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Neural mechanisms of acceptance-commitment therapy for obsessive-compulsive disorder: a resting-state and task-based fMRI study

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Abstract

Background. There is growing evidence for the use of acceptance-commitment therapy (ACT) for the treatment of obsessive-compulsive disorder (OCD). However, few fully implemented ACT have been conducted on the neural mechanisms underlying its effect on OCD. Thus, this study aimed to elucidate the neural correlates of ACT in patients with OCD using task-based and resting-state functional magnetic resonance imaging (fMRI).

Methods. Patients with OCD were randomly assigned to the ACT ($n = 21$) or the wait-list control group ($n = 21$). An 8-week group-format ACT program was provided to the ACT group. All participants underwent an fMRI scan and psychological measurements before and after 8 weeks.

Results. Patients with OCD showed significantly increased activation in the bilateral insula and superior temporal gyri (STG), induced by the thought-action fusion task after ACT intervention. Further psycho-physiological interaction analyses with these regions as seeds revealed that the left insular–left inferior frontal gyrus (IFG) connectivity was strengthened in the ACT group after treatment. Increased resting-state functional connectivity was also found in the posterior cingulate cortex (PCC), precuneus, and lingual gyrus after ACT intervention Most of these regions showed significant correlations with ACT process measures while only the right insula was correlated with the obsessive-compulsive symptom measure.

Conclusions. These findings suggest that the therapeutic effect of ACT on OCD may involve the salience and interoception processes (i.e. insula), multisensory integration (i.e. STG), language (i.e. IFG), and self-referential processes (i.e. PCC and precuneus). These areas or their interactions could be important for understanding how ACT works psychologically.

Introduction

Acceptance-commitment therapy (ACT) is a psychological intervention that applies six interrelated therapeutic processes to the creation of psychological flexibility, namely: acceptance, cognitive defusion, contact with the present moment, self-as-context, values, and committed action (Luoma, Hayes, & Walser, 2017). Being part of a larger group of acceptance- and mindfulness-based therapies (Hayes, Strosahl, & Wilson, 2011a) or the 'third wave' of cognitive behavioral therapy (CBT) (e.g. Hayes, 2004; Hayes, Villatte, Levin, & Hildebrandt, 2011b), ACT possesses many distinctive theoretical and practical features (Flaxman, Blackledge, & Bond, 2011).

First, ACT is based on relational frame theory, which holds that human behavior can be dominated by linguistic relational frames without direct experience. This connection to basic behavioral principles has created a unique and empirically based model of human functioning. Thus, ACT is fundamentally transdiagnostic (Flaxman et al., 2011). Second, unlike conventional CBT, ACT assumes that thoughts do not need to change for overt behavior to change and emphasizes on valued life even with some psychological distress than on symptom reduction. Technically, ACT uses very few cognitive challenging and restructuring; it tends to undermine problematic reasoning in many contexts. Instead, ACT focuses on the activation of value-congruent observable behavior (Ciarrochi & Bailey, 2008; Flaxman et al., 2011). Third, ACT also differs from mindfulness. From an ACT perspective, mindfulness is an emergent quality of four processes: acceptance, defusion, contact with the present moment, and self-as-context (Hayes et al., 2011a). Mindfulness is also seen in the service of potentiating valued, goal-directed action, which is the explicit function of defusion in ACT, rather than as a method of stress reduction or to facilitate decentering (Gillanders et al., 2014).

Accordingly, ACT offers a new paradigm for understanding obsessive-compulsive disorder (OCD) and has been employed to establish its efficacy as a standard treatment (Abramowitz, Blakey, Reuman, & Buchholz, 2018; Twohig et al., 2010). Obsessional thoughts are regarded as the product of excessive cognitive fusion, in which literal content is entangled with internal experiences such as thoughts and feelings. These thoughts can engender unnecessary contingencies of experiential avoidance in the form of compulsive behaviors or avoidance, which aims to avoid unwanted internal experiences (Abramowitz et al., 2018). More specifically, cognitive fusion is an overlapping yet broader concept than thought-action fusion (TAF), which is one of the major dysfunctional beliefs in OCD that thoughts and outcomes or actions are linked (Reuman, Buchholz, Blakey, & Abramowitz, 2017). In fact, cognitive fusion is correlated with TAF (Lee & Lee, 2021) as well as obsessive-compulsive (OC) symptoms (Reuman et al., 2017; Xiong et al., 2021). It added significant explanatory power, especially in the symptom dimension of unacceptable thoughts (Reuman et al., 2017; Reuman, Buchholz, & Abramowiz, 2018). At this point, TAF could serve an important bridging role in the study of ACT. Based on this premise, a TAF induction task would be a good candidate for functional magnetic resonance imaging (fMRI) task to measure both TAF that underlies OC symptoms and cognitive fusion/experiential avoidance in ACT.

Until date, only a few studies have explored the neural mechanisms of ACT. All participants in these studies were patients with chronic pain. In an fMRI study, those who had completed ACT showed decreased activation during pain in the middle frontal gyrus, inferior parietal lobule, insula, cingulate gyrus, and superior temporal gyrus (STG) (Aytur et al., 2021). Two other studies discovered that following the ACT intervention, key networks in the brain that are involved in self-reflection, emotion, and cognitive control were less active both within and between them (Meier et al., 2020; Smallwood, Potter, & Robin, 2016). However, previous studies were preliminary in nature: two studies had a single group of nine participants (Aytur et al., 2021; Meier et al., 2020) and one study had four and three participants in the ACT and control groups, respectively (Smallwood et al., 2016). Similarly, there are a few well-controlled and fully implemented ACT studies exploring its neural mechanism. To the best of our knowledge, no research has examined the neural correlates of ACT for OCD.

