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Chronotherapeutic intervention targeting emotion regulation brain circuitry, symptoms, and suicide risk in adolescents and young adults with bipolar disorder: a pilot randomised trial

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ABSTRACT

Background Mood episodes and high suicide risk of bipolar disorder (BD) are thought to derive from amygdala–ventral prefrontal cortex emotion regulation brain circuitry dysfunction and resulting emotion dysregulation, making these potential intervention targets.

Objective To assess feasibility, acceptability, and preliminary efficacy in engaging the emotion regulation targets of two Brain Emotion Circuitry-targeted Self-Monitoring and Regulation Therapy (BE-SMART) variations in adolescents and young adults with BD (BD_{AYA}): BE-SMART-ER, which directly targets emotion regulation, and BE-SMART-DR, a social rhythm therapy (SRT)-based chronotherapeutic intervention designed to reduce daily rhythm (DR) irregularities.

Methods In a single-blind, parallel, pilot-randomised trial, 60 BD_{AYA} (aged 16–29 years) were randomised to 12 weekly sessions (9 telehealth) of BE-SMART-DR or BE-SMART-ER. Nineteen BE-SMART-DR and 16 BE-SMART-ER participants completed the intervention, with 11 and 13, respectively, having pre-intervention and post-intervention functional MRI data.

Findings In addition to demonstrating feasibility, only BE-SMART-DR showed pre-treatment to post-treatment improvements in DR regularity (Cohen's d=0.55; 95% CI [0.06, 1.03]), associated with reductions in left amygdala responses to emotional face stimuli ($p_{\text{FWE (family-wise error)-SVC (small volume correction)}}<0.05$), difficulties in emotion regulation (d=0.75; 95% CI [0.23, 1.25]) and suicide risk (d=0.65; 95% CI [0.15, 1.14]). Significant correlations were observed among these changes ($p<0.05$). Both interventions showed high acceptability and improvements in depression and mania symptoms. No intervention-related adverse events were observed.

Conclusions Regularising DRs may enhance emotion regulation brain circuitry functioning, emotion regulation, and reduce suicide risk in BD_{AYA}.

Clinical implications Chronotherapeutic interventions regularising DRs, such as SRT, should be studied further as potential treatment strategies for BD_{AYA}.

Trial registration number NCT03183388.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Preliminary evidence suggests that chronotherapeutic interventions such as social rhythm therapy reduce mood symptoms in adults with bipolar disorder, but their effects on other symptoms, suicide risk, and the associated changes in brain circuitry have not been explored, especially in adolescents and young adults.

WHAT THIS STUDY ADDS

⇒ This is the first study to evaluate the effects of Brain Emotion Circuitry-targeted Self-Monitoring and Regulation Therapy for Daily Rhythms (BE-SMART-DR), an intervention employing chronotherapeutic strategies from social rhythm therapy, adapted for adolescents and young adults with bipolar disorder and delivered largely via telehealth, on symptoms and related brain functioning. The findings from this pilot randomised trial provide initial evidence supporting the benefits of this chronotherapeutic approach, highlighting associations among improvements in daily rhythm regularity, emotion regulation brain circuitry functioning, emotion regulation, and a reduction in suicide risk.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings suggest that chronotherapeutic interventions regularising daily rhythms, such as social rhythm therapy, may be a promising treatment strategy for reducing symptoms, emotion dysregulation, and suicide risk in adolescents and young adults with bipolar disorder, warranting further research in a larger-scale trial.

BACKGROUND

Bipolar disorder (BD) is characterised by pronounced emotion dysregulation associated with depressive and (hypo)manic episodes and a high suicide risk. Adolescence and young adulthood are pivotal epochs for the onset of BD and suicidal thoughts and behaviours (STBs), with an estimated BD prevalence of 4%[1]; it is estimated that about 50% of individuals with BD will attempt and 20% will die by suicide.[2] Therefore, this epoch represents a critical window to implement strategies that reduce symptoms and suicide risk. Prior randomised controlled trials (RCTs) provide evidence for the beneficial effects of psychosocial interventions for BD, including cognitive behavioural therapy, family-focused therapy, and interpersonal and social rhythm therapy (IPSRT).[3] However, these interventions were not designed to specifically target underlying neurobiological mechanisms, which could limit their effectiveness, and often require intensive therapist training and in-person visits, underscoring the need for more targeted and scalable interventions.

Emotion dysregulation has been considered a target for reducing suicide risk and has shown associations with STBs in both adolescents and adults.[4] Previous efforts have largely targeted emotion regulation directly.[5] Alternatively, there is growing interest in addressing circadian rhythm instabilities, which precipitate and worsen emotion dysregulation, mood episodes, and STBs, especially in BD.[6]

The amygdala–ventral prefrontal cortex system (AV) may be a key neurobiological target, as it links disruptions in circadian rhythms, emotion dysregulation, and STBs.[2] The amygdala and ventral prefrontal cortex (vPFC), both central to emotion regulation, exhibit strong bidirectional connections with each other, and with the hypothalamus, which is integral to circadian rhythms. The maturation of the AV, particularly the vPFC and its connections, occurs during adolescence and young adulthood; altered AV neurodevelopmental trajectories are thought to contribute to the emergence of BD symptoms and STBs during this epoch.[2] Growing evidence of this system's plasticity, especially during this critical period, further suggests that interventions that improve AV function could realign developmental trajectories, potentially reducing symptoms and suicide risk long-term.

