Archival Report

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# Functional Connectivity Mechanisms Underlying Symptom Reduction Following Lisdexamfetamine Treatment in Binge-Eating Disorder: A Clinical Trial

Kristi R. Griffiths, Isabella A. Breukelaar, Grace Harvie, Jenny Yang, Sheryl L. Foster, Anthony W. Harris, Simon Clarke, Phillipa J. Hay, Stephen Touyz, Mayuresh S. Korgaonkar, and Michael R. Kohn

## ABSTRACT

**BACKGROUND:** Speculation exists as to whether lisdexamfetamine dimesylate (LDX) acts on the functional connectivity (FC) of brain networks that modulate appetite, reward, or inhibitory control in binge-eating disorder (BED). Better insights into its action may help guide the development of more targeted therapeutics and identify who will benefit most from this medication. Here, we use a comprehensive data-driven approach to investigate the brain FC changes that underlie the therapeutic action of LDX in patients with BED.

**METHODS:** Forty-six participants with moderate to severe BED received LDX titrated to 50 or 70 mg for an 8-week period. Twenty age-matched healthy control participants were also recruited. Resting-state functional magnetic resonance imaging was used to probe changes in brain FC pre- and post treatment and correlated with change in clinical measures.

**RESULTS:** Ninety-seven percent of trial completers ($n$ = 31) experienced remission or a reduction to mild BED during the 8-week LDX trial. Widespread neural FC changes occurred, with changes in default mode to limbic, executive control to subcortical, and default mode to executive control networks associated with improvements in clinical outcomes. These connections were not distinct from control participants at pretreatment but were different from control participants following LDX treatment. Pretreatment connectivity did not predict treatment response.

**CONCLUSIONS:** FC between networks associated with self-referential processing, executive function, and reward seem to underlie the therapeutic effect of LDX in BED. This suggests that LDX activates change via multiple systems, with most changes in compensatory networks rather than in those characterizing the BED diagnosis.

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Binge-eating disorder (BED) is an eating disorder defined by recurrent BE episodes and is responsible for approximately 40% of the global burden from eating disorders (1). Worldwide, it has a 12-month weighted mean prevalence of 1.4% (0.5%–3%) for women and 0.6% (0%–1.2%) for men (2). BED is associated with increased risk of suicide and high levels of comorbidity (3).

Lisdexamfetamine dimesylate (LDX) is currently the only drug approved for the treatment of moderate to severe BED. It is a prodrug of d-amphetamine that significantly reduces intake of highly palatable food (4), BE frequency, and impulsivity (5–8) in people with BED. Despite its demonstrated efficacy in reducing BE episodes, there is speculation whether BED occurs predominantly via altering appetite, reward sensitivity, or cognitive control processes (9). Identifying the neural mechanisms by which LDX attenuates BE symptoms may not only help resolve this issue but also help identify who will benefit most from this medication.

To date, only 2 studies have used functional magnetic resonance imaging (fMRI) to examine the neural mechanisms by which LDX improves BE symptoms. One study reported reductions in ventromedial prefrontal cortex activation that were correlated with BE symptom reduction after 12 weeks of LDX (10). The other study reported reduced bilateral thalamic activation after an acute 50 mg dose of LDX administered to 22 women in a randomized, crossover, placebo-controlled design (4). However, both studies used task-evoked food stimuli designs, which examine LDX-related changes specifically related to the salience of food cues but not across a broader context.

Cognition and behavior are produced by dynamic interactions of disparate brain regions operating in functionally coherent networks (11). Thus, resting-state functional connectivity (FC) provides an opportunity to investigate multiple functional networks, independent of cue presentation. BED has been characterized by aberrant connectivity within and between functional networks that regulate inhibitory control





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(executive control network [ECN]), monitor for salient events such as food or reward cues (salience network [SN]), and process reward (limbic network [LN]) (12,13). Because homeostatic satiety is overridden during binge episodes, it is plausible that the default mode network (DMN) may also be involved due to its role in self-referential processing, including monitoring physical and emotional states. A holistic and integrated systems-level understanding of how LDX affects the brains of individuals with BED and produces symptom change is required.

Here, we used a comprehensive data-driven approach to investigate the neural mechanisms by which LDX improves BE symptoms in a cohort of individuals with moderate to severe BED. We conducted an 8-week clinical trial of LDX and analyzed FC from resting-state fMRI scans pre- and post treatment. We examined how LDX may change FC throughout the brain, whether there are specific neural network changes associated with its therapeutic effect, and whether LDX treatment is associated with normalization of these brain networks. Finally, we assessed whether pretreatment FC is able to predict which individuals would experience the best treatment response to LDX. Our whole-brain approach offers an unbiased way of examining changes across the highly interconnected functional networks of the brain to determine the neural underpinnings of LDX's therapeutic effect.

