction effect ($\beta = -5.47$ [95% CI: −10.93, −0.001]; SE = 2.84; $t[31] = -1.92$; $P = 0.06$). Pairwise contrasts showed significant improvements in MST + DBT participants at post-treatment ($\beta = 5.67$; SE = 2.06; $t(31) = 2.75$, $P = 0.03$), which were not sustained at follow-up ($\beta = 2.80$; SE = 2.15; $t(31) = 1.30$, $P = 0.40$). Within the DBT-only condition, no pairwise contrasts reached statistical significance ($P > 0.05$).

ZAN-BPD subscale severity. At post-treatment, a significant interaction effect was found on the interpersonal ZAN-BPD subscale, suggesting that only the MST + DBT arm showed improvements in interpersonal BPD symptoms ($\beta = -1.89$ [95% CI: −3.60, −0.18]; SE = 0.89; $t(31) = -2.12$; $P = 0.04$). Pairwise contrasts showed significant improvements in MST + DBT participants at post-treatment, relative to baseline ($\beta = 1.89$; SE = 0.65; $t(31) = 2.9$; $P = 0.02$), which were not sustained at follow-up ($\beta = 1.22$; SE = 0.67; $t(31) = 1.81$; $P = 0.18$). Within the DBT-only condition, pairwise contrasts did not reach statistical significance ($P > 0.05$). Regarding other ZAN-BPD subscales (affective, cognitive and impulsive symptoms), no significant time, treatment condition or time × treatment condition interaction effects were found ($P > 0.05$).

Depression response and suicidal ideation remission

Of the total of 19 participants in the treatment, 1 MST + DBT participant and 1 DBT-only participant exhibited an alleviation of depressive symptoms (as defined by a 50% reduction from baseline in HRSD-24 score). One MST + DBT and three DBT-only participants experienced remission from suicidal ideation (as defined by a score of zero on the MSSI on 2 consecutive weekly assessments), although the three DBT-only participants who remitted exhibited either complete remission or substantial reduction in suicidal ideation from enrolment to their baseline assessment, suggesting that their decreases in suicidal ideation were due to factors not directly related to DBT, such as an increase in hopefulness or perceived support, or extraneous factors.

Neuropsychological performance

Participants in both conditions demonstrated stable neuropsychological performance from baseline to post-intervention. Two significant time-by-condition interaction effects were observed for Brief Visuospatial Memory Test (BVMT) Learning ($F[1,16] = 7.14$; $P = 0.02$) and BVMT Retention ($F[1,16] = 5.64$; $P = 0.03$), with post hoc tests suggesting that

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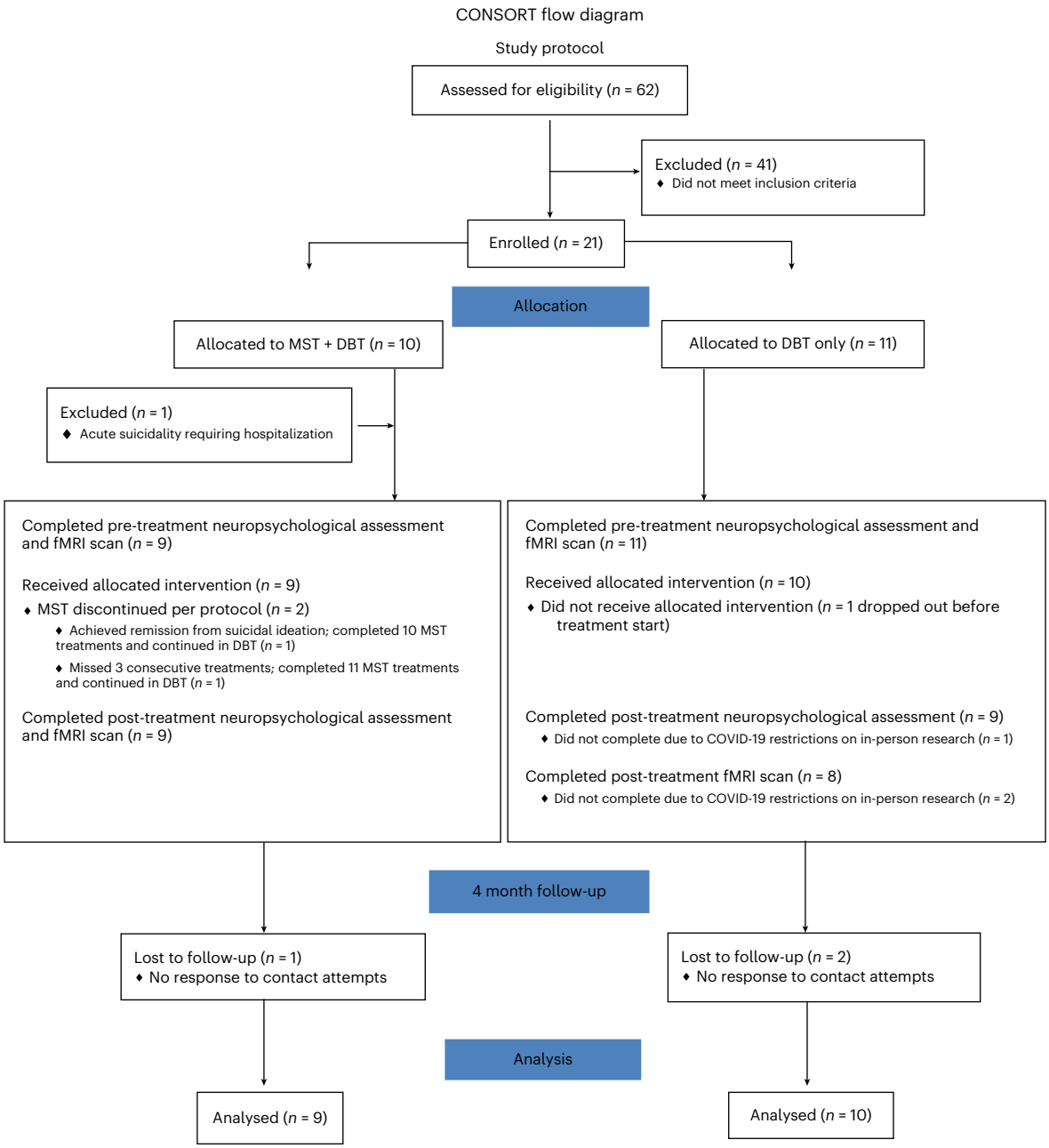