The SRT component of IPSRT was designed to stabilise both circadian rhythms and mood. The social zeitgeber theory of mood disorders posits that disruptions in circadian rhythms stem from disturbances in daily social routines, which trigger mood episodes.[7] Accordingly, SRT focuses on stabilising social anchors to regularise DRs, including waking, sleep, meal, and physical/social activity schedules. IPSRT is an evidence-based psychotherapy shown to reduce mood symptoms in adults with BD.[3 8] RCTs demonstrate its benefits as an adjunctive treatment in adolescents and young adults.[9 10] However, the chronotherapeutic SRT component alone remains underexplored.[11] One qualitative study of BD participants found the SRT component most beneficial for maintaining mood stability over five years.[12]

Building on these insights and addressing the research gaps, we developed the **B**rain **E**motion Circuitry-targeted **S**elf-**M**onitoring **a**nd **R**egulation **T**herapy (BE-SMART) programme. Two treatments were designed to target and enhance emotion regulation brain circuitry functioning: BE-SMART-DR, using SRT strategies to regularise DRs, and BE-SMART-ER, focusing on explicit emotion regulation skills. Each treatment consisted of 12 developmentally tailored manualised sessions, delivered primarily via telehealth.

Objective

This pilot randomised trial aimed to assess the feasibility, acceptability, and preliminary efficacy of BE-SMART-DR and BE-SMART-ER in adolescents and young adults with BD (BD_{AYA}), examining their effects on emotion regulation, its underlying brain circuitry targets, and their associations with daily rhythm regularity, symptoms, and suicide risk. While comparisons between BE-SMART-DR and BE-SMART-ER were made, these were exploratory and intended to provide context to facilitate interpretation of findings, rather than to directly compare the effects of two interventions. Findings would inform modifications to BE-SMART for a subsequent RCT.

METHODS

Participants and study design

This study took place in Mood Disorders Research Program at Yale School of Medicine in New Haven, Connecticut, USA. Seventy-six participants aged 16–29 years were recruited from the surrounding community between October 2017 and June 2022. Recruitment involved Yale-affiliated clinical programmes, clinics, media outreach, and community presentations in Connecticut. Inclusion criteria were (1) Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnosis of BD I, II, or other specified, assessed using the Structured Clinical Interview, or, for ages <18 years, the Kiddie Schedule for Affective Disorders and Schizophrenia, and (2) score of ≥15 on the 29-item Hamilton Depression Rating Scale (HDRS) and/or ≥12 on the Young Mania Rating Scale (YMRS). Exclusion criteria were (1) major neurological or medical conditions that could affect brain tissue (except treated hypothyroidism; n=2), (2) current participation in structured therapy, (3) substance use disorder (except cannabis) within the last 3 months, (4) contraindication to MRI, (5) intelligence quotient (IQ) <70, (6) pregnancy, or (7) too symptomatic by the principal investigator's clinical judgement. This trial is registered at ClinicalTrials.gov (NCT03183388), and the protocol is available online (online supplemental file 1).

Participants were randomised 1:1 in a parallel design to BE-SMART-DR or BE-SMART-ER using computer-generated randomisation by an independent data manager. The randomisation was stratified by mood symptoms: depression without elevated mood (HDRS ≥15 and YMRS <12) or elevated mood symptoms (YMRS ≥12). Although therapists were aware of the allocated intervention, the randomisation was concealed from participants, consenting staff, and outcome assessors.

Brain Emotion Circuitry-targeted Self-Monitoring and Regulation Therapy

Both BE-SMART treatments consisted of 12 manualised weekly sessions. Initial, middle, and final sessions occurred in-person with comprehensive assessments and imaging, while the remaining sessions were conducted via a secure, Health Insurance Portability and Accountability Act-compliant video/audio platform.

All treatment sessions were recorded. Therapists received training and supervision from senior research clinicians (WKS, HAS, HPB) to ensure fidelity, adherence to the manual, and to prevent overlap of treatment variations. Each participant was required to inform the community clinician of their study involvement, ensuring study treatments were administered adjunctive to treatment as usual.

BE-SMART-DR sessions focused on key SRT components: psychoeducation about BD and circadian rhythms (sessions 1–2); linking DR disruptions to mood (S3–5); regularising DRs that affect circadian rhythm (S6–8); symptom awareness and identifying relapse signs (S9–10); and relapse prevention planning

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(S11–12). Participants completed the five-item Social Rhythm Metric weekly as a therapeutic tool.[13]

BE-SMART-ER sessions focused on explicit emotion self-regulation domains drawing on prior research by our group and others on emotion regulation processes subserved by AV and effective emotion regulation strategies for adults and youths[14 15]: understanding emotion generation/regulation and identifying emotional vulnerabilities/triggers (S1–3); addressing extreme thought patterns, managing physical responses, and preparing for emotional challenges (S4–10); and relapse prevention planning (S11–12).