## METHODS AND MATERIALS

### Study Design

This is the primary analysis of an 8-week open-label trial of LDX that was conducted between April 2018 and January 2021 in Sydney, Australia (14). Participants with moderate to severe BED received LDX titrated to 50 or 70 mg for 8 weeks. A healthy control (HC) group of participants who received no intervention was also recruited. The primary clinical outcome measure was number of BE days in a week (BE frequency). Secondary outcome measures included the Clinical Global Impressions-Severity scale (15), the Eating Disorders Examination Questionnaire (16), the Brief Loss of Control Over Eating Scale (B-LOCES) (17), and the Binge Eating Scale (BES) (18). Further protocol and treatment details can be found in the Supplement.

The trial was registered with the Australian and New Zealand Clinical Trials Registry (anzctr.org.au) #ACTRN12618000623291 and received ethics approval from the Western Sydney Local Health District Human Research Ethics Committee. All participants provided written informed consent.

### Participants

Forty-six participants with moderate to severe BED and 20 HC participants, who were recruited from treatment centers and the community, were enrolled in the study. All clinical participants (ages 18–40 years) were required to meet DSM-5 criteria for BED as confirmed by the eating disorders module of the Structured Clinical Interview for DSM-5. To be considered moderate to severe, they were required to have reported a minimum of 3 days of BE per week during the past month and have a minimum score of 4 on the Clinical Global Impressions-Severity scale, a clinician-determined summary measure of a patient's global functioning (6). Inclusion criteria included a body mass index (BMI) between 20 and 45 and medical approval for LDX commencement. Exclusion criteria included current bulimia nervosa, anorexia nervosa, psychosis, mania, and substance dependence; history of physical brain injury; and psychostimulant use during the past 6 months [see (14) for the full list]. Table 1 shows included comorbidities. Age-matched HC participants were psychiatrically, neurologically, and medically healthy and were recruited from the same geographical location. Demographic information, including age, sex, and race, were collected via self-report questionnaire.

Resting-state fMRI analyses were conducted using 31 BED and 14 HC participants with good quality imaging data at both baseline (week 0) and medicated follow-up (week 8). Figure S1 shows the CONSORT (Consolidated Standards of Reporting Trials) diagram, including details of exclusions/withdrawals.

### Treatment

The dose schedule was based on existing clinical practice and efficacy literature (18,19). All participants started with 30 mg/day of LDX and were advised to take it at the same time each morning. Participants were provided with self-monitoring sheets to help track their medication compliance. After 2 weeks, participants with no abnormal changes to their blood pressure and heart rate (assessed by study clinician) increased their dose to 50 mg/day. At the 4-week clinic appointment, study clinicians determined whether participants continued with 50 mg/day or increased to 70 mg/day, depending on their responsiveness to the medication and experienced side effects. Participants remained on this dosage for the final 4 weeks. At the week 8 follow-up session, participants returned the completed self-monitoring sheets and any unused tablets.

**Table 1. Baseline Demographic and Clinical Characteristics of the BED and HC Groups**

| Measure | BED Group, $n$ = 39 | HC Group, $n$ = 20 |
|---|---|---|
| Age, Years | 26.3 (5.5) | 27.3 (6.1) |
| Sex, Female | 38 (97.4%) | 19 (95.0%) |
| Race or Ethnicity | | |
| Aboriginal and/or Torres Strait Islander | 2 (5.1%) | 0 (0%) |
| Asian | 7 (17.9%) | 8 (40.0%) |
| Caucasian | 20 (51.3%) | 8 (40.0%) |
| Hispanic | 0 (0%) | 1 (5.0%) |
| Other or multiple | 10 (25.6%) | 3 (15.0%) |
| Current Psychiatric Comorbidities | | |
| MDD | 5 (12.8%) | 0 (0%) |
| Anxiety | 5 (12.8%) | 0 (0%) |
| OCD | 1 (2.6%) | 0 (0%) |
| AUD/SUD | 7 (17.9%) | 0 (0%) |
| ADHD | 5 (12.8%) | 0 (0%) |

The statistics shown are mean (SD) or $n$ (%).

ADHD, attention-deficit/hyperactivity disorder; AUD, alcohol use disorder; BED, binge-eating disorder; HC, healthy control; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; SUD, substance use disorder.

### fMRI Acquisition, Preprocessing, and Generation of Functional Connectomes

Whole-brain resting-state echo-planar images and anatomical T1-weighted scans were acquired for each participant at the Westmead Hospital on a 3T Siemens Prisma magnet system (Siemens Healthineers). To generate whole-brain FC matrices, we parcellated each individual's preprocessed functional data into 200 cortical (19) and 32 subcortical (20) regions. Each region was mapped onto 7 canonical resting-state networks: DMN, dorsal attention network, ECN, LN, SN, somatomotor network (SMN), and visual network (19). This mapping was used to quantify and categorize significant connections for ease of interpretation (21,22). Subcortical regions (thalamus/basal ganglia/amygdala) are collectively referred to as subcortical (SC).