Thus, this study aimed to investigate the neural correlates of ACT in patients with OCD using task-based and resting-state (rs) fMRI. First, hemodynamic changes were measured using a modified TAF induction task following ACT intervention. Our previous study using the same task characterized lower functional connectivity (FC) of the mid-cingulate cortex–insula in patients with OCD compared to the healthy controls (Lee et al., 2022). Changes in the insula and its associated network have been noted in recent meta-analyses of both mindfulness-based interventions and CBT (Pico-Perez et al., 2022; Young et al., 2018). Therefore, we hypothesized that following ACT intervention, the aforementioned psychological treatments would all have a common effect of altering the insula and its associated network. Second, although predicting the effect of cognitive defusion is difficult due to fewer observations following ACT intervention, several experimental fMRI studies (Creswell, Way, Eisenberger, & Lieberman, 2007; Koenigsberg et al., 2010; Wang et al., 2022) suggest greater activation in prefrontal cortices, including the ventrolateral prefrontal cortex (vlPFC), and lesser activation in subcortical areas as potential neural correlates of the ability to disengage from autopilot in a process similar to defusion, which thus reduces the emotional impact of verbal activity (Fletcher, Schoendorff, & Hayes, 2010). Additionally, we hypothesized that changes in these areas would involve defusing affect from language processing. Third, we predicted that alterations in the cingulate gyrus would be found in rsFC analysis. Previous studies have frequently cited the effects of mindfulness and meditation on the subregions of the cingulate (Zsadanyi, Kurth, & Luders, 2021) in terms of local activity (Fox et al., 2014, 2016) and connectivity (Sezer, Pizzagalli, & Sacchet, 2022). A few previous studies have reported decreased posterior cingulate cortex (PCC) activity following ACT intervention (Smallwood et al., 2016) and decreased FC between the anterior cingulate cortex (ACC) and other networks (Aytur et al., 2021) in patients with chronic pain.

Methods

Participants

The current study was part of our randomized controlled trial (RCT) to evaluate the effectiveness of the ACT in treating OCD. A total of 118 participants (age 18–40 years) were screened after referral through subway advertisements, the online boards of OOO National University, and psychiatric clinics at OOO National University Hospital. Eighty-seven participants were selected for in-person interviews. The participants were interviewed and diagnosed by two psychiatrists using the Structured Clinical Interview for DSM-5 Disorders-Clinical Version; only those with OCD as the primary diagnosis were included. Patients with acute medical or neurological, mental retardation, a history of brain trauma, or other major psychiatric illnesses were excluded. Thus, 72 patients with OCD, who met the study criteria, were randomly assigned equally to the ACT and wait-list control (WLC) groups, with a block randomization (block size = 4). An 8-week group-format ACT program was provided to the ACT group. Detailed information about our entire RCT including the program was described in our paper (Lee, Choi, & Lee, 2023).

Among 72 participants, 48 participated in the fMRI experiment and completed the MR scan and psychological measurements twice at intervals of 8 weeks. After excluding six patients ($n = 4$ for head motion, $n = 2$ for new diagnosis), all 42 patients (21 per group) were included in the final analysis (online Supplementary Fig. S1). All participants agreed to participate in the experiments with informed consent. This study was approved by the Institutional Review Board of OOO National University Hospital (2021-04-032).

Psychological measures

Symptom measures

OCD symptoms were evaluated using the self-report version of the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS; Baer, 1994; Seol, Kwon, & Shin, 2013) and the Obsessive-Compulsive Inventory-Revised (OCI-R; Foa *et al.* 2002; Woo, Kwon, Lim, & Shin, 2010). Depressive symptoms were measured using the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961; Lee & Song, 1991).

Process measures

The Acceptance and Action Questionnaire-II (AAQ-II; Bond *et al.* 2011; Heo, Choi, & Jin, 2009) was used to measure the psychological inflexibility and experiential avoidance emphasized in ACT. The Acceptance and Action Questionnaire for Obsessions and Compulsions (AAQ-OC; Jacoby, Abramowitz, Buchholz, & Reuman, 2018) was used to evaluate the experiential avoidance related to OC symptoms. We translated the AAQ-OC for this study. The Cognitive Fusion Questionnaire (CFQ; Gillanders *et al.* 2014; Kim & Cho, 2015) was used to assess cognitive fusion. The Thought–Action Fusion Scale (TAFS; Lee & Lee, 2021; Shafran, Thordarson, & Rachman, 1996) was used to measure the degree of TAF belief.

TAF induction fMRI task

Before brain imaging, the authors received the name of two close and neutral persons each (CPs and NPs, respectively) from the participants, and these names were applied in the fMRI TAF paradigm (Fig. 1a). The participants were asked to look at the name (CP or NP) on the screen and think about the person for 4 s (name phase). They were instructed to silently read the displayed negative statement (NS), such as 'I hope that the person (CP or NP) will soon be in a car accident,' for 10 s (sentence phase). After the sentence phase, they were asked to rate their feelings about the sentence on a Likert scale from 1 (very little) to 4 (very much) using the button box, within 4 s (evaluation phase). After the evaluation, a fixation cross was displayed on the center of the screen for 10 s (resting phase). Thus, the modified TAF experiment included two conditions, NS/CP and NS/NP, with eight statements for each. The NS/CP and NS/NP conditions were represented in a pseudorandomized order, and the paradigm lasted for 7 min 28 s (= 28 s for each trial × eight NSs × CP and NP conditions). The TAF paradigm was developed and modified for fMRI experiments (Lee et al., 2019) based on an original experiment (Rachman, Shafran, Mitchell, Trant, & Teachman, 1996).