Feasibility and acceptability

Feasibility was assessed by the percentage of 'completers', defined as participants who completed the intervention and the behavioural/clinical assessments, among those who attended more than one session. To assess acceptability, participants rated client satisfaction and therapeutic alliance at the end of treatment using the Client Satisfaction Questionnaire (CSQ, maximum score 36) and Working Alliance Inventory (WAI, maximum score 84 per subscale; four participants missed a total of 1 to 4 items).[16]

Behavioural and clinical assessments

The following behavioural and clinical assessments were administered at baseline ('pre-treatment') and at the end of treatment ('post-treatment').

DRs and emotion regulation

Social rhythm regularity, the primary measure of DR-related behavioural changes, was assessed using the Brief Social Rhythm Scale (BSRS).[17] Subjective sleep quality was explored using the Pittsburgh Sleep Quality Index (PSQI).[18] Emotion regulation, the primary measure to assess engagement of the emotion regulation target, was assessed with the Difficulties in Emotion Regulation Scale (DERS).[19] Emotion reactivity was also explored using the Emotion Reactivity Scale (ERS).[20]

Mood symptoms and suicide risk

Mood symptoms were evaluated by an independent evaluator blinded to treatment assignment using the YMRS (manic symptoms) and the 29-item HDRS (depressive symptoms), the latter as it includes measures of anergic atypical depression symptoms common in BD_{AYA} and related to diurnal variation.[21] Suicide risk was assessed with the Concise Health Risk Tracking (CHRT) Scale, validated for adolescents and adults, demonstrating reliability, sensitivity to change, and predictive value for future suicidal events.[22] Additional assessments to explore mood and suicide risk-related symptoms included the Beck Anxiety Inventory (BAI) and Beck Hopelessness Scale (BHS).

Imaging acquisition and processing

Scans were performed on a 3-Tesla PRISMA MR scanner (Siemens, Erlangen, Germany). Three-dimensional magnetisation-prepared rapid gradient-echo (MPRAGE) images (repetition time (TR)=1500 ms, echo time (TE_1)=2.77 ms, (TE_2)=2.83 ms, flip angle (FA)=15°, matrix=256×256, field of view (FOV)=256×256 mm^2, slice thickness=1.0 mm without gap, 160 contiguous slices) were iteratively registered non-linearly to an evolving group average template. T1 data (TR=300 ms, TE=2.47 ms, FA=60°, matrix=256×256, FOV=256×256 mm^2, 32 3 mm contiguous slices aligned with the anterior commissure–posterior commissure plane) were registered to MPRAGE, then fMRI data. fMRI data were collected using a single-shot echo planar imaging sequence: TR=2000 ms, TE=2.5 ms, FA=80°, matrix=64×64, FOV=240×240 mm^2, 32 3 mm contiguous slices, while participants performed an emotional face gender-labelling task.[2] In brief, they viewed faces from the Ekman series depicting happy, fearful, or emotionally ambiguous (Ekman termed neutral) expressions for 2 s, separated by 4–12 s fixation crosshair viewing, and pressed a button to indicate face gender, for 4 min 50 s runs.

Processing of fMRI data was performed using Statistical Parametric Mapping V.12 (SPM12) (Wellcome Institute of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm12). Images were corrected for differences in interscan slice acquisition timing and spatially normalised and coregistered to the Montreal Neurologic Institute template. Normalised images were resampled into 3 mm^3 voxels and smoothed at 8 mm full-width-at-half-maximum. Event-related blood oxygen level-dependent (BOLD) response amplitudes were estimated using the general linear model at the individual subject level for each of the three emotion event types, relative to crosshair viewing.

Statistical analysis

Demographic and clinical variables

Analyses were conducted using SPSS, V.29.0.1.0. Potential baseline differences between the BE-SMART-DR and BE-SMART-ER completer groups were evaluated using independent t-tests for continuous variables. For categorical variables, χ^2 tests and Fisher's exact tests were used as appropriate. Pre–post group differences were compared within and between BE-SMART-DR and BE-SMART-ER completers using linear mixed models with BE-SMART group as a between-subjects factor and time (pre-treatment vs post-treatment) as a within-subject factor. The interaction between group and time was modelled, and the best variance–covariance structure was selected based on information criteria. For each outcome, the *a priori* comparison of interest was the least squares means change from baseline compared with zero within each group. Group differences in changes from baseline were assessed by examining the interaction effect. Correlation analysis (Pearson) was used to assess associations among scales showing significant pre–post changes. All tests were considered significant based on a two-tailed alpha=0.05 threshold. Given the preliminary nature of the study, analyses were not adjusted for multiple comparisons. Assuming a two-tailed alpha=0.05, the study was powered (80%) to detect large within-subject changes (d'=0.68–0.75) and interaction effects (d=0.98), and medium/large associations (r=0.59–0.64).