### Statistical Analysis

To evaluate the effect of LDX on BE frequency, a linear mixed model was performed with BE frequency as the dependent variable, individual as a random effect, and time point (week 0, week 8) as a fixed effect. As per previous literature (6), BE frequency was log-transformed to reduce skewness (number of BE days/week + 1).

FC data were analyzed using network-based statistics (NBS) (23), which is a nonparametric approach designed to address the multiple comparisons problem associated with mass univariate testing by evaluating the null hypothesis at the level of subnetworks rather than individual connections (23). Familywise error–corrected inference was performed for each NBS model using a conservative $t$ statistic threshold (equivalent to a primary component–forming threshold of $p < .005$) to minimize false discovery and improve the specificity of identified subnetworks. See the Supplement for more details on the NBS method.

Statistical analyses were designed in a stepwise manner: First, to determine the effect of LDX on FC, paired $t$ tests were conducted using NBS to compare week 0 and 8 FC matrices for the BED group and the control group to see whether FC changes occurred in this time frame without LDX treatment. A group × time mixed-model analysis was also conducted (Supplement). Second, to identify whether changes in FC were associated with clinical symptom change, FC estimates were extracted from subnetworks that were identified in analysis 1. Average connectivity estimates were computed for each resting-state network combination and used to compute change in connectivity values. Pearson correlations were conducted between normalized change in number of BE days (to account for baseline severity) and change in connectivity values. Spearman correlations were conducted across both time points to determine the clinical measure (Eating Disorders Examination Questionnaire, B-LOCES, BES) that was most associated with BE frequency. Change in this measure was subsequently correlated with change in connectivity values. Third, to determine whether resting-state networks that were associated with clinical change (from analysis 2) were impaired at baseline and underwent normalization with LDX treatment, independent samples $t$ tests were conducted to compare the BED and HC groups at week 0 and week 8, respectively. The BED and HC groups were also compared at the whole-brain level at week 0 and week 8 (Supplement). Fourth, to investigate whether there is an FC signature that is predictive of treatment response in BED, baseline whole-brain resting-state FC was correlated with normalized change in BE frequency from week 0 to week 8, as well as in secondary outcome measures using NBS. Because in-scanner motion is known to contribute to noise in resting-state fMRI connectivity, it was included as a covariate in all NBS analyses (24). Statistical analyses were conducted in R Studio, version 1.4.1717 (R Studio Team). All $p$ values were two sided, with Benjamini-Hochberg false discovery rate–corrected $p < .05$ applied to control for multiple comparisons. Reported effect sizes (ESs) are Cohen's $d$. Data were analyzed from February 2022 to December 2022.

## RESULTS

Sample demographics are shown in Table 1. Clinical information at week 0 and week 8 is shown in Table 2.

There was a significant effect of LDX treatment in reducing BE frequency from baseline (mean 4.26 binge days/week) to week 8 (mean 1.27 binge days/week) ($t_{60} = -10.07$, $p < .001$,

**Table 2. Clinical Measures in the BED and HC Groups at Baseline (Week 0) and Follow-up (Week 8)**

| Clinical Measure | BED Week 0, $n$ = 39, Mean (SD) | HC Week 0, $n$ = 20, Mean (SD) | BED Week 8, $n$ = 31, Mean (SD) | HC Week 8, $n$ = 14, Mean (SD) | BED Change Cohen's $d$ ES (95% CI) |
|---|---|---|---|---|---|
| BE Frequency (Days/Week) | 4.3 (1.2) | – | 1.3 (1.0)[a] | – | 1.6 (1.3–2.4) |
| CGI-S | 4.5 (0.7) | – | 1.8 (0.9)[a] | – | 1.1 (1.8–3.2) |
| EDE-Q Global | 4.7 (1.0) | 2.1 (1.0)[b] | 2.9 (1.1)[a] | – | 1.1 (1.1–2.2) |
| B-LOCES Total | 28.3 (3.2) | 9.5 (2.4)[b] | 15.0 (5.4)[a] | – | 5.7 (1.6–3.0) |
| BES Total | 49.4 (5.1) | 22.4 (4.0)[b] | 33.8 (9.1)[a] | – | 9.2 (1.1–2.2) |
| BES Behavioral | 28.3 (2.7) | 12.8 (2.5)[b] | 19.1 (5.5)[a] | – | 5.9 (1.0–2.1) |
| BES Em-Cog | 21.2 (3.0) | 9.6 (1.7)[b] | 14.7 (4.0)[a] | – | 3.9 (1.1–2.2) |
| BMI | 27.8 (4.7) | 23.0 (2.7)[b] | 26.5 (4.8)[a] | 23.2 (2.3) | 1.19 (0.4–1.1) |
| Mean FD | 0.18 (0.06) | 0.17 (0.08) | 0.15 (0.04)[a] | 0.16 (0.04) | 0.6 (0.2–1.0) |

Network-based statistics for longitudinal change are based on paired-sample $t$ tests using time 2 completers only.