Fig. 1 | CONSORT flow diagram. Study protocol from eligibility assessment to follow-up for participants allocated to MST + DBT (left) and DBT only (right).

within the DBT-only group, participants scored better on BVMT Learning ($F[1,8] = 4.50$; $P = 0.07$) and worse on BVMT Retention ($F[1,8] = 3.68$; $P = 0.09$) at post-treatment relative to baseline. Main effects of time were found on Delis Kaplan Executive Functioning Category Switch Total Correct ($F[1,16] = 7.98$; $P = 0.01$) and Total Switch ($F[1,16] = 5.07$; $P = 0.04$), indicating that participants in both conditions performed worse at post-treatment relative to pre-treatment. No other significant effects were found ($P > 0.05$), including no significant main or interaction effects in autobiographical memory ($P > 0.05$), suggesting that MST + DBT did not impact cognitive performance relative to DBT. All neuropsychological test scores are provided in Supplementary Table 2.

Safety

Among the 21 participants who signed consent, there were three serious adverse events that were deemed unrelated to MST treatment, including attempted suicide before completing study-related treatments ($n = 1$) and ureteroscopic surgeries related to a pre-existing kidney condition ($n = 2$).

DBT attendance

Across the 5-week intervention, participants in MST + DBT attended a mean of 4.4 (±1.0) individual DBT therapy sessions and 4.3 (±1.7) DBT skills training sessions. DBT-only participants attended a mean of 4.9 (±1.0) individual therapy sessions and 4.7 (±1.3) skills training sessions. There were no significant between-group differences in the number of sessions attended for individual DBT therapy ($t = 0.94$: $P = 0.36$) or DBT skills training ($t = 0.52$; $P = 0.61$).

Electroencephalogram seizure duration

Seizure duration was calculated as the mean duration of the second treatment and the last treatment. The mean (s.d.) seizure duration was 65.72 (±58.3) s.

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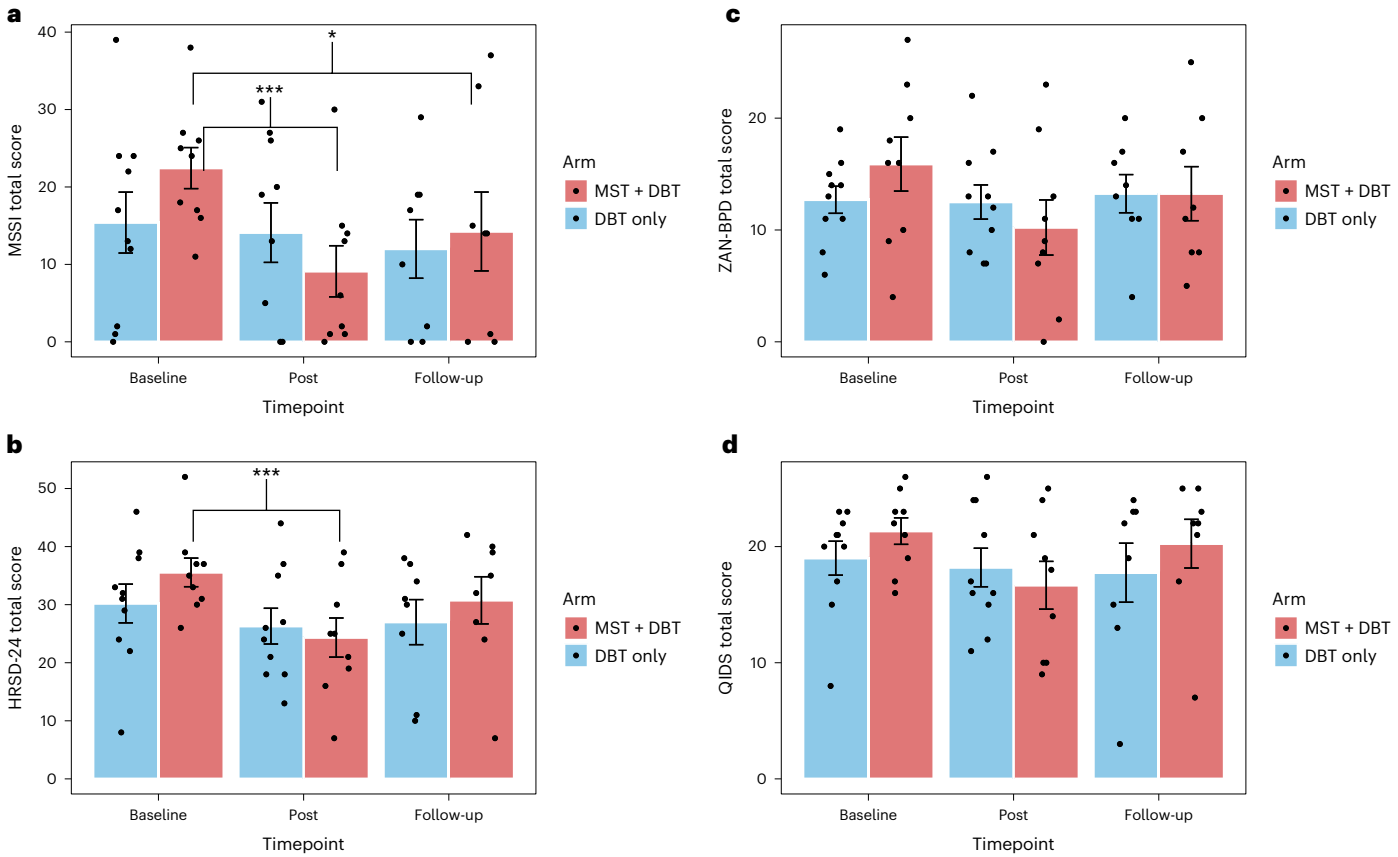