Neuroimaging

Analyses were conducted using SPM12 for subjects with neuroimaging data that passed quality control pre-treatment and post-treatment, meeting criteria of <3 mm in translation, <3° in rotation, and <8 missed button presses. Voxel-wise regression analyses identified brain regions where the BOLD signal change correlated significantly with changes in the BSRS scores for BE-SMART-DR, and changes in the DERS scores for BE-SMART-ER. The Harvard-Oxford Cortical Structural Atlas in the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) was used to anatomically define amygdala and vPFC (atlas termed 'orbitofrontal cortex') regions of interest (ROIs), thresholded at 25% and binarised.[23] Analyses within these *a priori* ROIs were assessed for significance using a voxel-wise threshold of $p_{uncorrected}<0.001$, with multiple comparisons corrected using small volume correction (SVC) applied with

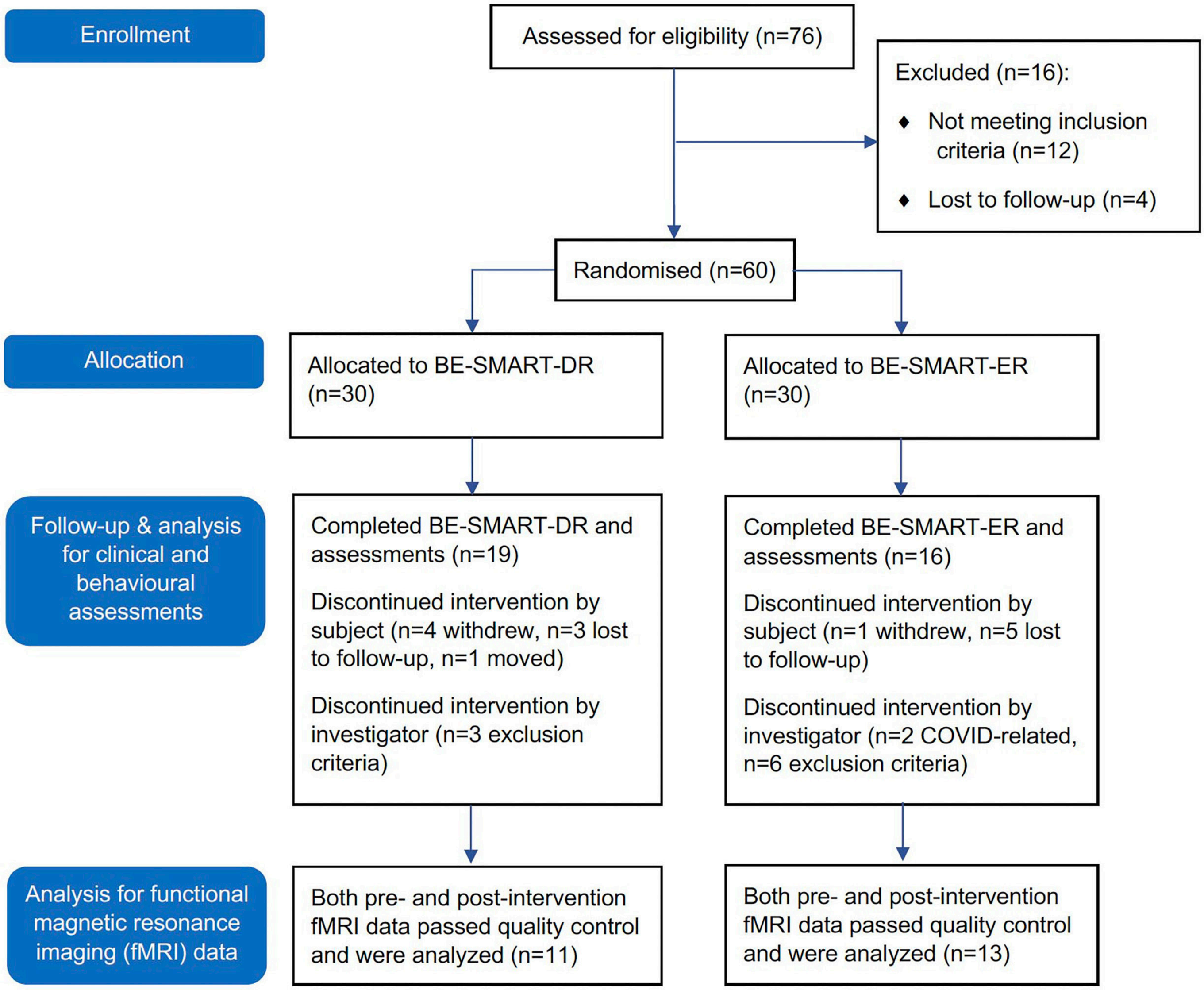

Figure 1 Participant flow diagram. BE-SMART, Brain Emotion Circuitry-targeted Self-Monitoring and Regulation Therapy; DR, daily rhythm; ER, emotion regulation.

family-wise error (FWE) correction at $p_{FWE\text{-}SVC}<0.05$. Whole-brain analyses were conducted to explore regions outside the *a priori* ROIs, considered significant if they survived a voxel-wise correction for multiple comparisons using FWE correction at $p_{FWE}<0.05$. For each significant brain region cluster, average BOLD signal values (beta estimates) were extracted using the MarsBaR (http://marsbar.sourceforge.net/). Pearson correlation analysis was used to assess the relationships between changes in these values with changes in the behavioural and clinical outcomes that changed significantly over the treatment (considered significant at $p<0.05$).