BED, binge-eating disorder; BES, Binge Eating Scale; B-LOCES, Brief Loss of Control Over Eating Scale; BMI, body mass index; CGI-S, Clinical Global Impressions-Severity; EDE-Q, Eating Disorders Examination Questionnaire; Em-Cog, emotional-cognitive; ES, effect size; FD, framewise displacement; HC, healthy control.

[a]Denotes significant change from week 0 to week 8 in the BED group, $p < .05$.

[b]Denotes significant group difference between the BED and HC groups at week 0, $p < .05$.

ES = 1.60). This effect remained significant after controlling for baseline severity ($t_{59}$ = −10.24, $p < .001$). Eight participants achieved remission (i.e., <1 binge per week; cf. DSM-5), 22 reduced to mild BED (1–3 binges per week), and 1 remained at moderate BED severity (4–7 binges per week). There was a significant reduction in BMI in the BED group (but not control group) from week 0 to week 8 ($t_{30}$ = 7.81, $p < .001$, ES = 1.40). Attrition from week 0 to week 8 was not associated with age, BMI, or baseline BE frequency.

## Eight Weeks of LDX Was Associated With Widespread Changes in Whole-Brain FC

FC was reduced in a subnetwork of 632 connections between 183 regions with LDX treatment (familywise error–corrected $p$ = .002, ES = 1.06). The networks with the largest proportion of change (relative to network size) in this subnetwork were within-network changes in the SMN (20%), ECN (12%), and DMN (6%) and between the DMN and ECN (18%) and the DMN and LN (6%). The right-side panel of Figure 1A highlights these networks, showing the largest proportion of affected connections of total connections (normalized proportion, accounting for differences in network size) in the upper right triangle. The lower left triangle shows the connections with the strongest statistical change ($t$ values).

A significant subnetwork of 329 connections between 151 regions was also identified where FC increased with LDX treatment (familywise error–corrected $p$ = .032, ES = 1.06). The networks with the largest proportion of change (relative to network size) in this subnetwork comprised connections between the DMN and subcortical network (9%), SMN and ECN (5%), and SMN and SN (5%) (Figure 1B, right upper triangle).

There were no increases or decreases in FC in the HC group between time points ($p$ = .69 and $p$ = .17, respectively).

A significant time × group interaction for in-scan motion ($t_{43}$ = 2.74, $p$ = .009) was observed, which could indicate that reduced scan motion occurred as part of the effect of LDX treatment; thus, analyses without scan motion as a covariate are included in the Supplement.

## Changes in DMN-LN, DMN–ECN, and ECN–SC Connectivity Were Associated With Symptom Change

Within the reduced connectivity subnetwork, there were no significant correlations with change in normalized BE frequency.

The clinical measure that was most associated with BE frequency was the B-LOCES total score ($r$ = 0.82, $p < .001$; BES, $r$ = 0.73, $p < .001$; Eating Disorders Examination Questionnaire, $r$ = 0.55, $p < .001$). There were associations between greater reduction in B-LOCES total score (better clinical outcome) and a smaller reduction in connectivity between the DMN and LN ($r$ = −0.468, $p$ = .008) and the ECN and subcortical network ($r$ = −0.498, $p$ = .004) (Figure 2).