Image acquisition

All magnetic resonance images were obtained on a 3.0 Tesla GE SIGNA architect scanner (GE Healthcare, Milwaukee, WI,

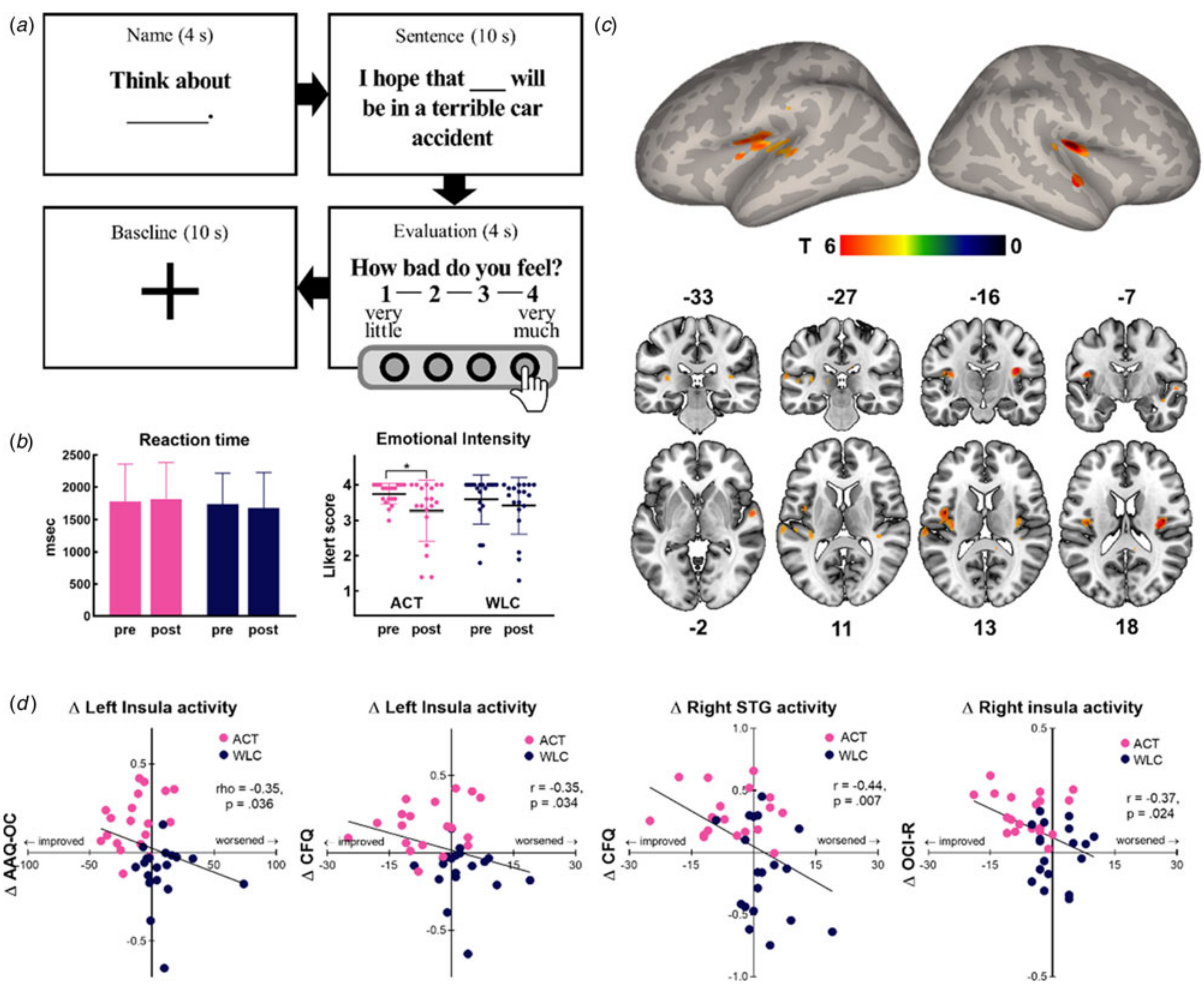

Figure 1. Changes in task-based brain activation after acceptance-commitment therapy (ACT) intervention a. The fMRI paradigm for thought-action fusion (TAF) induction. b. Results of behavioral data, showing a significant decrease in emotional intensity in the ACT group. c. Changes in task-based brain activation after ACT intervention [false discovery rate (FDR) corrected, $p < 0.05$; minimum cluster size, $k = 10$]. d. The correlation of brain activity with the Acceptance and Action Questionnaire for Obsessions and Compulsions (AAQ-OC), Cognitive Fusion Questionnaire (CFQ), and Obsessive-Compulsive Inventory-Revised (OCI-R) across the entire participants.

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USA) with a 48-channel head coil. Functional brain images were obtained using a T2*-weighted gradient echo planar imaging pulse sequence with a field of view (FOV) = 23 cm, matrix size = 64 × 64, slice thickness = 4 mm, repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle = 90°. Structural images were obtained using a 3D brain-volume image pulse sequence with an FOV = 25.6 cm, matrix size = 256 × 256, slice thickness = 1 mm, TR = 8.5 ms, TE = 3.2 ms, flip angle = 12°.

Imaging data analysis

Preprocessing

All functional images were preprocessed using Statistical Parametric Mapping (SPM12; http://www.fil.ion.ucl.ac.uk/spm) and Computational Anatomy Toolbox (CAT12; https://www.nitrc.org/projects/cat). The preprocessing steps included slice timing, realignment, co-registration, segmentation, normalization to the Montreal Neurological Institute coordinate space, and smoothing (full width at half maximum = 6 mm). The head motion and outlier factors were detected according to the intermediate setting using Artifact Detection Tools (https://www.nitrc.org/projects/artifact_detect), and removed in the first-level analysis.