Findings

Demographic and clinical characteristics

Nineteen BE-SMART-DR and 16 BE-SMART-ER participants completed the treatment and both pre-treatment and post-treatment clinical assessments (figure 1). Five BE-SMART-DR and five BE-SMART-ER participants had baseline YMRS scores ≥12 (table 1). Eleven BE-SMART-DR and 13 BE-SMART-ER participants had neuroimaging data passing quality control at both time points. The BE-SMART-DR and BE-SMART-ER completer groups showed no significant differences in demographics, clinical characteristics, and baseline assessment measures, except for younger age (p=0.045), higher baseline BAI scores (p=0.026), and lower stimulant usage (p=0.035) in the BE-SMART-DR group. However, covariate adjustment for age and baseline BAI in the models did not change results and were, therefore, dropped. Sensitivity analyses excluding four BE-SMART-ER participants on stimulants showed consistent outcomes for all measures.

Feasibility and acceptability

Of the 24 participants who attended more than one session of BE-SMART-DR and the 29 of BE-SMART-ER, a higher percentage completed BE-SMART-DR (79.2%, 19 participants) than BE-SMART-ER (55.2%, 16 participants); however, the difference in completion rates was not statistically significant ($p=0.066$). In BE-SMART-DR, the average WAI subscale scores were 73.6 (95% CI [71.27, 75.93]) for alliance on tasks, 75.9 (95% CI [74.15, 77.65]) for therapeutic bond and 75.8 (95% CI [73.37, 78.23]) for alliance on goals. In BE-SMART-ER, the average WAI subscale scores were 73.2 (95% CI [70.41,

Table 1 Demographic and clinical characteristics of the intervention completers

	BE-SMART			
	DR		ER	
	M (SD)	N (%)	M (SD)	N (%)
Age	20.9 (3.0)		22.9 (2.5)	
Years of education	13.4 (1.8)		14.1 (2.0)	
Female		13 (68.4)		9 (56.3)
BDI diagnosis*		15 (78.9)		14 (87.5)
Rapid cycling		9 (47.4)		5 (31.3)
Current comorbidities				
Attention deficit hyperactivity disorder		11 (57.9)		11 (68.8)
Generalised anxiety disorder		8 (42.1)		5 (31.3)
Social anxiety disorder		7 (36.8)		7 (43.8)
Specific phobia		3 (15.8)		1 (6.3)
Panic disorder		2 (10.5)		1 (6.3)
Cannabis use disorder (mild–moderate)		3 (15.8)		3 (18.8)
Post-traumatic stress disorder		2 (10.5)		2 (12.5)
Other specified trauma- and stressor-related disorder		1 (5.3)		0 (0)
Obsessive-compulsive disorder		1 (5.3)		2 (12.5)
Binge eating disorder		3 (15.8)		0 (0)
Bulimia nervosa		1 (5.3)		0 (0)
Medications at baseline				
Unmedicated		3 (15.8)		1 (6.3)
Antipsychotics		9 (47.4)		11 (68.8)
Anticonvulsants		8 (42.1)		6 (37.5)
Lithium		4 (21.1)		5 (31.3)
Antidepressants		7 (36.8)		3 (18.8)
Benzodiazepines		4 (21.1)		3 (18.8)
Stimulants		0 (0)		4 (25.0)
Atomoxetine		0 (0)		1 (6.3)
Sedative hypnotics		1 (5.3)		0 (0)

*10.5% of the DR group and 12.5% of the ER group were diagnosed with BDII; 10.5% of the DR group were diagnosed with BD-OS.
BDI, bipolar I disorder; BDII, bipolar II disorder; BD-OS, Other Specified Bipolar and Related Disorders; BE-SMART, Brain Emotion Circuitry-targeted Self-Monitoring and Regulation Therapy; DR, daily rhythm; ER, emotion regulation.

75.99]) for alliance on tasks, 73.7 (95% CI [70.84, 76.56]) for therapeutic bond and 71.4 (95% CI [68.07, 74.73]) for alliance on goals. CSQ-8 scores averaged 28.9 (95% CI [27.93, 29.87]) in BE-SMART-DR and 28.6 (95% CI [26.99, 30.21]) in BE-SMART-ER.

Behavioural and clinical outcome measures

Significant pre–post improvements were observed for HDRS, YMRS, and PSQI in both BE-SMART-DR and BE-SMART-ER (table 2). In BE-SMART-DR group only, significant improvements were observed for BSRS, DERS, ERS, CHRT, BAI, and BHS. The group-by-time interaction was significant for BSRS.

Among BE-SMART-DR, changes in BSRS were significantly correlated with changes in DERS ($r=0.65$; $p=0.003$), ERS ($r=0.54$; $p=0.017$), and CHRT ($r=0.53$, $p=0.020$). Changes in CHRT were also significantly correlated with changes in DERS ($r=0.70$, $p<0.001$), ERS ($r=0.79$, $p<0.001$), and BHS ($r=0.46$, $p=0.047$). Additionally, changes in DERS were significantly correlated with changes in ERS ($r=0.57$; $p=0.011$).

Neuroimaging

Following BE-SMART-DR, improvements in BSRS were associated with decreases in left amygdala responses when participants viewed fearful ($p_{FWE\text{-}SVC}=0.037$) and emotionally ambiguous faces ($p_{FWE\text{-}SVC}=0.020$) (figure 2). The decreases in left amygdala responses to fearful/ambiguous faces correlated significantly with decreases in DERS ($r=0.77$, $p=0.006$/$r=0.82$, $p=0.002$) and CHRT ($r=0.74$, $p=0.009$/$r=0.72$, $p=0.012$) scores. Additionally, decreases in left amygdala responses to fearful faces correlated significantly with ERS ($r=0.64$, $p=0.035$). No additional brain regions showed significant pre–post BE-SMART-DR changes associated with changes in BSRS. No brain regions exhibited significant pre–post BE-SMART-ER changes associated with changes in DERS.

