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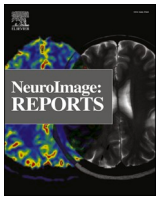

Acceptance and Commitment Therapy and white matter plasticity in individuals with subclinical depression and psychotic experiences: A Randomised Controlled Trial

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A B S T R A C T

Background: Research indicates that Acceptance and Commitment Therapy in Daily Life (ACT-DL) is effective in reducing symptoms of depression, anxiety and psychosis. During adolescence, vulnerability to psychopathology peaks, creating a window for early interventions, while white matter development is ongoing. This study aims to examine microstructural white matter after ACT-DL intervention in youngsters with mild psychopathology.

Methods: Forty-five individuals with mild psychopathology were randomly allocated to ACT-DL (n=20) or topic discussion control (TD, n=25). Symptomatology was assessed with the Community Assessment of Psychic Experiences (CAPE), Montgomery–Åsberg Depression Rating Scale (MADRS) and the Experience Sampling Method (ESM). Diffusion Weighted Imaging (DWI) and network-connectivity parameters were obtained and compared before and after the intervention/control condition. Interactions between microstructural white matter change and condition were examined in models of CAPE positive symptoms and ESM subclinical psychotic experiences (PE) and negative affect (NA) levels.

Results: ACT-DL, compared to TD, was associated with changes on subclinical depressive and psychotic symptom levels. There was no significant change in DWI or network connectivity in either condition and no significant difference between both conditions. In the model of NA, several regional interactions between condition and network measures were significant, but stratification per condition provided no significant associations. There were no significant interactions between DWI or network connectivity parameters and condition in the models of the CAPE positive symptoms, MADRS and PE.

Conclusions: The findings suggest that behavioral (symptom) changes are more sensitive to a five-week psychological training than microstructural white matter changes which did not show significant changes over time.

1. Introduction

During adolescence white matter development is ongoing and it is during this critical phase that youngsters could acquire subclinical depressive and psychotic symptoms. Structural dysconnectivity has been shown in adults with depression (Tae et al., 2018) and psychotic disorder (Parnanzone et al., 2017) and this may even be detectable in early stages of the illness (Kochunov and Hong, 2014). This raises the question to what degree such structural alterations can be impacted by non-pharmacological training. It seems that even slight but powerful everyday life experiences can affect brain structure as demonstrated by an interventional study on a complex whole-body balancing task in which participants learned new balancing skills which resulted in decreased FA in prefrontal white matter (Taubert et al., 2010). How white matter contributes to learning is unclear, but it is plausible that changes in impulse transmission through spatially distinct, but functionally related regions, may be an important aspect of learning (Zatorre et al., 2012). There is limited understanding about psychological

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training/therapy effects on white matter plasticity.

Magnetic Resonance Imaging (MRI) studies in humans have shown that white matter volume steadily increases from childhood into adolescence, accompanied by changes in Diffusion Weighted Imaging (DWI) parameters, suggesting that maturation of axons/myelin sheaths represents an ongoing (developmental) process (Paus et al., 2008). DWI may be a valuable instrument to detect structural white matter dysconnectivity alterations over time and describe white matter plasticity using parameters such as Fractional Anisotropy (FA; white matter 'integrity'), Axial Diffusivity (AXD; number of axons), Radial Diffusivity (RAD; a measure for water diffusion perpendicular to the white matter tracts and a potential marker for myelin content) and Mean Diffusivity (MD; free water movement) (Kochunov and Hong, 2014). A longitudinal study in healthy students showed decreased RAD and AXD accompanied by increased FA after a 4-week integrative body-mind training compared to a relaxation training (Tang et al., 2012). Furthermore, in the longer term, experienced mindfulness meditators showed increased FA compared to meditation-naïve controls (Kang et al., 2013; Luders et al., 2011; Laneri et al., 2015).