Task-evoked fMRI

Individual task-evoked functional images were analyzed based on the general linear model with the TAF task design matrix and temporal high-pass filtering (0.008 Hz) was applied. Changes in task-evoked brain activity were analyzed in the NS/CP and NS/NP conditions. Furthermore, a generalized psycho-physiological interaction (PPI) was conducted to investigate task-modulated connectivity on significant brain activation regions using the CONN toolbox (https://web.conn-toolbox.org).

Resting-state fMRI

Independent component analysis (ICA) was carried out on rs-fMRI data to examine the alteration of spontaneous activity in the functional brain network using the CONN toolbox. All rs-fMRI data were subjected to temporal band-pass filtering (0.008–0.09 Hz). In the first-level analysis, G1 fast ICA (Hyvarinen, 1999) and GICA3 back-reconstruction (Calhoun, Adali, Pearlson, & Pekar, 2001) were applied to estimate independent spatial components and separation of spatial components at the individual level. The subject-level reduction dimension applied was 64, the target component number was 57, and the average dimension for individual component factors was calculated using the minimum description length criteria (Li, Adali, & Calhoun, 2006). Our previous research suggested that components of the default mode network (DMN) and salience network (SN) were important for processing the TAF stimuli (Lee et al., 2019, 2022). Therefore, alterations in interconnectivity within the DMN and SN as well as among the large-scale networks (Yeo et al., 2011) were evaluated in the resting-state fMRI analyses.

Group analysis

The group-by-time interaction of brain activity (ACT *v.* WLC × pre- *v.* post-treatment) was determined by a 2-by-2 full factorial analysis of variance (ANOVA). Additionally, a paired *t* test comparing pre- and post-treatment was carried out within the ACT group to evaluate the alterations in brain activity brought about by the treatment. The task-evoked activation maps were thresholded at $p < 0.05$, with false discovery rate (FDR) correction across the whole brain. The gPPI and ICA maps were thresholded at cluster-level FDR corrected, $p < 0.05$, and voxel threshold uncorrected, $p < 0.001$ (Worsley et al., 1996). All regions of interest (ROIs) were created as spheres with a 4 mm radius located at the maximum T value of multiplied significant regions in both post-treatment minus pre-treatment and group-by-time interaction maps. The REX toolbox was used to extract all beta and connectivity values (https://www.nitrc.org/projects/rex).

Statistical analysis

The Jeffreys's Amazing Statistics Program (JASP; https://jasp-stats.org) was used for normality test, *t* test between the demographic and clinical characteristics of the groups, task performance, and the correlation analysis between the changes in brain and psychological measures. Depending on assumptions of normality, the correlation coefficient was calculated using Pearson or Spearman correlation analysis, controlling out the depressive score. Because the TAFS and AAQ-OC, the two process measures, had an outlier (>3 standard deviations, SDs), only the results that maintained significance even after removing outliers were reported as meaningful.

Results

Baseline demographic and clinical characteristics of the participants

The mean (±S.D.) age of the ACT and WLC groups was 24.9 ± 5.1 and 26.5 ± 6.4 years, respectively. No group differences were found in age, sex, education level, or duration of illness. The participants reported moderate to severe OC symptoms measured by Y-BOCS at baseline, with no group differences (22.5 ± 7.0 and 23.5 ± 6.8 for the ACT and WLC groups, respectively). There were no group differences in the other baseline symptoms and process measures. Table 1 presents the detailed demographic and clinical characteristics.

Effects of ACT on clinical symptoms, process measures, and behavioral task

Online Supplementary Table S1 presents the effects of the ACT on clinical and process measures. All variables in the repeated measures ANOVA except BDI showed significant group-by-time interactions (all p values < 0.05). Within the ACT group, paired t tests showed significant reductions in OC symptoms post-treatment ($t = 3.9$, $p < 0.001$ for Y-BOCS; $t = 3.7$, $p = 0.001$ for OCI-R). The ACT group also showed significant decreases post-treatment in all ACT-related process measures, such as the AAQ-OC ($t = 4.0$, $p < 0.001$), CFQ ($t = 3.5$, $p = 0.002$), and TAFS ($t = 2.4$, $p = 0.029$) scores, except for the AAQ-II scores. However, after treatment, the WLC group did not show any positive changes in outcome measures. Independent t test revealed significant group differences in the post-treatment scores of Y-BOCS ($t = 2.4$, $p = 0.024$) and AAQ-OC ($t = -3.7$, $p < 0.001$).

There were significant changes in the TAF induction task performance following the ACT intervention (Fig. 1b). In the

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Table 1. Baseline demographic, clinical and pharmacological characteristics of patients with obsessive-compulsive disorder (mean ± S.D.)

Characteristics	ACT $N = 21$	WLC $N = 21$	Statistics t/χ^2	Statistics p
Age, years	24.9 ± 5.1	26.5 ± 6.4	−0.9	0.387
Male/female, N	12/9	15/6	0.9	0.520
Level of education, years	14.4 ± 1.6	14.3 ± 1.7	0.3	0.783
Age at onset of OCD, years	19.2 ± 5.8	19.4 ± 5.8	−0.1	0.914
Duration of illness, years	5.7 ± 4.3	7.4 ± 4.6	−1.2	0.219
Medication status				
No medication	14	9	3.4	0.064
Medication[a]	7	13		
Symptom measure				
Y-BOCS	22.5 ± 7.0	23.5 ± 6.8	−0.5	0.919
OCI-R	25.7 ± 12.1	26.7 ± 12.7	−0.3	0.318
BDI	13.3 ± 7.5	16.6 ± 10.3	−1.2	0.567
Process measure				
AAQ-II	34.3 ± 9.8	33.1 ± 10.0	0.4	0.878
AAQ-OC	59.6 ± 17.0	53.0 ± 17.3	1.3	0.219
CFQ	34.9 ± 9.3	30.7 ± 11.4	1.3	0.239
TAFS	27.4 ± 17.2	25.4 ± 20.0	0.4	0.436