Adverse events

No intervention-related adverse events were observed.

DISCUSSION

Findings from this pilot randomised trial of BE-SMART provide preliminary evidence that BE-SMART-DR, an intervention primarily delivered through telehealth that employs chronotherapeutic strategies from SRT to regularise DRs, is a feasible and acceptable intervention for BD_{AYA} that may improve emotion regulation brain circuitry functioning, reducing emotion dysregulation and suicide risk. DR regularity, measured by BSRS, significantly improved among BE-SMART-DR participants, alongside decreases in emotion dysregulation and suicide risk. In contrast, BE-SMART-ER, which focuses on explicit emotion regulation skills, did not yield significant improvements in these areas. The significant group-by-time interaction in BSRS suggests that BE-SMART-DR contains therapeutic elements that effectively regularise DRs, which are absent or less effective in BE-SMART-ER. Interactions did not reach significance for other outcomes, such as emotion dysregulation ($d=0.51$) and suicide risk ($d=0.49$); however, this preliminary study was underpowered for group-by-time interactions, requiring $d=0.98$ for 80% power.

With BE-SMART-DR, improvements in DR regularity were associated with decreases in left amygdala responses when participants viewed fearful or emotionally ambiguous faces, which also correlated with reductions in emotion dysregulation and suicide risk. We and others previously demonstrated that elevated amygdala responses to emotional face stimuli are linked to emotion dysregulation in BD_{AYA}, and that decreased functional connectivity between the amygdala and vPFC is associated with suicide attempts in BD_{AYA}.[2] This study suggests that decreasing excessive amygdala responses to negative stimuli may be beneficial in reducing suicide risk. Emotionally ambiguous face stimuli yielded the most robust findings. This may be due to the ambiguity being processed differently in individuals with emotion dysregulation and STBs, suggesting that these stimuli could be useful for future research. Together, our findings suggest that improving amygdala system functioning may be a mechanism through which DR-regularising chronotherapeutic interventions like SRT improve emotion regulation and reduce suicide risk. Significant changes in vPFC were not detected. This may be partly due to younger participants whose vPFC is still

Table 2 Behavioural and clinical outcome measures

	BE-SMART							
	DR			ER			DR vs ER	
	LS means (SE)			LS means (SE)			Group-by-time interaction	
	Pre/post	Δ [95% CI]	d' [95% CI]	Pre/post	Δ [95% CI]	d' [95% CI]	DRΔ – ERΔ [95% CI]	d [95% CI]
HDRS	22.5 (2.5)/10.5 (2.5)	12.0*** [6.2, 17.8]	0.83 [0.29, 1.34]	18.4 (2.7)/11.4 (2.7)	6.9*** [0.6, 13.3]	0.75 [0.18, 1.29]	5.1 [−3.5, 13.6]	0.41 [0.27, 1.07]
YMRS	7.7 (1.7)/1.4 (0.8)	6.3*** [3.1, 9.4]	0.84 [0.31, 1.36]	8.1 (1.9)/2.9 (0.9)	5.2*** [1.8, 8.6]	0.90 [0.31, 1.48]	1.1 [−3.6, 5.7]	0.16 [−0.51, 0.82]
PSQI†	7.4 (0.7)/6.1 (0.7)	1.3* [0.1, 2.5]	0.53 [0.04, 1.00]	7.8 (0.7)/5.9 (0.7)	1.9*** [0.7, 3.2]	0.79 [0.21, 1.34]	−0.6 [−2.3, 1.1]	−0.24 [−0.91, 0.44]
BSRS	32.9 (2.2)/25.9 (2.2)	7.0* [1.7, 12.3]	0.55 [0.06, 1.03]	27.5 (2.4)/30.4 (2.4)	−2.9 [−8.6, 2.9]	−0.31 [−0.81, 0.20]	9.9* [2.1, 17.7]	0.88 [0.16, 1.55]
DERS	97.5 (5.3)/84.3 (5.3)	13.3** [4.8, 21.7]	0.75 [0.23, 1.25]	95.6 (5.7)/91.5 (5.7)	4.1 [−5.1, 13.3]	0.22 [−0.28, 0.72]	9.1 [−3.3, 21.6]	0.51 [−0.18, 1.17]
ERS	39.7 (4.7)/33.8 (4.7)	5.9* [0.2, 11.5]	0.49 [0.01, 0.96]	40.7 (5.1)/36.3 (5.1)	4.4 [−1.7, 10.6]	0.40 [−0.11, 0.91]	1.5 [−6.9, 9.8]	0.12 [−0.55, 0.78]
CHRT	18.9 (2.2)/14.3 (2.2)	4.7* [0.5, 8.9]	0.65 [0.15, 1.14]	17.7 (2.4)/17.4 (2.4)	0.3 [−4.3, 4.9]	0.03 [−0.46, 0.52]	4.4 [−1.9, 10.6]	0.48 [−0.20, 1.15]
BAI	21.9 (2.4)/13.2 (2.4)	8.7** [3.5, 14.0]	0.78 [0.26, 1.29]	13.4 (2.6)/10.6 (2.6)	2.9 [−2.8, 8.6]	0.25 [−0.25, 0.75]	5.9 [−1.9, 13.6]	0.52 [−0.17, 1.19]
BHS	6.5 (1.2)/4.2 (1.2)	2.3* [0.6, 4.0]	0.59 [0.09, 1.07]	7.2 (1.3)/5.5 (1.3)	1.7 [−0.2, 3.6]	0.50 [−0.03, 1.01]	0.6 [−1.9, 3.2]	0.17 [−0.50, 0.83]