Fig. 2 | Multilevel-modelling post hoc tests of primary outcomes of suicide ideation and clinician-assessed depression severity and additional outcomes of BPD symptom severity and self-reported depression. a–**d**, Total mean symptom scores by treatment arm for MSSI suicidality (**a**), HRSD-24 depression (**b**), ZAN-BPD severity (**c**) and QIDS-SR depression (**d**). Data are presented as mean values. Error bars represent standard error. All tests were two-tailed. Outcomes at baseline and post-treatment comprise $n = 9$ independent MST + DBT participants and $n = 10$ independent DBT-only participants. Follow-up outcomes include $n = 8$ independent participants in each of MST + DBT and DBT only. *$P = 0.03$; ***$P < 0.001$, uncorrected.

Time to reorientation

Time to reorientation was calculated as the mean time of the second treatment and the last treatment. The mean (s.d.) reorientation time was 9.08 (±3.07) min.

Discussion

The current findings provide initial evidence to support the feasibility of conjoint MST and DBT for the treatment of moderate to severe suicidal ideation in individuals with BPD and TRD. We observed large, clinically meaningful reductions in suicidal ideation following conjoint treatment with MST and DBT, with improvements sustained at four-month follow-up. Significant reductions in clinician-rated depression and BPD interpersonal symptom severity were also seen from baseline to post-intervention in the MST + DBT condition, although these gains were not sustained at follow-up. All participants were evaluated from pre- to post-treatment using a neuropsychological battery of gold-standard measures spanning major domains of cognitive functioning most relevant to non-invasive neurotherapeutics[24]. Given the impact of ECT on memory, the battery was selected to allow for comprehensive assessment of verbal and non-verbal memory. There were no differential effects on cognitive performance observed between treatment arms. The intervention was feasible to implement across a multidisciplinary treatment team, and MST treatments were well tolerated across participants with no serious adverse events related to the treatment.

Chronic suicidality in BPD is one of the most challenging symptoms of the disorder, precluding patients from fully engaging in psychotherapy and reducing the willingness of clinicians to work with BPD due to beliefs that clinical management is too difficult[25]. Although individuals with BPD are at an exceptionally high risk of suicide, with estimates of up to 84% attempting suicide at least once[26], there is a paucity of research on biological treatments to reduce suicide risk in BPD. Current evidence points to DBT and mentalization-based therapy as the most effective psychotherapy interventions for suicidal behaviour in BPD[27], both of which require specialized clinician training and where reductions in suicidal ideation are slow and often observed only after months of treatment[28]. The innovative design of the present clinical trial is optimal in the sense that severely suicidal individuals concurrently engaged in a convulsive treatment while participating in DBT, a treatment combination that led to a reduction in suicidal ideation over 5 weeks with sustained and clinically meaningful improvements (average MSSI score reduction from the 'severe' range to 'mild to moderate'). We propose that the success of this conjoint treatment would be unlikely if ECT were instead chosen due to its adverse side effects on cognition. Even brief ECT (ultra-brief pulse width) is associated with post-treatment amnesia across randomized controlled trials (RCTs)[29]. This is probably due to the differences in induced field strength between ECT and MST: MST uses a rapid, high-intensity, time-varying magnetic field that limits seizure spread[30], resulting in stimulation that is not impeded by the skull and is five to ten times more focal, relative to right unilateral ultra-brief pulse ECT[31,32]. Taken together with previous findings of poorer ECT outcomes in depressed patients with BPD[8,9], ECT even being more readily accessible than MST may not be the most optimal approach to combine with psychotherapy. However, since findings suggest that there are less-efficacious treatment options