ACT, acceptance-commitment therapy; WLC, wait-list control; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; OCI-R, Obsessive-Compulsive Inventory-Revised; BDI, Beck Depression Inventory; AAQ-II, -OC, Acceptance and Action Questionnaire-II, -for Obsessions and Compulsions; CFQ, Cognitive Fusion Questionnaire; TAFS, Thought-Action Fusion Scale.
[a]Among those who took the medication, all participants remained on the same regimen during the study except for 3 in the WLC who had minor changes in dosage or deletion of previous medication, or addition of new adjunctive drugs.

repeated measures ANOVA, there were no significant group-by-time interactions. However, paired t test revealed that mean (±S.D.) emotional intensity induced by negative statements in the task significantly decreased in the ACT group (3.7 ± 0.3 v. 3.3 ± 0.9, $t = 2.3$, $p = 0.031$) whereas no significant change was found in the WLC group (3.6 ± 0.7 v. 3.4 ± 0.8, $t = 1.4$, $p = 0.182$). Furthermore, both groups showed no significant change in reaction times between pre- and post-treatment.

Effects of ACT on TAF-related brain activity

Four participants (two in each group) were excluded from the analyses due to no (two participants) or unreliable (two participants) behavioral responses on the TAF task during fMRI. An unreliable response was defined as a 'very little' response of emotional intensity over 3 SDs to all NSs at the pre-treatment scan.

Significant group-by-time interactions were observed in the bilateral insula, STG, and middle cingulate gyrus in the NS/CP condition (online Supplementary Table S2). In the post-hoc paired t test, the ACT group demonstrated a significant increase in activity in the bilateral insula and STG posttreatment (FDR-corrected $p < 0.05$) (online Supplementary Tables S3, S4, Figs 1c and 4). The NS/NP condition had no significant findings, and the results with an uncorrected statistical threshold are shown in online Supplementary Fig. S2.

Correlation analyses for all participants revealed that increases in the left insular activity were significantly related to decreases (i.e. improvements) in the AAQ-OC (rho = −0.346, $p = 0.036$) and CFQ ($r = -0.349$, $p = 0.034$) scores. In addition, right insular and STG activity was related to the reduction in the OCI-R ($r = -0.371$, $p = 0.024$) and CFQ ($r = -0.436$, $p = 0.007$), respectively. Detailed results are presented in online Supplementary Table S5 and Fig. 1d. However, no significant correlation was found within the ACT group only (online Supplementary Table S6).

Effects of ACT on TAF-related brain connectivity

PPI analyses revealed that the connectivity between the left insular–left inferior frontal gyrus (IFG) showed a significant group-by-time interaction (FDR-corrected $p < 0.05$) (online Supplementary Table S2), and this connectivity was strengthened after the ACT intervention (FDR-corrected $p < 0.05$) (Figs 2a and 4). Moreover, changes in the left IFG connectivity were significantly related to changes in the CFQ ($r = -0.375$, $p < 0.05$) scores for all participants (online Supplementary Table S5 and Fig. 2b). However, no significant correlations were found within the ACT group (online Supplementary Table S6).

Additionally, there was no significant task-dependent FC from other seed regions, such as the right insula and bilateral STG.

Effects of the ACT treatment on resting brain connectivity

No significant changes were found in interconnectivities among large-scale networks (online Supplementary Fig. S3), and within the SN, therefore, the analyses within the DMN were described. The components of the DMN were selected based on the results of correlation for matching ($r = 0.22$). Within the DMN, the

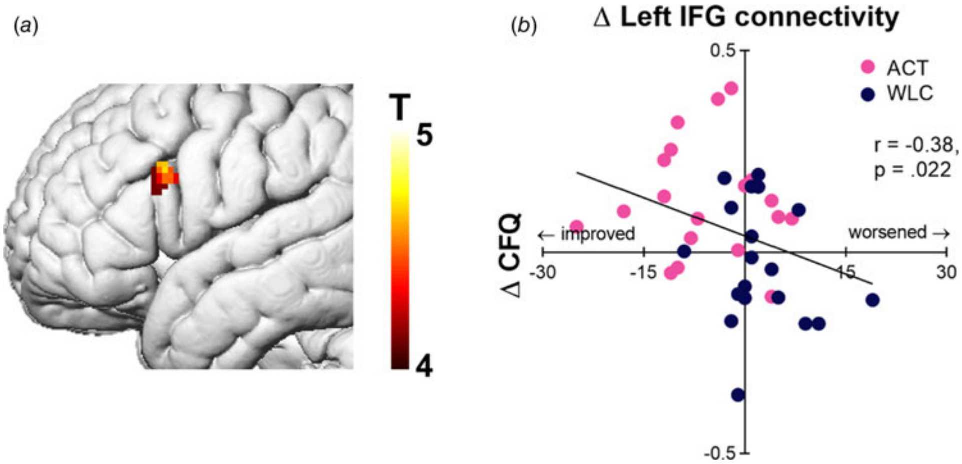

Figure 2. Psycho-physiological interaction (PPI) results for task-based brain activation after acceptance-commitment therapy (ACT) intervention a. PPI analysis revealed a significant increase in functional connectivity between the left insula (seed; $x = -46$, $y = -4$, $z = 14$) and left inferior frontal gyrus (IFG; $x = -40$, $y = 16$, $z = 24$) [false discovery rate (FDR) corrected, $p < 0.05$; minimum cluster size, $k = 10$]. b. Correlation between the functional connectivity of the left insula and left IFG and the Cognitive Fusion Questionnaire (CFQ) across the entire participants.

bilateral PCC, left lingual gyrus, and bilateral precuneus demonstrated a significant group-by-time interaction; in addition to these regions, connectivity in the middle temporal gyrus was enhanced after ACT intervention in paired *t* test (FDR-corrected $p < 0.05$) (online Supplementary Table S2, S4, Figs 3a and 4).