So-called third generation psychotherapies for mental disorders are on the rise, of which Acceptance and Commitment Therapy (ACT) (Hayes et al., 2006) has been extensively investigated. In ACT, it is the aim to increase psychological flexibility which allows to adapt behavior integrated in daily living and it teaches the participant to relate to thoughts, feelings and sensations that can be present (Hayes et al., 2006). Within ACT there are values to aim at and one can focus on important goals in their personal life in order to stimulate and increase the individuals' psychological flexibility (Hayes et al., 2006). Randomized controlled trials (RCT) have shown an Hedges's g effect size of 0.68 in favor of the ACT intervention in samples with clinical anxiety, depression and psychotic disorder compared against a mix of waiting list, treatment as usual and active treatment options (Ost, 2008). In a meta-analysis on individuals with psychotic disorder, ACT has shown to reduce positive psychotic symptoms and duration of hospitalization (Cramer et al., 2016), while other studies showed that ACT reduced distress related to hallucinations in psychotic disorder (Gaudiano et al., 2010) and improved emotional functioning reducing the number of crisis contacts after treatment (White et al., 2011). The application of ACT in individuals with major depression with psychotic features led to sustained improvements in depressive and psychotic symptoms as well as improved psychosocial functioning (Yildiz, 2020). Moreover, some evidence suggests efficacy of ACT in reducing subclinical depressive symptomatology in student populations via both regular therapy programs (Bohlmeijer et al., 2011; Burckhardt et al., 2016; Danitz and Orsillo, 2014; Fledderus et al., 2012; Jeffcoat and Hayes, 2012; Levin et al., 2014) as well as online interventions (Lappalainen et al., 2015; Rasanen et al., 2016). Taken together, ACT has the potential to be a cost-efficient, feasible and acceptable intervention (van Aubel et al., 2020).

In the current study, we hypothesized that ACT-DL could result in white matter plasticity. Plasticity is operationalized by an FA increase, unchanged AXD and decrease in RAD in response to the ACT-DL intervention compared to the control condition. This was investigated from a whole-brain perspective, with the use of global and regions of interest (ROI) measures. In addition, network connectivity alterations as a result of the ACT-DL intervention were examined and it was hypothesized that the intervention would change network efficiency and clustering, although it remains exploratory in which direction it would change.

Furthermore, symptom changes over time were examined in relation to microstructural regional changes. As individuals were selected on the basis of their level of subclinical positive psychotic and depressive symptoms, the effect of the psychological intervention on these two symptom dimensions were a priori selected as most relevant. Lastly, it was explored whether the DWI parameter change was predictive of symptom change, and whether these associations were different between the two conditions. The ACT-DL condition might result in DWI parameter change compared to the control condition, potentially predicting the symptom changed caused by ACT-DL.

2. Methods

This RCT took place at Maastricht University, The Netherlands, as part of the Smartscan project (Dutch Trial Register Number: NTR3808). DWI was part of the project to examine longitudinal white matter alteration in response to the active intervention/control condition. The study comprised individuals who were between 16 and 25 years of age with subclinical PE and subclinical depressive symptoms recruited in the Maastricht area and neighbouring cities. The criteria for inclusion were defined using the Community Assessment of Psychic Experiences (CAPE (Stefanis et al., 2002)) positive symptom subscale frequency score $\geq$10 and/or the positive symptom subscale distress score $\geq$2. Participants with a Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) score $\geq$10 were also included.

Exclusion criteria were current psychological or psychiatric treatment, significant need for care (as discussed in consensus meetings with a psychiatrist), left-handedness and a history of neurological disorder (e.g., severe brain injury with unconsciousness, meningitis, migraine or epilepsy). Other exclusion criteria were MRI contraindications (e.g., diabetes and claustrophobia, ferromagnetic implants) or (suspected) pregnancy in female participants.

The local medical ethics committee approved this study according to the declaration of Helsinki. All participants gave written informed consent in person and additional parental consent was required for participants <18 years of age.

2.1. Trial design

The RCT was designed to have equal random block allocation to the conditions, independently from the researchers via a research coordinator ensuring blinding. All analyses were done with blinding for conditions and this was revealed after the analyses. The procedure was executed via preparation of lists using a computer-generated random table. A total of 55 participants were included in the RCT and were assigned to a group to attend weekly training sessions during five weeks (on average 5 participants per training group).

The active and control condition were, respectively, the Acceptance and Commitment Therapy in Daily Life (ACT-DL) and a topical discussion group (TD). The ACT-DL condition followed a specific protocol during five weekly meetings according to the guidelines (Hayes and Smith, 2015). The ACT-DL and TD conditions are described in more detail in the supplementary materials and a previous paper on the intervention study (van Aubel et al., 2020).