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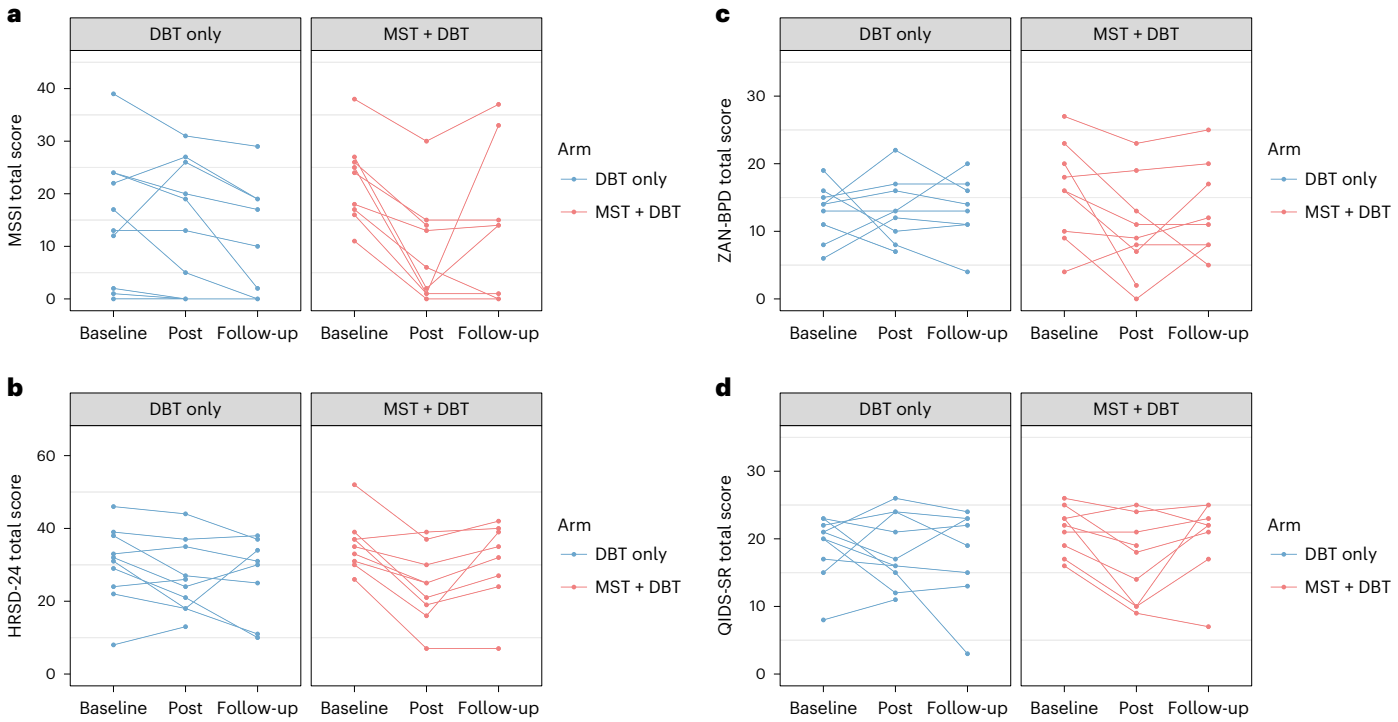

Fig. 3 | Individual symptom trajectories of suicidal ideation, clinician-assessed depression severity, total BPD symptom severity and self-reported depression. **a**–**d**, Individual symptom trajectories by treatment arm: suicidality (**a**), clinician-rated depression (**b**), total BPD symptom severity (**c**) and self-reported depression (**d**).

for individuals with depression and comorbid personality disorder features[33], and since ECT is one of the most effective interventions for depression[34], all potential treatment avenues for individuals with depression and BPD should be empirically investigated. As such, a clinical trial of ultra-brief pulse ECT plus psychotherapy versus MST plus psychotherapy could empirically investigate their comparative efficacy. Alternatively, non-invasive brain stimulation more widely used across treatment settings, such as rTMS, should be studied. To further prolong the decline in suicidal ideation observed in the current study, an MST tapering phase that consists of completing a full course of DBT could be considered.

Of note, rather than employing the Colombia Suicide Severity Rating Scale (C-SSRS[35]), suicidal ideation in the current study was assessed using the MSSI, a suicide-specific measure with excellent psychometric properties[20] that has been tested across inpatient[20] and outpatient[36,37] samples. Whereas the C-SSRS has been recommended by the Food and Drug Administration to monitor for treatment-emergent suicidal ideation in clinical trials[38], our study required participants to experience suicidal ideation at baseline. The MSSI was chosen as the primary outcome measure as it provides increased specificity and additional range of items (compared with the C-SSRS) and a continuous total score with a wide range from 0 to 54 that is ideal for statistical analysis in a small sample. Moreover, the MSSI has established severity thresholds, which ensured standardized assessment of the suicidal ideation inclusion criteria.

Regarding mechanisms of action, initial research suggests that MST induces cortical neuroplasticity via mechanisms related to long-term potentiation[39], but further studies should investigate the specific biological pathways leading to reduction in depression and suicidal ideation after MST. Suicidality across psychiatric disorders is associated with disruptions in the frontolimbic and frontotemporal circuits subserving emotion regulation and cognitive control[40]. MDD is also associated with greater instability of connectivity in the default mode network (DMN)[41] implicated in self-referential processing, rumination and social cognition[42]. Finally, interpersonal symptoms in BPD (for example, rejection sensitivity) have been associated with functional disruptions in the medial prefrontal cortex (MPFC)[43], a region in the DMN involved in social cognition[44]. In the present study, MST was delivered frontally with the maximum electrical field activation in the dorsomedial PFC (DMPFC), which is a common shared hub among frontolimbic, frontotemporal and DMN networks. Modified functioning in these affective, executive and social cognitive-related pathways could be one of the potential mechanisms underlying symptom improvements after MST treatment.