Correlation analyses for all participants showed that changes in right PCC connectivity were related to the reduction in AAQ-OC (rho = −0.488, $p = 0.001$) and CFQ ($r = -0.322$, $p = 0.040$) scores; the precuneus connectivity change was associated with changes in TAFS scores (rho = −0.321, $p = 0.041$) (online Supplementary Table S5 and Fig. 3b). However, no significant correlations were found within the ACT group (online Supplementary Table S6).

Overall, all regions that were significant in the analyses above are depicted together in Fig. 4.

Discussion

The current fMRI study demonstrated that patients with OCD show significantly increased activation in the bilateral insula and STG in the TAF task after ACT intervention. Further PPI analyses with these regions as seed ROIs revealed that the left insular–left IFG connectivity was strengthened post-treatment in the ACT group. Differences in rsFC were also found in the PCC, precuneus, and lingual gyrus post-treatment in the ACT group. Some of these regions demonstrated significant correlations with ACT process measures, although our whole group correlation analyses could not confirm that these changes were ACT specific.

Increased TAF task-induced activation of the insula and STG

Bilateral activation of the insula

In this study, patients with OCD demonstrated robustly increased activation of the bilateral insula during the TAF task after an 8-week ACT intervention. Mindfulness-based interventions, overlapping with the ACT, have revealed increased insular cortex activity as the most consistent longitudinal effect (Young et al., 2018). The insula is considered to support interoceptive awareness, such as attending to bodily sensations in the present moment (Marchand, 2014; Tang et al., 2010). Interestingly,

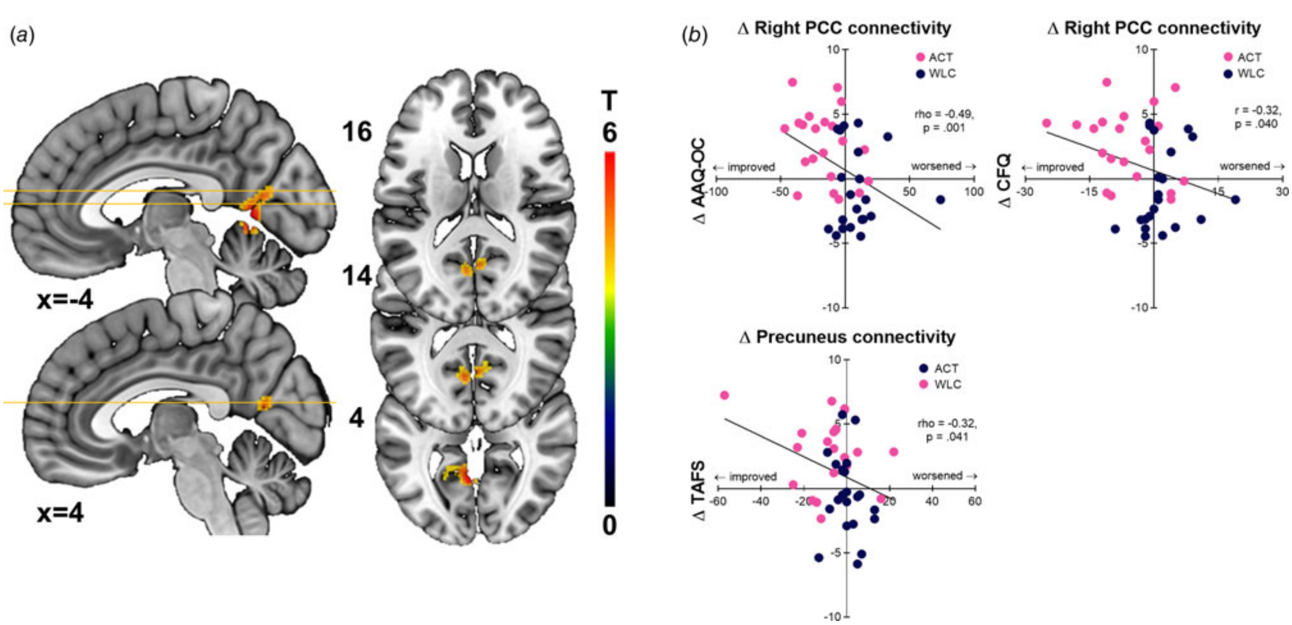

Figure 3. Brain regions showing differences in resting state (rs) functional connectivity (FC) after acceptance-commitment therapy (ACT) intervention a. Brain regions showing differences in rsFC between pre- and post-treatment in the ACT group [false discovery rate (FDR) corrected, $p < 0.05$; minimum cluster size, $k = 10$]. b. The correlation of resting-state FC with the Acceptance and Action Questionnaire for Obsessions and Compulsions (AAQ-OC), Cognitive Fusion Questionnaire (CFQ), and Thought-Action Fusion Scale (TAFS) across the entire participants.