2.2. Demographics and symptom measures

The level of education was defined by the accomplished level of education ranging from 0 (no education) to 7 (master degree or higher). Lifetime cannabis and other drug use was assessed with the Composite International Diagnostic Interview (CIDI) section L (WHO. Composite International Diagnostic Interview, 1990). Lifetime use was calculated by multiplying the frequency per week times the number of weeks of used.

Subclinical symptom scores were constructed using the self-report CAPE questionnaire over four dimensions; positive (range 0–60), negative (range 0–42), depressive (range 0–24) and total (range 0–126), with both frequency and distress scores calculated per dimension. In addition, the MADRS total score (range 0–60) was used to assess subclinical depressive symptoms (Montgomery and Asberg, 1979). MADRS was administered by trained interviewer, assessing sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts and suicidal thoughts during the last week (Williams and Kobak, 2008).

2.3. ESM data collection and analysis

The Experience Sampling Method (ESM) allows for daily life self-reported assessment of mental states and behaviour using the PsyMate (an electronic device with a touchscreen to store answers). The ESM assessment comprised 40 days of self-monitoring: first, 15 consecutive days before the intervention (baseline), then three days per week during the five week intervention period (self-monitoring and ACT-based exercises) and, lastly, seven days after the intervention. At ten random moments during the day, the PsyMate signalled a beep, at which the ESM questionnaire had to be filled in within 15 min after the beep. Data from baseline and post-intervention were included for analyses if >30% of completed beep questionnaires were available (in the current study >45 out of 150 beep moments (baseline) and >21 out of 70 beep moments (post-intervention), conform earlier work (Delespaul, 1995). Items for assessing subclinical PE in daily life were 'I feel suspicious' and 'I feel unreal'. These items were highly correlated (r=0.87) and therefore averaged and named 'PE-score'. The PE-score per participant was calculated per time point before and after intervention. Similarly, negative affect (NA) was assessed by calculating the average of the items 'Feeling down', 'Feeling insecure', 'Feeling lonely', 'Feeling anxious' and 'Feeling guilty'. NA per participant per time point was assessed before and after intervention. All items were quantified on 7-point Likert scales (ranging from 1=not at all to 7=very).

2.4. MRI acquisition and processing

The MRI scans were acquired on a 3T Siemens Magnetom Prisma system (Siemens, Erlangen, Germany) equipped with a 64-channel head/neck coil at Scannexus, Maastricht, The Netherlands. Anatomical T1-weighted whole brain images were acquired at a 1.0 mm x 1.0 mm x 1.0 mm resolution (repetition time (TR) = 2250 msec, echo time (TE) = 2.21 msec, flip angle = 9°, field of view (FOV) = 256x256, 192 sagittal orientated slices, GRAPPA = 2, no fat suppression, acquisition time (TA) = 5.05 min). Diffusion Weighted Imaging (DWI) scans were acquired at 2 mm x 2 mm x 2 mm resolution using 119 directions (field of view 200 x 200 mm2, TR 7300 ms, TE 49 ms, voxel size 2 x 2 x 2 mm^3, b-value 1000 s/mm^2, 72 slices, no overlap). Total acquisition time was 14m52s. Data were processed in ExploreDTI (Leemans et al., 2009) and provided maps of FA, AXD, RAD and MD per individual dataset. Whole brain tractography and network analyses were conducted using ExploreDTI. The network connectivity-based measures global efficiency, clustering coefficient and local efficiency were calculated using the Brain Connectivity Toolbox (Rubinov and Sporns, 2010). Details on the MRI protocol and processing are provided in the supplementary materials.

2.5. Statistical analyses

2.5.1. Comparison of pre-post CAPE and MADRS scores

While the focus of the current manuscript is on white matter changes in association with subclinical psychopathology, the symptoms changes were also described. See for the descripton of the symptom analyses, the article of van Aubel et al. (Hayes and Smith, 2015). The current analyses include a slightly different sample, for which complete MRI data were available.