* $p<0.05$, ** $p<0.01$, *** $p<0.001$.
†PSQI data were missing for one BE-SMART-DR participant; the analysis was conducted without this subject's data.
BAI, Beck Anxiety Inventory; BE-SMART, Brain Emotion Circuitry-targeted Self-Monitoring and Regulation Therapy; BHS, Beck Hopelessness Scale; BSRS, Brief Symptom Rating Scale; CHRT, Concise Health Risk Tracking; *d'*, Cohen's *d* for within-subjects changes; *d*, Cohen's *d* for interaction effects; DERS, Difficulties in Emotion Regulation Scale; DR, daily rhythm; ER, emotion regulation; ERS, Emotion Reactivity Scale; HDRS, Hamilton Depression Rating Scale; LS, least squares; PSQI, Pittsburgh Sleep Quality Index; YMRS, Young Mania Rating Scale; Δ, difference (pre- minus post-).

maturing, though this study's sample size limited power to assess development-related influences. Current 3-Tesla fMRI methods are limited in studying the hypothalamus; future research with improved methods could better assess the effects of chronotherapeutic interventions on the hypothalamus.

Previous studies on interventions targeting circadian rhythms to reduce STBs are scarce, primarily focused on adults with depression, and did not incorporate neuroimaging to assess neurobiological mechanisms. RCTs of zolpidem and cognitive-behavioural therapy for insomnia have shown reduced insomnia symptoms and suicidal ideation in adults.[24 25] However, these studies focused on insomnia, a different construct from DR, and did not assess measures of social or other DR regularity. One study on IPSRT adjunctive to pharmacotherapy in adults with BD supported its potential to reduce suicidal behaviour.[26] Combined with our current study, this suggests that further research on chronotherapeutic interventions such as SRT, along with using measures like BSRS across different therapies, could help develop new therapeutic strategies and improve understanding of mechanisms to reduce STBs.

Participants in both intervention groups exhibited significant improvements in depressive and elevated mood symptoms,