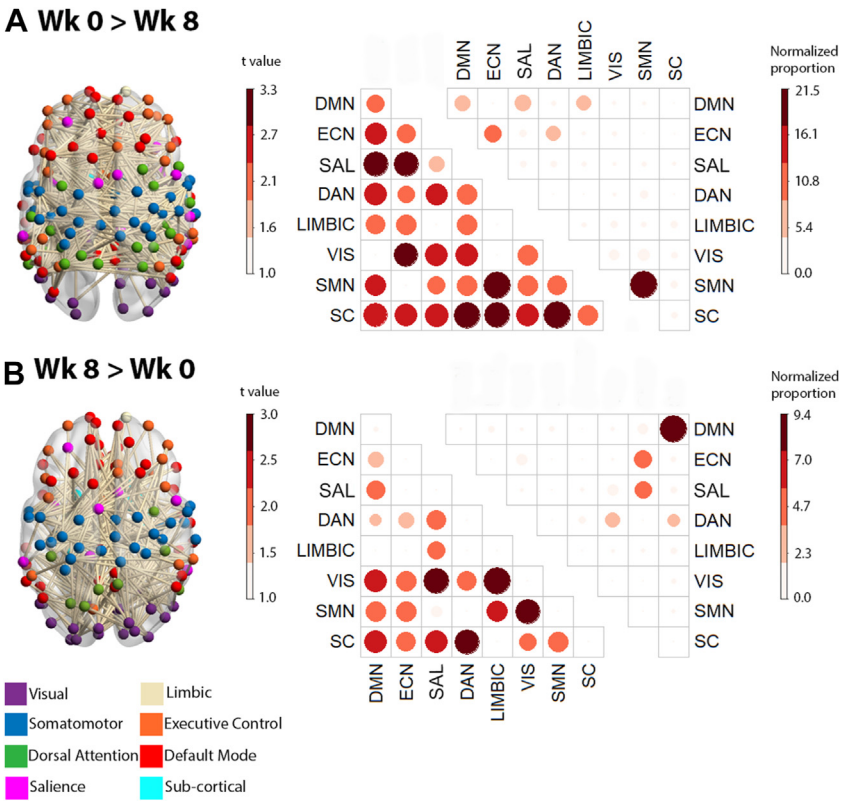


**Figure 1.** Longitudinal functional connectivity changes due to lisdexamfetamine dimesylate treatment in the binge-eating disorder group. Panel **(A)** shows reduction from baseline (unmedicated) to week 8 (medicated). Panel **(B)** shows increase from baseline to week 8. (Left) A visualization of the significant subnetwork, with node colors representing the 7 canonical resting-state networks and weighted by $t$ values. (Right) A heat map showing the mean $t$ values of edges within the network-based statistic component for each canonical network (lower triangle) and the proportion of edges in each network after accounting for differences in network size (i.e., normalized proportion) (upper triangle). DAN, dorsal attention network; DMN, default mode network; ECN, executive control network; SAL, salience network; SC, subcortical; SMN, somatomotor network; VIS, visual network.

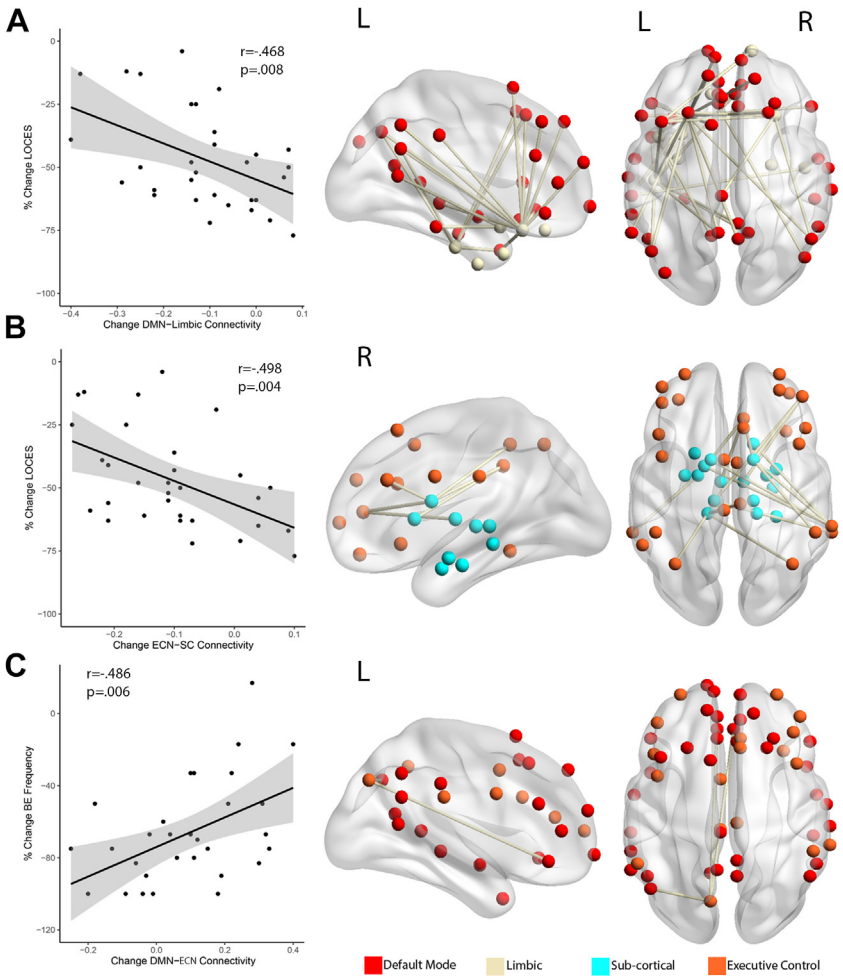


**Figure 2.** Associations between changes in clinical symptom measures and intranetwork mean connectivity in individuals with binge-eating (BE) disorder after lisdexamfetamine dimesylate treatment. Change in mean connectivity (week 8–week 0) is calculated from 37 default mode network (DMN)–limbic connections, 17 executive control network (ECN)–subcortical (SC) connections, and 3 DMN-ECN connections, shown on the brain image with connecting edges. L, left; B-LOCES, Brief Loss of Control Over Eating Scale; R, right.