Alterations over time were compared between conditions using a multilevel random effects regression model in R, version 3.2 (Team, 2008) as in van Aubel et al. (Hayes and Smith, 2015). The R package "nlme" was used to run the linear mixed-effects models. The confounding variables age, sex, level of education, days between assessment (T0 and T1), lifetime cannabis and other drug use were included. Condition was coded as '1' for the ACT-DL and '0' for the TD condition. Paired sample t-tests were performed to compare the mean CAPE positive frequency/distress and MADRS scores between timepoint T0 (before intervention) and T1 (after intervention) per condition. A p-value < 0.05 was noted as significant.

2.5.2. Comparison of pre-post momentary daily life PE and NA symptom levels

Paired sample t-tests were performed to compare the mean PE and NA scores between T0 and T1 per condition using a multilevel random regression model with ESM symptoms (PE and NA) at T1 as dependent variable and condition as independent variable. Confounders were age, sex, educational level and days between the assessments. Baseline ESM symptom levels were included as a covariate. Details on the white matter statistical approach are provided in the supplementary materials. Since 37 regions were quantified into four white matter measures and compared within five symptom models, a multiple test adjusted p-value of $p<0.00007$ was applied in the DWI models. In the network models 90 regions were quantified into two connectivity models and compared within five symptom models, a multiple test adjusted p-value of $p<0.00006$ was applied.

3. Results

3.1. Participant characteristics

A total of 398 participants were telephone screened, resulting in the inclusion of 89 participants for the study, as shown in Fig. 1. Next, 55 participants were allocated for randomisation (25 ACT-DL and 28 film). In the ACT-DL condition, two participants were unable to attend the weekly sessions and withdrew from the study. Three participants in the ACT-DL condition and two in the film condition were excluded from the analysis due to claustrophobia and excessive movement during the MRI scan. ESM data were incomplete (based on <30% of data availability) for two participants in the ACT-DL-condition and one in the TD-condition. Therefore 45 participants were included in the main analyses. The sample included 20 individuals in the ACT-DL-condition and 25 in the TD-condition. Analyses for NA were conducted in a sample of 30 participants (n=13 in the ACT-DL and n=17 in the TD condition because of missing data for the NA items). This sample is slightly different from a previous sample (van Aubel et al., 2020) based on MRI exclusion (in both conditions two participants had artifacts in the MRI datasets, and one participant had claustrophobia in the ACT-DL condition and were excluded from analysis).

Individuals within the ACT-DL (n=20) and TD condition (n=25) did not differ with respect to age, sex, educational level and subclinical symptom scores at baseline (CAPE subscales and MADRS; see Table 2). There was no difference between groups at baseline on ESM PE. Lifetime cannabis and other drug use were equal in both conditions. The number of days between pre- and post-assessments did not differ between conditions. See Table 1 for an overview of the conditions.

3.2. Training effect (ACT-DL vs. control condition) on symptom change

3.2.1. Associations between condition (ACT-DL vs. TD) and CAPE score

As described in a previous paper (van Aubel et al., 2020), there were no significant associations between condition and CAPE positive symptom frequency/distress score (at T1, corrected for T0) (Table 2).

3.2.2. Within-condition momentary daily life symptom levels

There were no significant differences between T1-T0 in PE-score in the ACT condition (B=0.14, p=0.17) and the TD condition (B=−0.05, p=0.11). There were no significant differences between T1-T0 in NA in the ACT condition (B=0.18, p=0.20), while in the TD condition this was significant (B=−0.20, p=0.02).

3.2.3. Association between condition and ESM momentary daily life symptom levels

The PE-score (at T1, corrected for T0) was significantly higher for the ACT condition than for the TD condition (B=0.33, p=0.03). The NA scores (at T1, corrected for T0) were not significantly different between the two conditions (Table 2).