Moreover, there is a strong association between interpersonal distress and suicidal ideation in BPD[1,45,46]. Relationship conflict and low perceived warmth in others have been shown to precipitate increases in suicidality in BPD[1,46]. Although it is not possible to determine whether improvements in interpersonal BPD symptoms were a cause or consequence of reductions in suicidal ideation, it is plausible that improvements in these two domains were not independent.

Pertaining to depression severity, although a significant reduction in clinician-rated depressive symptoms was observed from pre- to post-treatment, these gains were not sustained at follow-up. No improvements were observed in self-reported depression. These results are surprising given that recent preliminary findings show that rTMS, a less-intense form of magnetic stimulation, yields substantial alleviation of MDD symptoms in individuals with BPD[17]. Notably, in our trial, moderate to severe suicidal ideation on the MSSI was required to meet eligibility criteria. This level of baseline severity could be related to the less-robust depression response observed, whereby participants with greater suicidal ideation at baseline may require longer to experience improvements in MDD symptoms. As we did observe a 12-point mean reduction in HRSD-24 depression from baseline to post-treatment in the MST + DBT arm, there is a need for the study of maintenance treatments on depression and suicidal ideation, which could extend clinical benefits. Indeed, rates of depression relapse following ECT are high without maintenance treatment, which may indicate that additional treatments are similarly necessary to prolong MST-related treatment effects in severely ill individuals.

In addition, although participants in the DBT-only arm of this study did not exhibit a significant clinical response, a modest reduction in suicidality was observed at follow-up ($P = 0.07$), which is consistent with findings showing slower remission for suicide-related symptoms after interventions for BPD (for example, DBT)[28]. As such, these results do not suggest that DBT was ineffective, but rather the combination of MST + DBT was associated with a more rapid reduction in suicidality compared with 5 weeks of DBT alone. It is important to emphasize that participants in this study received MST in conjunction with DBT, which may be superior to either treatment alone.

Finally, our findings warrant future investigation into the utility of combining MST with more generalist or accessible treatments for BPD, such as community-based emotion regulation skills groups. In fact, the study of brain stimulation for BPD is an emerging research area[47,48]. Whether various types of brain stimulation interventions may be combined with psychotherapy for BPD is an important future direction for BPD treatment research. Overall, the quality of evidence for ECT in BPD is low; most findings are derived from case studies or retrospective chart review and suggest that ECT is less efficacious in BPD[47]. However, there is preliminary evidence that transcranial direct current stimulation may target affective dysregulation by altering the executive processes involved in the cognitive control of emotions in BPD[47]. Finally, four sham-controlled pilot RCTs have investigated rTMS for BPD[16–19], with preliminary findings suggesting that stimulation of the dorsolateral PFC or DMPFC may improve core BPD symptoms, although some improvements have also been noted after sham stimulation[16,17], emphasizing the need for large, adequately powered RCTs.

Notably, our finding that MST + DBT had broad effects on suicidal ideation, depression and interpersonal BPD symptoms converges with findings from two recent 5 Hz (ref. [18]) and 20 Hz (ref. [17]) rTMS trials that also targeted the bilateral DMPFC, leading to active rTMS-related improvements in interpersonal and behavioural BPD symptoms[18] and in depression severity[17]. As such, the DMPFC warrants further exploration as a potential stimulation site to target various BPD symptoms, given its functional role in social[44] and non-social cognition[49]. Of note, participants in the current study were unique in their severity of suicidal ideation. It remains to be explored whether other non-convulsive therapies can reduce moderate to severe suicidal ideation in BPD.

Limitations and future directions

The open-label case-controlled design, small sample size and women-only participants in the current study are limitations, and investigation using a sham-controlled RCT with a gender-diverse sample is warranted. As participants in this study self-selected their treatment arm, patient expectations regarding the effectiveness of conjoint MST + DBT over DBT alone may have moderated or mediated the between-condition treatment effects observed; MST treatment involves a complex intervention with an advanced technology that has the potential for large expectation and non-specific effects. A sham-controlled design that includes DBT in both arms may address this critical limitation. Finally, although the ZAN-BPD is a standard measure used in clinical research, it assesses symptoms across a 1-week period. Given the 5 weeks between post-treatment and follow-up in the current study, a measure that is sensitive to change across a longer period (for example, The Borderline Personality Disorder Severity Index-IV[50]) would have been optimal.

Conclusions

This study represents a step towards addressing the long-standing problem of suicidality in BPD. The combination of MST + DBT led to a rapid and clinically meaningful reduction in suicidal ideation by 5 weeks in participants who did not respond to first-line treatments for depression. MST did not affect cognitive processes. Our findings provide evidence to support MST as a conjoint treatment for suicidal ideation in severely symptomatic patients with BPD and treatment-resistant depression.