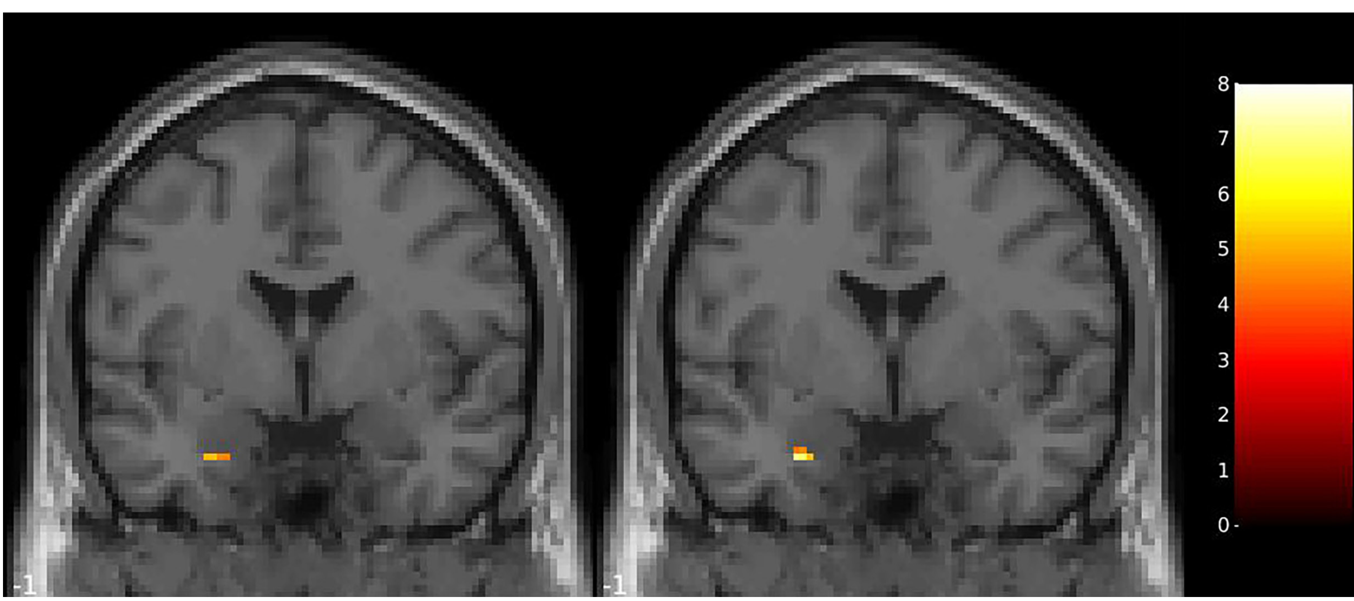

Figure 2 Decreases in left amygdala responses to face stimuli associated with improvements in daily rhythm regularity with Brain Emotion Circuitry Targeted Self-Monitoring and Regulation Therapy for Daily Rhythm (BE-SMART-DR). Coronal images display the left amygdala regions where decreases in brain oxygen level-dependent (BOLD) signal correlated significantly with improvements in Brief Social Rhythm Scale (BSRS) scores from before to after BE-SMART-DR. BSRS scores improved significantly from before to after BE-SMART-DR ($p<0.05$) and these changes were significantly associated with decreases in BOLD signal in the left amygdala when participants viewed faces depicting fearful (left image, $p_{FWE-SVC}<0.05$) and emotionally ambiguous (right image, $p_{FWE-SVC}<0.05$) expressions. The decreases in BOLD signal in the left amygdala to both face types also correlated significantly with reductions in scores on the Difficulties in Emotion Regulation Scale (DERS) and scores on the Concise Health Risk Tracking (CHRT) that reflect reductions in suicide risk. The colour bar represents the range of t-values. $p_{FWE-SVC}$, *p*-value corrected using family-wise error (FWE) correction with small volume correction (SVC).

consistent with evidence that combining pharmacotherapy with skill-based psychosocial interventions improves mood symptoms in individuals with BD.[3] Additionally, both groups showed improvements in subjective sleep quality. This was unexpected for BE-SMART-ER, as it does not explicitly incorporate sleep regularisation in its therapeutic framework; however, it aligns with research indicating bidirectional interaction between emotion regulation and sleep regulation[27] and the impact of sleep disturbances to mood dysregulation in BD.[28] This suggests that improved sleep may have contributed to improved mood symptoms, or vice versa, though the lack of significant correlations between changes in PSQI and HDRS/YMRS suggests other contributing factors. No significant association was found between changes in mood symptoms and measures of the presumptive 'active ingredients' of the treatments, BSRS and DERS. Mood improvements may be linked to non-specific treatment components, such as consistent weekly therapist contact. Participants in both groups reported high therapeutic alliance and satisfaction, which align with research showing that therapeutic alliance significantly influences treatment outcomes in depressed patients receiving psychotherapy.[16] These elements, among others, may have contributed to broader psychological well-being, as reflected in mood and subjective sleep improvements. Future studies should incorporate measures specifically designed to assess psychological well-being and its underlying mechanisms.

Additional symptoms that improved only with BE-SMART-DR included anxiety and hopelessness. A cross-sectional study linked greater social rhythm regularity with lower anxiety.[29] However, in our current study, improvements in BSRS did not significantly correlate with changes in BAI, suggesting that reductions in anxiety were not solely mediated by DR regularisation. Improvements in hopelessness were significantly associated with reductions in suicide risk, but not with improvements in DR regularity. As hopelessness is a key suicide risk factor and has been shown to mediate the relationship between emotion dysregulation and future STBs,[30] its reduction may have contributed to the observed suicide risk reduction in the BE-SMART-DR group, alongside the reduction potentially resulting from DR regularisation.

Emotion regulation was the hypothesised 'active ingredient' for BE-SMART-ER, yet DERS scores did not significantly improve with BE-SMART-ER. Several factors could explain this: the therapy may not have robustly addressed emotion regulation, the DERS measure might have lacked sensitivity to detect the types of emotion regulation changes that occurred, or the results may reflect heterogeneity within the ER group. Interestingly, DERS scores improved significantly in BE-SMART-DR, correlating with changes in emotion regulation brain circuitry functioning. This suggests that BE-SMART-DR may have a greater impact on improving emotion regulation, or that the constructs measured by DERS align more closely with the brain changes observed in BE-SMART-DR.

Study limitations include the small sample size, which limited the power to detect changes in additional measures and hindered the ability to investigate the heterogeneous clinical features of the sample or potential effects of different outside treatments, including pharmacotherapies. Analyses limited to completers may limit generalisability. Without a control condition, distinguishing the effects of BE-SMART-DR from treatment as usual is challenging, though differing outcomes between BE-SMART-DR and BE-SMART-ER suggest that these differences may arise from the distinct effects of each intervention. Measurements of PSQI, BSRS, DERS, ERS, CHRT, BAI, and BHS relied on retrospective self-reports, which may introduce recall response bias. Participants ranged from 16 to 29 years, covering a broad developmental range. Telehealth delivery likely facilitated high acceptability and session compliance, particularly among younger participants with busy schedules and transportation constraints. The intervention's flexibility enabled tailoring content to developmental needs, such as school-related or work-related routines. However, the study was not powered or designed to systematically assess development-related differences, which would be an important consideration for future research.

Clinical implications

Findings from this pilot randomised trial suggest that BE-SMART-DR, a chronotherapeutic intervention employing strategies from SRT to regularise daily rhythms, is a feasible and acceptable intervention that may alleviate clinical symptoms, enhance emotion regulation brain circuitry functioning, and reduce suicide risk. These results highlight its potential as a therapeutic strategy in adolescents and young adults with bipolar disorder and warrant further investigation in a larger RCT.

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