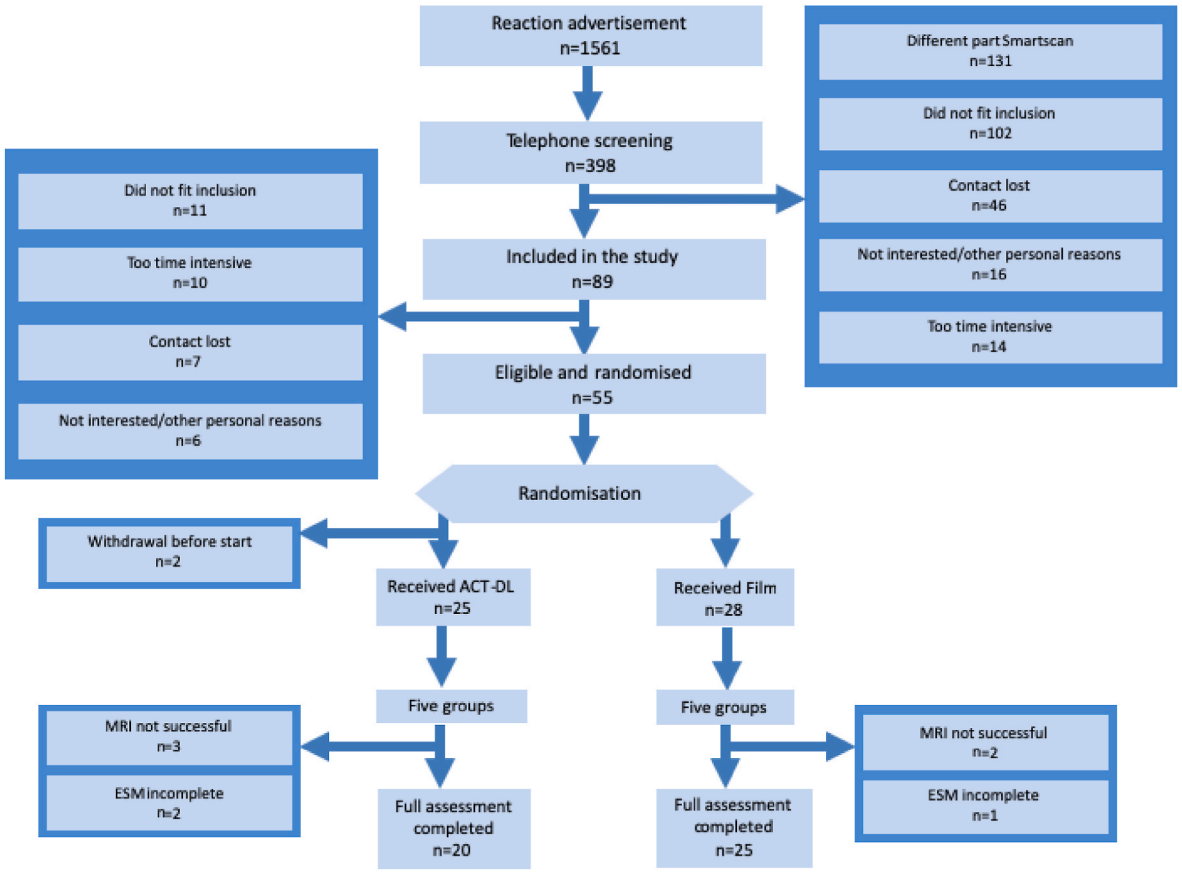

Fig. 1. Overview of the randomized controlled trial (RCT) with both acceptance and commitment therapy in daily life (ACT-DL) and topological film discussion (TD) condition arms. For each phase, the number of withdrawals is provided and classified based on exclusion criteria. ESM; Experience Sampling Method. MRI; Magnetic Resonance Imaging.

Table 1
Participant characteristics for both the ACT-DL and control (TD) condition.

	ACT-DL-condition (n=20)	TD-condition (n=25)
Age (mean (sd))	21.09 (2.56)	21.74 (2.51)
Sex = Female (%)	16 (80.0)	18 (72.0)
Educational level category:		
High school (%)	2 (10.0)	3 (12.0)
Higher education (Bachelor) (%)	16 (80.0)	17 (68.0)
University (Master) (%)	2 (10.0)	5 (20.0)
Days between T0 and T1 (mean (sd))	165.85 (64.59)	168.20 (87.42)
Lifetime cannabis use (mean (sd))	10.50 (64.59)	14.48 (29.57)
Lifetime other drug use (mean (sd))	3.15 (9.21)	15.96 (68.04)

ACT-DL: Acceptance and Commitment Therapy in Daily Life, TD: Topic Discussion, T0: time point before intervention.

Table 2
Symptom scores before (T0) and after (T1) the active and control intervention.