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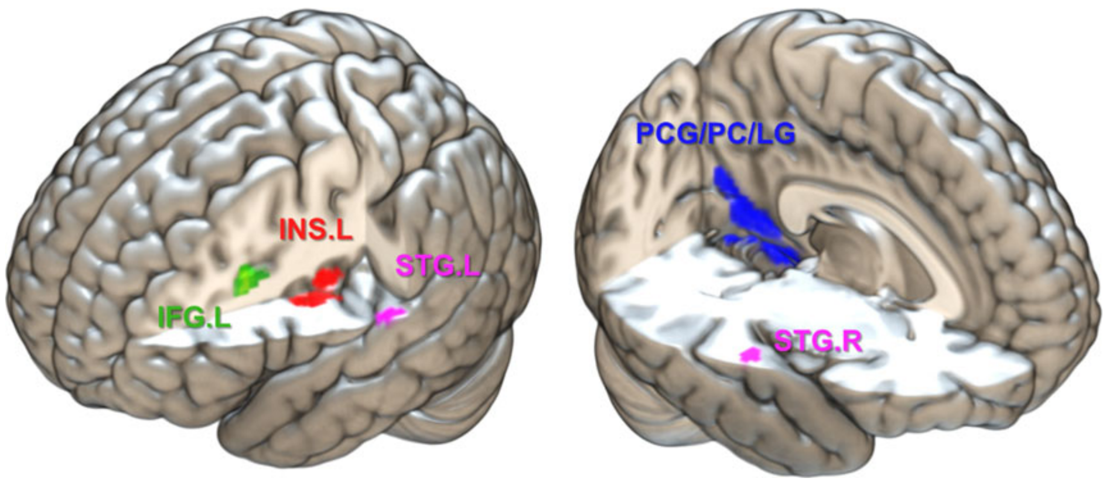

Figure 4. Summary of neural correlates of the effect of acceptance-commitment therapy (ACT) Thought-action fusion (TAF) task-based signal changes in the bilateral insula (INS, red) and superior temporal gyrus (STG, pink), strengthened the psycho-physiological interaction between the left insula (seed) and left inferior frontal gyrus (IFG, green), and the resting-state functional connectivity between the bilateral posterior cingulate gyrus (PCG), precuneus (PC), and left lingual gyrus (LG) (in blue).

change in insula activity is closely related to the efficacy of CBT (Pico-Perez et al., 2022) and psychotherapy (Marwood, Wise, Perkins, & Cleare, 2018). A recent meta-analysis of task-based fMRI studies demonstrated that brain response in a network of regions involved in salience and interoception processing, encompassing fronto-insular and fronto-limbic cortices was associated with a positive CBT outcome (Pico-Perez et al., 2022). Based on our results on the neural effect of ACT, the strengthening of insula-related networks may be a pivotal region of trans-therapeutic mechanisms across different psychosocial treatments.

Our finding of insula activation also had OCD-specific implications. The right insula was the only region correlated with the symptom measure of OCI-R in this study. Anxiety has been linked to altered interoceptive sensitivity, which focuses on insular cortex dysfunction (Paulus & Stein, 2006). Patients with OCD exhibit impaired interoception, which may be maintained during the course of CBT (Schultchen, Zaudig, Krauseneck, Berberich, & Pollatos, 2019), and are differentially associated with rsFC of the insula (Eng et al., 2022). Specifically, in OCD, disgust sensitivity has been focused on as a specific psychological vulnerability for the development of contamination-based OCD (Mataix-Cols et al., 2004; Olatunji, Tart, Ciesielski, McGrath, & Smits, 2011). Another type of OCD associated with abnormal interoception appears in individuals who focus on the physical sensations (i.e. sensation of skin contact with clothing or swallowing saliva), rather than primary disturbing thoughts. Although we consider the increase in insular activation to be the 'typical' response to ACT and mindfulness intervention, future studies may need to investigate the differential hemodynamic changes in these OC symptom dimensions after ACT.

Bilateral activation of STG

The STG is the site of language processing and higher-order multimodal integration. It also regulates amygdala activity (Muller, Cieslik, Turetsky, & Eickhoff, 2012), reflecting its association with social cognition. Considering that our task stimuli were socio-affective written sentences, increased STG activation in the ACT group compared to the WLC group may help the patients with OCD reinterpret negative statements in other contexts, such as an experimental situation rather than interpreting them literally. This may modulate affective arousal via effective connectivity to the amygdala (Kohn et al., 2014). Abnormalities in the STG have also been found with other neuroimaging modalities, such as decreased white matter volume (Goncalves et al., 2017b) and increased FC in the right STG (Peng et al., 2014), and increased fractional anisotropy in the bilateral STG (Shaw et al., 2015; Yoo et al., 2007).

Task-specific increase in the relationship between the left insula and left IFG

Another novel finding of the current study was the increase in left IFG connectivity with the seed region, left insula, during the TAF induction task. Similar findings have been observed in previous experimental studies, such as the mere labeling of affective stimuli (Creswell et al., 2007) and the effect of distancing to regulate emotional responses to aversive images (Koenigsberg et al., 2010). As these evidenced, Fletcher et al. (2010) proposed a pattern of increased IFG activity (in their paper, vlPFC) and decreased amygdala activity as possible neural correlates of cognitive defusion. The current study is the first to report IFG involvement after full-scale and real ACT intervention in OCD.