Methods

Study design

This study was conducted at the Centre for Addiction and Mental Health (CAMH) between October 2017 and March 2020, with follow-up assessments ending in June 2020 (NCT03361826). The study protocol was approved by Health Canada and the CAMH and University of Toronto ethics boards (053-2015) and complied with all relevant ethics regulations. All participants provided written informed consent to participate. Study aims were to investigate the feasibility and clinical and cognitive effects of MST for suicidal ideation in BPD with comorbid TRD. No statistical methods were used to pre-determine sample size, but our sample size is similar to previous publications[17–19]. Moderate to severely suicidal participants were recruited using convenience and voluntary response sampling with a case-control design, comparing individuals receiving MST + DBT with a matched patient group receiving DBT only. Participants were enrolled by postdoctoral-level study staff under the supervision of the principal investigator. Across 5 weeks, participants in both arms received 1 h of weekly individual DBT and 1 h of weekly DBT skills training focused on distress tolerance. Participants in the MST + DBT group additionally received up to 15 MST treatments (3 treatments per week) across the 5-week protocol. Participants completed weekly symptom assessments from baseline to post-intervention to monitor the severity of primary outcomes in suicidal ideation and clinician-rated depression. Additional symptom outcomes included self-reported depression and BPD symptom severity. Participants returned for a follow-up symptom assessment at four months. To investigate cognitive effects of MST, all participants completed neuropsychological testing before and after the 5-week intervention. Participants also completed pre- and post-treatment functional magnetic resonance imaging scans to explore potential biomarkers of treatment response. Due to the impact of COVID-19 halting recruitment and resulting in a smaller sample size, functional magnetic resonance imaging data are too underpowered to detect reliable effects and will not be analysed or reported. As the result of an oversight, ethnicity data were not collected.

MST protocol

A MagVenture MagPro MST with Cool TwinCoil device with 100% machine output at 25 Hz was used, consistent with findings suggesting that 25 Hz is associated with the greatest reduction in suicidality in TRD[11]. Each circular coil was centred over the dorsolateral PFCs, bilaterally. This placement results in maximum e-field activation in the DMPFC of both hemispheres[51]. See Supplementary Information for the full MST and anaesthesia protocol.

Clinical assessments and neuropsychological testing

Participants were assessed for BPD, MDD and other comorbidities using the International Personality Disorders Examination – BPD Section[52] and the Structured Clinical Interview for DSM-IV[53]. The Antidepressant Treatment History Form[54] was used to quantify antidepressant resistance. The Antidepressant Treatment History Form rates each medication trial on a scale from 1 to 5, with scores ≥3 indicating an adequate trial at least 4 weeks in length, and with higher scores suggesting greater antidepressant resistance[55].

Primary outcomes of MSSI suicide ideation and HRSD-24 depression, and additional outcomes of the QIDS-SR[22] and the clinician-administered ZAN-BPD[23], were administered at screening/baseline and then once weekly from baseline to post-treatment and again at four-month follow-up. The Young Mania Rating Scale[56] was administered once weekly during the 5-week treatment protocol as a safety measure to monitor for the emergence of manic symptoms.

Neuropsychological testing was carried out at baseline and post-treatment to assess cognitive functioning in the domains of auditory–verbal learning and episodic memory (California Verbal Learning Test Second Edition[57]), autobiographical memory (Autobiographical

Memory Test[58]), visual–spatial learning and episodic memory (BVMT Revised[59]), auditory–verbal working memory and visual attention/psychomotor speed (Digit Span and Coding subtests, respectively, from the Weschler Adult Intelligence Scale Fourth Edition[60]), executive functioning (Delis Kaplan Executive Functioning[61] Verbal Fluency, Color Word Interference and Sorting subtests) and visual attention/processing speed and cognitive flexibility (Trail Making Test Parts A and B, respectively[62]). The Weschler Test of Adult Reading[63] was used to assess for the study exclusion criteria of a reading level below eighth grade.

Statistical analyses

Statistical analyses were completed using the 'nlme', 'multcomp', and 'emmeans' packages in R programming (version 4.1.2). Multilevel models evaluated changes in primary outcome measures of MSSI and HRSD-24 scores, and in the QIDS-SR and ZAN-BPD scores, at post-treatment and four-month follow-up relative to baseline. The assumptions of normality and homoscedasticity of the residuals of each multilevel model were formally tested using the Shapiro–Wilk and Levene's F test, respectively. Residuals of the model of MSSI scores did not violate the assumption of normality ($W = 0.98$; $P = 0.34$) but displayed some heteroscedasticity (F [18,35] = 2.43; $P = 0.01$). The residuals for the model of HRSD-24 scores did not violate the assumption of normality ($W = 0.98$; $P = 0.69$) or homoscedasticity (F [18,35] = 1.50; $P = 0.15$). The residuals for the model of ZAN-BPD scores did not violate the assumption of normality ($W = 0.98$; $P = 0.89$) or homoscedasticity (F [18,35] = 1.83; $P = 0.06$). On the basis of a previously proposed four-factor structure of the ZAN-BPD[64], changes in ZAN-BPD subscale scores within the domains of affective, cognitive, impulsive and interpersonal symptoms were also explored. Within each multilevel model, effects of time, treatment condition and time × treatment condition interactions were examined. Initial fixed- and random-effects models, as well as models with a CAR1 autoregressive correlation structure, were built and compared to test the best-fitting model for each outcome, which was selected according to the Akaike and Bayesian information criteria. To explore whether BPD symptom severity impacted the results, associations between baseline BPD symptom severity and the effects of time, treatment condition or time × treatment condition interactions were explored. No other covariates were examined. A linear random-effects model with a time × condition interaction term fit best for all variables. Post hoc pairwise comparisons were examined within each treatment arm. Due to the preliminary nature of the findings, effects are reported as significant at an uncorrected alpha threshold of $P < 0.05$. All tests were two-tailed.