	ACT-DL condition		TD condition			
	T0 Mean (SD)	T1 Mean (SD)	T0 Mean (SD)	T1 Mean (SD)	B	p-value
CAPE positive *frequency score*	3.2 (3.3)	3.4 (3.0)	3.2 (3.0)	3.4 (3.2)	0.38	0.54
distress score	2.8 (3.1)	3.1 (3.4)	3.2 (3.5)	3.4 (4.0)	0.007	0.99
PE-score	1.55 (0.80)	1.82 (1.09)	1.44 (0.57)	1.34 (0.47)	0.41	0.03
Negative Affect	2.23 (0.83)	2.31 (0.96)	2.20 (0.75)	1.96 (0.63)	−0.31	0.24

Life, TD: Topic Discussion, CAPE: Community Assessment of Psychic Experiences. Reported B and p-values are based on multilevel random effects regression models (ACT vs controls on symptom change). PE-score; the average of the two ESM items 'feeling unreal' and 'suspicious mood'.

3.2.4. *Within-condition symptom change (T1-T0)*

The change in symptoms over time per condition showed no significant T1-T0 difference in CAPE positive symptom frequency score in the ACT-DL condition (B=−0.20, p=0.53) and the TD condition (B=−0.16, p=0.56). There was no significant T1-T0 difference in CAPE positive symptom distress score in the ACT-DL condition (B=0.30, p=0.36) or TD condition (B=0.12 p=0.59). There was a significant T1-T0 difference in MADRS score in the ACT-DL condition (B=−5.65, p=0.00020), but not in the TD condition (B=−1.08, p=0.20).

Reported are the mean and standard deviation per symptom score per condition. ACT-DL: Acceptance and Commitment Therapy in Daily

3.3. *Training-effect (ACT vs. control condition) on DWI parameters and network connectivity*

3.3.1. *Whole brain analyses of DWI parameters*

Based on the whole brain analyses in TBSS, the ΔFA, ΔMD, ΔAXD and ΔRAD did not significantly differ between conditions. There were no significant voxels above the threshold of $p<0.05$.

3.3.2. Regional analyses of DWI parameters

The analyses did not reveal any significant interaction between condition and ROI in the models of FA (χ^2=35.39, p=0.50, df=36), AXD (χ^2=34.39, p=0.55, df=36), RAD (χ^2=26.12, p=0.89, df=36) and MD (χ^2=22.91, p=0.96, df=36) at T1, corrected for T0 (Table 3).

3.3.3. Network connectivity analysis

There was no significant association between condition and ΔGE (B=−0.0013, p=0.82). The interactions between condition and ROI in the models of ΔLE (χ^2=2.49, p=0.99, df=90) and ΔCC were not significant (χ^2=5.58, p=0.99, df=90) (Table 3).

3.4. Interactions between DWI parameter change and condition in the models of subclinical depressive and psychotic experience change

3.4.1. CAPE positive symptom frequency and distress score

The whole brain analyses revealed no significant interactions between condition and DWI parameters in the model of CAPE positive symptom score (ΔFA; χ^2=0.83, p=0.36, ΔAXD; χ^2=1.88, p=0.17, ΔRAD; χ^2=2.60, p=0.11, ΔMD; χ^2=3.54, p=0.06, all with df=1) or CAPE positive distress symptom score (ΔFA; χ^2=0.57, p=0.45, ΔAXD; χ^2=1.10, p=0.30, ΔRAD; χ^2=2.01, p=0.16, ΔMD; χ^2=2.15, p=0.14, all with df=1).

The analyses did not reveal any significant interaction between condition and ROI in the models of CAPE positive symptom frequency and distress score (Bonferroni corrected for 740 tests; see supplementary materials: ΔFA in table 1, ΔAXD in table 2, ΔRAD in table 3 and ΔMD in table 4).

3.4.2. MADRS total score

The whole brain analyses revealed no significant interaction between condition and DWI parameters in the model of MADRS total score (ΔFA; χ^2=0.28, p=0.59, ΔAXD; χ^2=0.81, p=0.37, ΔRAD; χ^2=0.53, p=0.47, ΔMD; χ^2=0.87, p=0.35, all with d=1). The regional analyses, corrected for 740 tests, did not reveal any significant interaction between condition and ROI in the models of MADRS total score (see supplementary materials: ΔFA in table 5, ΔAXD in table 6, ΔRAD in table 7 and ΔMD in table 8).