Within the increased connectivity subnetwork, there was a positive association between greater reduction in BE frequency (better clinical outcome) and a smaller increase in connectivity between the DMN and ECN ($r$ = 0.486, $p$ = .006) (Figure 2). It should be noted that these correlations did not survive false discovery rate correction for multiple comparisons ($q < .002$).

Individual connections contributing to the mean networks are listed in the Supplement.

## Networks Associated With Improved Clinical Outcome Were Not Impaired at Baseline and Became More Different From Control Participants With Treatment

At baseline, there were no significant differences between the BED and HC groups in the mean connectivity between the DMN and LN ($t_{43}$ = 1.96, $p$ = .057, ES = 0.60) or the ECN and the subcortical network ($t_{43}$ = 0.58, $p$ = .564, ES = 0.18) within the LDX reduced connectivity subnetwork or in DMN-ECN connectivity within the LDX increased connectivity subnetwork ($t_{43}$ = 1.77, $p$ = .083, ES = 0.54).

At week 8, there was no significant difference between the BED and HC groups in the mean connectivity between the DMN and LN ($t_{43} = -1.81$, $p$ = .077, ES = 0.55); however, mean ECN–subcortical network connectivity was significantly lower in the BED group than the HC group ($t_{43} = -2.46$, $p$ = .018, ES = 0.75). Within the LDX increased connectivity subnetwork, default–executive control connectivity was significantly higher in the BED group than in the control group at follow-up ($t_{43}$ = 4.14, $p < .001$, ES = 1.26) (Figure 3).

To explore the notion of normalization further, a whole-brain connectivity comparison was conducted using NBS between the HC and BED groups at baseline and week 8. Only 10 of 229 connections that differed between groups at baseline remained different at follow-up. There were 170 new connections with differences in FC between the HC and BED groups at week 8 (following LDX treatment) (see the Supplement for details).

## No Subnetwork Was Identified at Baseline That Could Predict Treatment Response to LDX

Connectivity at baseline did not predict the degree of treatment response using normalized change in BE frequency,

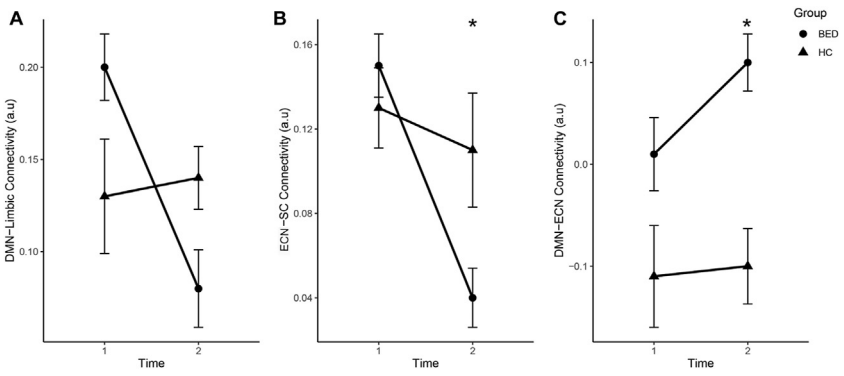


**Figure 3.** Mean connectivity of binge-eating disorder (BED) and healthy control (HC) groups at baseline (week 0) and week 8 for the mean network connections associated with improved clinical outcome. Panel **A** shows default mode network (DMN) - limbic network connectivity, panel **B** shows executive control network (ECN) - subcortical (SC) connectivity, and panel **C** shows DMN - ECN connectivity. Asterisk indicates significant group difference at that time point, $p < .05$. a.u., arbitrary unit.

B-LOCES scores, or BES total scores. Change in these clinical measures was also not associated with the baseline connectivity of the networks that were associated with change in clinical outcomes.

## DISCUSSION

To our knowledge, this study is the first to use comprehensive data-driven analyses to examine the functional brain network mechanisms underlying LDX efficacy in people with BED. Ninety-seven percent of participants experienced remission or a reduction to mild BED during the 8-week LDX trial. Widespread neural FC changes occurred in these participants, with changes in 3 network pairs—DMN to LN, ECN to subcortical network, and DMN to ECN—associated with improvements in clinical outcomes. There was minimal overlap between the connectivity of nodes associated with improvement by LDX treatment and those in which the BED group differed from the control group, suggesting that this medication does not act by normalizing aberrant connectivity. This study highlights that in addition to the previously identified targets for treatment in BED (i.e., reward and inhibitory control), connectivity with the interoceptive network (DMN), which allows the individual to be aware of/understand their body's internal state, is also involved in reducing the core symptom of loss of control over eating.