Suicidal remission and depression response rates were also examined and defined as a score of zero on the MSSI for 2 consecutive weeks and ≥50% reduction in HRSD-24 scores from baseline, respectively.

Neuropsychological data were analysed using mixed ANOVA models examining effects of time, treatment condition and time × treatment condition interaction effects.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Study participants did not consent to have their data shared publicly. Deidentified participant data from all study timepoints, along with data dictionaries and the study protocol, can be made available, beginning 12 months and ending 3 years after publication of this paper, to researchers who provide a methodologically sound proposal that includes a protocol and a statistical analysis plan and is not in conflict with the investigators' research plans. Proposals should be directed to the corresponding author and will need to be reviewed by the study's principal investigators. To gain access, data requestors will need to sign a data access agreement.

Code availability

Data were analysed using custom scripts created in freely-available R Programming (v.4.1.2). All custom code used to analyse the data in this manuscript are available on Open Science Framework (OSF): https://osf.io/2hwcg/.

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Author contributions

A.C.R., S.F.M., D.M.B. and Z.D. designed the study and supervised the work. J.M.T., A.C.R., N.H., D.M.B. and Z.D. were involved in preparation and submission of regulatory approvals. J.M.T., S.F.M., N.H., R.C., D.M.B. and Z.D. were involved in data collection. J.M.T. analysed the data and drafted the manuscript. All co-authors discussed the results and commented on the manuscript.

Competing interests

The authors declare the following competing interests: Z.D. has received research and equipment in-kind support for an investigator-initiated study through Brainsway Inc and Magventure Inc. He is also on the scientific advisory board for Brainsway Inc. D.M.B. received research support and in-kind equipment support for an investigator-initiated study from Brainsway Ltd, and he has been the site principal investigator for sponsor-initiated studies for Brainsway Ltd. He also receives in-kind equipment support from Magventure for investigator-initiated studies. He received medication supplies for an investigator-initiated trial from Indivior. He has participated in advisory boards for Welcony Inc and for Janssen. None of these organizations played a role in the conceptualization, design, data collection, analysis, decision to publish or preparation of this manuscript.

Additional information

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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No software was used for data collection.
Data analysis	Statistical analyses were completed using custom multilevel modeling codes created in freely available R Programming (version 4.1.2) using the R statistical packages 'nlme' (v 3.1-155), 'multcomp'(v 1.4-18), and 'emmeans' (v 1.7.2). All custom code used in the analysis of this manuscript is available as a public project on OSF and can be found here: https://osf.io/2hwcg/

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Participants in this study did not consent to have their data shared publicly. Deidentified participant data from all study timepoints, along with data dictionaries and the study protocol, can be made available, beginning 12 months and ending 3 years after publication of this paper, to researchers who provide a methodologically

sound proposal that includes a protocol and a statistical analysis plan, and is not in conflict with the investigators research plans. Proposals should be directed to Dr. Anthony Ruocco (anthony.ruocco@utoronto.ca) and will need to be reviewed by the study PIs. To gain access, data requestors will need to sign a data access agreement.

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	Only female participants were recruited for this pilot study, as the majority of treatment-seeking patients with BPD are female and the planned small sample size of our pilot trial would not have support an analysis of sex differences.
Population characteristics	Participants in MST+DBT (mean age 30.1, SD 9.4) and DBT-only (mean age 28.4, SD 7.9) had diagnoses of BPD and MDD. In MST+DBT, n = 5 participants had comorbid PTSD and n=1 had comorbid Bipolar II Disorder. In DBT- only, n = 4 had comorbid PTSD. Baseline BPD symptom severity (MST+ DBT mean = 15.89, SD = 6.8; DBT only mean = 12.7, SD = 3.6) was included as a covariate in the analyses of primary outcomes.
Recruitment	Participants were recruited using convenience and voluntary response sampling with a case-control design, comparing individuals receiving MST and DBT with matched patient control group receiving DBT alone. Participant self-selected their treatment arm. There is a possibility that patient expectations regarding the effectiveness of conjoint MST+DBT over DBT-alone may have moderated or mediated the between-condition treatment effects observed; the MST treatment involves a complex intervention with a novel technology that has the potential for large expectation and non-specific effects and a sham-controlled design is required in the future to replicate these findings.
Ethics oversight	The Research Ethics Boards at the Centre for Addiction and Mental Health (CAMH) and the University of Toronto (UofT) approved the ethics protocol. The clinical trial was approved by Health Canada. All participants provided informed consent to participate in the study. Participants were compensated $25 CAD per fMRI scan completed.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