In this study, an increase in left insular–left IFG connectivity correlated with a decrease in cognitive fusion scores. Defusion refers to processes that undermine the domination of language primarily by becoming aware of the process of thinking itself and being able to become aware of thoughts, emotions, and memories as passing events rather than 'things' that are literally true or false (Fletcher et al., 2010). We also assume that the left IFG may play a significant role in processing cognitive defusion because of its fundamental role in human thinking. Specifically, first, the left IFG performs the actual integration of information from speech and gestures, resulting in a new representation with abstract and non-literal meaning (Steines, Nagels, Kircher, & Straube, 2021). Second, the left IFG is actively involved in both declarative and procedural systems. The anteroventral IFG is associated with the encoding, selection, and retrieval of declarative memories (Ullman, 2004) while the posterior-dorsal left IFG processes rule-governed grammar and automatized procedural memories

(Ullman, 2016). Third, the IFG is the most distinguished prefrontal region for cognitive control processes in cognitive reappraisal, which regulates emotions by manipulating semantic representation of affective scenarios (Buhle et al., 2014; Ochsner, Silvers, & Buhle, 2012). Taken together, these functions are thought to be involved in suppressing the excessively learned, rule-based literal interpretation, distinguishing formal and arbitrary stimulus properties, and forming a new response (i.e. representation), which focus on the process of contextual thinking as mere private events passing by (Ciarrochi & Bailey, 2008).

Changes in the rs connectivity of DMN

After ACT, participants reported increased intrinsic connectivity of the PCC and precuneus within the DMN. The DMN is activated during passive resting rather than goal-oriented tasks (Raichle & Snyder, 2007) and is related to self-referential processing, focusing on one's own feelings or thoughts (Whitfield-Gabrieli & Ford, 2012), or autobiographical memory processing (Svoboda, McKinnon, & Levine, 2006). The PCC and precuneus appear to be important functional hubs of the posterior part of the DMN (Washington & VanMeter, 2015), which involves episodic memory, self-referential processing, and theory of mind (Barnett et al., 2021).

Previous studies using rs-fMRI have reported alterations in the DMN in patients with OCD. The magnitude of FC in the PCC and precuneus was reduced in these patients (Cheng et al., 2013). Patients with OCD and their siblings also demonstrated a decrease in FC in the PCC (Peng et al., 2014). In addition, in a task fMRI study, the OCD patients showed difficulties in reducing DMN activation during non-rest emotional conditions (Goncalves et al., 2017a). In an electroencephalogram study using the TAF task, a group with high OC symptoms showed greater precuneus activity, which was correlated with the TAF scores (Jones & Bhattacharya, 2014). In our previous study using the TAF paradigm, overengagement of the SN-DMN connection was found to be related to an increased TAF response (Lee et al., 2022). In summary, (1) decreased PCC/precuneus FC during resting and (2) aberrant functional involvement of the DMN during the task have indicated alterations in the DMN in OCD. Therefore, increased PCC/precuneus FC during rs-fMRI could be related to the therapeutic effects of the ACT in patients with OCD. This is corroborated by the associations between increased PCC/precuneus FC and decreased scores of psychological inflexibility measures.

DMN dysfunction could be a transdiagnostic factor, as it has been found in many psychiatric illnesses including schizophrenia, major depressive disorder, and OCD (Doucet et al., 2020). Since DMN is involved in several mental activities (Kleckner et al., 2017), it is challenging to determine how its increased FC affects ACT. However, among the various mental activities related to PCC/precuneus function, we believe that improved self-referential processing (Koban, Gianaros, Kober, & Wager, 2021) may help patients with OCD to view themselves contextually. The PCC/precuneus function can be modulated by the self-relatedness of stimuli (Knyazev, Savostyanov, Bocharov, Levin, & Rudych, 2020) and whether the self-judgment is context-dependent or -independent (Martial, Stawarczyk, & D'Argembeau, 2018). Further fMRI studies on ACT can clarify our preliminary suggestions.

There are several limitations to our study. First, the results of a task-based fMRI study largely depend on the task. Although we believe that our paradigm could sensitively evaluate the response to verbal stimuli, which is associated with ACT effects (i.e. acceptance and cognitive defusion), it could hardly measure other ACT components, such as value and committed action. In the same context, it is challenging to draw any conclusion about the involvement of the prefrontal cortex or ACC, which have been well elucidated as an effect of CBT, since our task is simple and passive. It is necessary to create novel challenges to identify more specific ACT constructs. Second, although two-thirds of the ACT group was drug-naïve or drug-free during the study period, we could not completely exclude the possibility that medication affected our results. Third, unlike AAQ-OC, AAQ-II did not correlate with neural correlates in this study. This observation may support that AAQ-II does not capture experiential avoidance as it specifically relates to obsessional thoughts (Jacoby et al., 2018) and underestimates treatment effects concerning psychological flexibility (Benoy et al., 2019). Fourth, although the WLC group is frequently employed as a control (Öst, Havnen, Hansen, & Kvale, 2015), this study cannot demonstrate the specific characteristics of ACT that set it apart from CBT. Further studies are required to directly compare CBT and ACT in order to find an answer to the question. Fifth, our study cannot find any significant correlation results within the ACT group. Although we used changes between post-intervention and pre-intervention, the correlation results cannot be determined as ACT specific. Furthermore, the significance of our correlation results disappeared after multiple comparison corrections, and some of the significant results in uncorrected levels decreased after removing outliers or controlling baseline symptoms. Therefore, it is important to carefully assess our preliminary correlation results, and it is preferable to use them as insightful cornerstones for subsequent research.

In conclusion, this is the first fMRI study to report the neural mechanisms underlying ACT in OCD treatment. Our task-based and rs-fMRI analyses suggest that the therapeutic effect of ACT on OCD may involve the salience and interoception process (i.e. insula), multisensory integration (i.e. STG), language (i.e. IFG), and self-referential processes (i.e. PCC and precuneus). These areas or their interactions may be relevant to the psychological processes of ACT, in particular acceptance, contact with the present moment, self-as-context, and cognitive defusion.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723001769

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Conflict of interest. The authors declare none.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Declaration of Helsinki of 1975, as revised in 2008

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