Previous work has focused predominantly on the role of the reward network in BED (12,13). While we did not use an explicit reward network, many of the regions that we labeled as limbic overlap with this traditional reward network. More than half of the DMN-limbic connections that were associated with clinical outcome were between default mode regions and a single left lateral orbitofrontal cortex region (Brodmann area 47) (Table S1). This area has previously been implicated in reward learning, specifically in encoding the predicted value of cues (25). Motivationally salient food cues bias our attention and may strain inhibitory control processes for people with BED, thereby enabling binge episodes (26). Therefore, one plausible mechanism by which LDX is effective in reducing loss of control over eating is through dampening the salience of reward-predictive cues. Thus, LDX may act as a neuromodulator, enhancing the person's ability to regulate and modify reward-driven behaviors, thereby reducing the likelihood of losing control over eating, which then may drive reduction in BE episodes.

The change in connectivity between the DMN and LN was associated with the self-reported B-LOCES rather than BE frequency. This may be due to the greater range and sensitivity of the former scale relative to BE frequency (1–7 days). Furthermore, because subjective loss of control over eating is the aspect of BED that is associated with distress, this outcome measure may be best for capturing broader clinical improvement (27,28). The results also support current shifts in diagnostic understanding, i.e., that loss of control is the salient feature of BE in the ICD-11 diagnostic scheme although it has not yet been recognized in the DSM scheme (29,30).

The DMN is mostly active during rest and plays a central role in mind-wandering and interoception (31). Typically, it is suppressed during activity within task-positive networks (such as the ECN and LN), i.e., they are anticorrelated. The default mode interference hypothesis proposes that difficulties with cognition may occur when there is insufficient suppression of the DMN during goal-oriented processes (32). Consistent with this, LDX reduced connectivity and led to greater anticorrelation between the DMN and LN. However, within the group, the individuals who had smaller reductions in this connectivity experienced better clinical outcomes. In contrast, there was a group-level increase in DMN-ECN connectivity after LDX treatment. Again, within the group, individuals with the smallest change in connectivity experienced better clinical outcomes. These findings seem counterintuitive because we had expected individuals who demonstrated more prominent neural changes in response to LDX to have the best clinical outcomes. This highlights the complex nature of neural networks and their response to pharmacotherapy in producing behavioral change. Importantly, the finding of clinical change being correlated with change in DMN-ECN connectivity was a measure that was the average of only 3 connections, and not all regions within a network will function in the same manner. Replication is required to shed light on this counterintuitive finding. Positron emission tomography may be another tool that could provide useful information to help us understand interactions between neurotransmitter receptor availability at baseline and follow-up, drug dose, and clinical outcomes.

Individuals with the best treatment response maintained greater subcortical modulatory control over the ECN. These systems are complex, with the drug itself and any subsequent weight loss both potentially contributing to increased

dopamine levels and striatal dopamine $D_2$ receptor availability (33,34). Notably, changes in ECN-subcortex connectivity were not associated with change in BMI in the current study. The bilateral posterior caudate and left anterior and dorsoposterior thalamus, both rich in $D_2$ receptors, were key regions contributing to the ECN-subcortex connectivity change that was associated with clinical outcome. Corticostriatal connections play a critical role in goal-directed behavior, with the posterior caudate involved specifically in cognitive aspects of determining appropriate actions to obtain a desired outcome (35). As such, it is logical that changes in circuitry that underlie goal-directed behavior may be associated with changes in a sense of control over eating.

Whole-brain comparisons between the BED and control groups show that LDX ameliorated a significant amount of somatomotor dysconnectivity. This is supported behaviorally by a reduction of in-scanner motion in the BED group while medicated. This increased in-scanner motion in unmedicated individuals with BED highlights an interesting effect of the disorder that has not previously been reported, but also a methodological challenge for future studies. Connections that differed between the HC and BED groups at baseline were generally not those that were related to improved clinical outcomes after LDX treatment; there were only 3 significant connections that overlapped between the diagnostic group and medication analyses. Similarly, an 8-week course of LDX did not normalize aberrant connectivity in individuals with BED. Rather, LDX seemed to activate change in other networks, which enabled the desired behavioral and cognitive change. While we typically assume that neural connections that differ from control participants at baseline must be responsible for the clinical symptoms observed, studies of other psychiatric disorders have also found a dissociation between neural signatures relating to diagnosis versus prognosis or medication effects (22). This highlights the benefits of conducting whole-brain, data-driven analyses for determining the therapeutic mechanisms of treatments.