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Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	In an open-label pilot trial of suicidal patients with comorbid BPD and treatment-resistant depression (N=19), we investigated the feasibility and initial clinical effects of five weeks of conjoint MST and Dialectical Behavior Therapy (MST+DBT) compared to five-weeks of DBT alone. Changes in primary symptom outcomes of suicidal ideation and clinician-rated depression severity were investigated using multilevel models examining time, condition, and time by condition interactions. Additional outcomes included self-reported depression severity, BPD symptom severity, and cognitive functioning.
Research sample	Female participants between 18 and 50 years old who met DSM-IV criteria for BPD and a current non-psychotic depressive episode in the context of MDD and with the following additional criteria were eligible to participate: moderate to severe suicidal ideation on the MSSI (score > 9) or at least 2 weeks prior to enrollment; severe depression on the Hamilton Rating Scale for Depression-24 (HRSD-24; score > 22); and TRD defined by failure to achieve a clinical response to two or more adequate antidepressant treatment trials during the current depressive episode or an inability to tolerate at least two antidepressants. As only female participants were recruited, the sample is not representative. We chose to study females given that the majority of treatment-seeking patients with BPD are female.
Sampling strategy	Convenience and voluntary response sampling were used to recruit participants. Participants eligible for treatment at CAMH and meeting study eligibility criteria, as well as participants from the community who heard about our trial from our clinicaltrials.gov posting were screened. Our target sample size was N=30 however due to covid-related restrictions on research, our final sample size is N=19, which is still sufficient for a pilot trial to examine feasibility and initial clinical effects but will require replication in the future using a larger, sham-controlled design. No calculations were used to determine sample size. The sample size is similar to published trials of non-invasive brain stimulation in BPD.
Data collection	Data were recorded using pen and paper source and CRF documents and were logged at each assessment and treatment timepoint by the relevant research and treatment teams. No one was present during study appointments besides the participant and researcher. Researchers were not blinded to experimental conditions or hypotheses.
Timing	The study was conducted between October 2017 to March 2020, with follow up assessment continuing until June 24 2020. No

Timing	additional participants were recruited after March 2020 due to COVID-19 research restrictions.
Data exclusions	No data were excluded from the analysis.
Non-participation	A CONSORT Flow diagram is included in the manuscript and includes a description of all participants who withdrew or terminated treatment and reasons for termination. Out of the 10 participants enrolled in the MST+DBT arm of the study, n = 1 was excluded before treatment start for acute suicidality requiring hospitalization. Out of the 11 participants enrolled in the DBT-only arm, n = 1 dropped out before treatment start due to disinterest in DBT.
Randomization	This was a non-randomized, open-label pilot study. We opted not to randomize participants given that this was an initial pilot study to investigate the feasibility and clinical effects of magnetic seizure therapy in suicidal patients with BPD and MDD. Only participants meeting pre-established inclusion and exclusion criteria were eligible to participate. An analysis of participant characteristics revealed no significant differences in baseline severity of depression, suicidal ideation or BPD symptom severity between the two arms (see Table 1 in the manuscript).

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☐	☒ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	NCT03361826
Study protocol	The protocol can be made available upon request by emailing the corresponding author anthony.ruocco@utoronto.ca. A full description of the MST protocol is published in supplementary material.
Data collection	Data from this study were collected at the Centre for Addiction and Mental Health between Oct 2017 - June 2020.
Outcomes	Pre-defined primary outcomes were registered on clinical trials.gov. Primary outcomes included improvement in clinician-rated depression severity (measured by Hamilton Rating Scale for Depression-24 score) and suicide ideation (measured by Modified Scale for Suicide Ideation score). Additional outcomes included self-reported depression severity (measured by the Quick Inventory of Depressive Symptoms - Self Report), BPD symptom severity (assessed with the ZAN-BPD clinician-administered interview) and cognitive performance assessed with a comprehensive neuropsychological battery described in Methods.

Magnetic resonance imaging

Experimental design

Design type	Task-based fMRI; three block-designed tasks (An implicit emotional recognition task involving the presentation of fearful and neutral faces whereby the participant was asked to identify the gender of the face; a Go/No Go task; and an autobiographical memory task involving the presentation of familiar and novel naturalistic scenes). Each task was administered over two runs, resulting in 6 total runs per participant. The tasks were administered in a counterbalanced fashion. The fMRI data are not analyzed or presented in the paper: due to the impact of COVID-19 on our final sample size, we cannot determine reliable fMRI effects as they are too underpowered. Researchers who are interested in learning specific details about the design of each fMRI task can contact the corresponding author at anthony.ruocco@utoronto.ca
Design specifications	Contact corresponding author.
Behavioral performance measures	A button press was used to record responses. The data were not analyzed.

Acquisition

Imaging type(s)	Functional
Field strength	3T
Sequence & imaging parameters	All participants underwent an axial echo planar imaging sequence. TR/TE = 2500/30 ms. 46 interleaved slices, slice thickness 3.0mm, flip angle = 60 degrees, matrix = 64x64, bandwidth =250 Hz/Px. A high resolution structural T1-weighted scan was also acquired using the BRAVO sequence.
Area of acquisition	Whole brain

Diffusion MRI ☐ Used ☒ Not used

Preprocessing

Preprocessing software	N/A
Normalization	N/A
Normalization template	N/A
Noise and artifact removal	N/A
Volume censoring	N/A

Statistical modeling & inference

Model type and settings	N/A
Effect(s) tested	N/A

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference (See Eklund et al. 2016)	N/A
Correction	N/A

Models & analysis

n/a	Involved in the study
☒	☐ Functional and/or effective connectivity
☒	☐ Graph analysis
☒	☐ Multivariate modeling or predictive analysis