We previously demonstrated that individuals in this cohort with higher impulsivity experienced greater response to LDX (8). However, in this study, we were not able to identify a connectomic signature that predicted treatment response to LDX in BED. Other clinical, social, and biological factors may prove more effective in predicting treatment response.

The widespread nature of neural changes suggests that the therapeutic mechanism of action for LDX in BED goes beyond homeostatic appetite suppression. However, future research is needed to better disentangle the contribution of effects that LDX has on appetite, reward sensitivity, and cognitive control. Control of eating is regulated by several systems, which include homeostatic (hypothalamus), attention (including parietal and visual cortices), emotion (amygdala), cognitive control (prefrontal cortex), and reward (36). These results build on previous findings to help provide a basis for theoretically driven seed-based analyses to dissociate specific systems. This has potential clinical implications because triggers for BE may differ between individuals, and LDX may be optimal for people whose BE is driven by one or more specific predispositions, e.g., high levels of impulsivity or reward dependence.

This study has several strengths and limitations. The whole-brain, data-driven approach provides a good overview of the mechanisms of LDX and can contribute to the formation of theoretical models and hypothesis-driven analyses. Common comorbidities were not excluded from this sample, thus enhancing ecological validity; however, it will be important for future studies to examine whether mechanisms of LDX vary based on comorbid conditions and explore the effects of LDX on depression and anxiety severity. Our control participants were not BMI matched to the BED group participants, which may affect conclusions regarding the normalization of aberrant networks. Higher BMI has been associated with sensitization of the brain's SN, highlighting the fact that weight may affect brain function and connectivity (37). We did not find any associations between change in FC and change in BMI, suggesting that our connectivity results were not driven by change in weight. However, we cannot rule out weight change as a contributing factor. Finally, despite being the largest neuroimaging study to date to examine LDX in BED, the sample size in the current study was relatively modest. Associations between connectivity and clinical symptom change did not survive stringent multiple comparison corrections, which may be due to lack of power for the ESs observed. The fact that these results occurred within prehypothesized networks enhances our confidence in their veracity (14); however, replication is required.

While psychotherapies are the gold standard for treating BED, approximately 40% of treated individuals remain symptomatic (38). Therefore, it is important that we explore how other interventions, such as LDX, fit into the treatment landscape. LDX acts rapidly to reduce BE frequency, impulsivity, and obsessive cognitions in people with BED (5). As shown by the current research, these changes occur in concert with changes to neural circuitry related to reward, executive functioning, and interoception. These neural, cognitive, and behavioral changes suggest that augmenting psychotherapy with LDX may help facilitate engagement in treatment, particularly during the early phases. Future research is required to determine whether combining LDX with psychotherapy would enhance treatment outcomes, and if so, for whom.

Identifying the neural mechanisms by which LDX attenuates BE symptoms may guide the development of more refined and tolerable therapeutics. We identified key networks involved in the treatment effect of LDX in BED. Importantly, some networks that were implicated were beyond the typically studied reward and appetite networks. This work provides rich grounds for future work to replicate and explore brain network mechanisms.

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KRG, SLF, ST, PJH, and MRK designed the study protocol. KRG, GH, JY, AWH, and MRK collected the data. KRG, IAB, and MSK conducted neuroimaging analyses. KRG drafted the manuscript, and all authors contributed to editing and approving the final manuscript.

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## ARTICLE INFORMATION

From the Brain Dynamics Centre, Westmead Institute for Medical Research, The University of Sydney, Westmead, New South Wales, Australia (KRG, IAB, GH, JY, SLF, AWH, MSK, MRK); InsideOut Institute, University of Sydney, Sydney Local Health District, Sydney, New South Wales, Australia (KRG, ST); School of Psychology, University of New South Wales, Sydney, New South Wales, Australia (IAB); Department of Radiology, Westmead Hospital, Sydney, New South Wales, Australia (SLF); Specialty of Psychiatry, Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia (AWH); Centre for Research into Adolescents' Health, University of Sydney, Sydney, New South Wales, Australia (SC, MRK); Adolescent and Young Adult Medicine, Westmead Hospital, Sydney, New South Wales, Australia (SC, MRK); Translational Health Research Institute, School of Medicine, Western Sydney University, Sydney, New South Wales, Australia (PJH); Mental Health Services, Camden and Campbelltown Hospitals, South Western Sydney Local Health District, Sydney, New South Wales, Australia (PJH); and Clinical Psychology Unit, School of Psychology, University of Sydney, Sydney, New South Wales, Australia (ST, MRK).

MSK and MRK contributed equally to this work as joint senior authors.

Address correspondence to Kristi Griffiths, Ph.D., at Kristi.griffiths@sydney.edu.au.

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