3.4.3. Momentary PE and NA

The whole brain analyses revealed no significant interactions between condition and DWI parameters in the model of PE score (ΔFA; χ^2=1.14, p=0.29, ΔAXD; χ^2=0.72, p=0.40, ΔRAD; χ^2=0.26, p=0.61, ΔMD; χ^2=0.62, p=0.43, all with df=1) and NA score (ΔFA; χ^2=0.97, p=0.32, ΔAXD; χ^2=0.05, p=0.83, ΔRAD; χ^2=1.66, p=0.20, ΔMD; χ^2=1.24, p=0.27, all with df=1). In the regional analyses (corrected for 740 tests), the models of PE and NA (at T1, corrected for T0) showed no significant interaction between condition and change in DWI measures (see supplementary materials: PE; FA in table 5, AXD in table 6, RAD in table 7 and MD in table 8 and NA; FA and AXD in table 9, RAD and MD in table 10).

3.5. Interactions between network connectivity change and condition in the models of subclinical depressive and psychotic experience change

3.5.1. CAPE positive symptom frequency and distress score

There were no significant interactions between condition and ΔGE in the models of CAPE positive symptom frequency (χ^2=0.39, p=0.53, df=1) and distress score (χ^2=0.40, p=0.53, df=1).

Similarly, the whole brain analyses showed no significant interactions between condition and network parameters in the models of CAPE positive symptom frequency (ΔLE; χ^2=0.07, p=0.80, ΔCC; χ^2=0.02, p=0.90, both df=1) and CAPE positive symptom distress score (ΔLE; χ^2=0.49, p=0.48, ΔCC; χ^2=0.39, p=0.53, both df=1). The analyses did not reveal any significant interaction between condition and ROI in the models of CAPE positive symptom frequency and distress score (Bonferroni corrected for 900 tests; see supplementary materials: ΔLE in table 11, ΔCC in table 12).

3.5.2. MADRS total score

The interaction between condition and ΔGE in the model of MADRS total score was not significant (χ^2=1.05, p=0.30, df=1). In the whole brain analyses, no significant interaction was found between condition and network parameters in the model of MADRS total score (ΔLE; χ^2=0.02, p=0.90, ΔCC; χ^2=0.01, p=0.92, both df=1). Regional analyses with the model of MADRS total score (at T1, corrected for T0), showed no significant interactions between condition and ΔLE and ΔCC in any ROI (Bonferroni corrected for 900 tests; see supplementary materials: ΔLE in table 13 and ΔCC in table 14).

3.5.3. Momentary PE and NA

The association between condition and ΔGE in the model of PE-score was not significant (χ^2=2.92, p=0.09, df=1). The whole brain analyses revealed no significant interactions between condition and the other two network parameters (ΔLE and ΔCC) in the models of PE score (ΔLE; χ^2=0.08, p=0.78, ΔCC; χ^2=0.13, p=0.72, both df=1), while the models for NA did not run (singularity error as a result of a lack of variance).

Regional analyses showed that, in the model of PE (at T1, corrected for T0), there were no significant interactions between condition and ΔDWI network measures (ΔLE and ΔCC, corrected for 900 tests) in the ROIs (see supplementary materials: ΔLE in table 13 and ΔCC in table 14). In the model of NA (at T1, corrected for T0) there were significant interactions between condition and ΔLE in the right anterior cingulum: χ^2=24.99, p=0.0005 (df=1), left parahippocampal gyrus: χ^2=23.30, p=0.001 (df=1) and left angular gyrus: χ^2=27.28, p=0.0002 (df=1), (see Supplementary Table 15) and between condition and ΔCC in the left frontal superior medial gyrus: χ^2=18.15, p=0.02 (df=1), left parahippocampal gyrus: χ^2=40.76, p=0.0000002 (df=1), left angular gyrus: χ^2=22.21, p=0.002 (df=1), right paracentral lobule: χ^2=20.50, p=0.005 (df=1) and left caudate: χ^2=18.29, p=0.02 (df=1), after correction for 900 tests (see Supplementary Table 15). Stratification per condition showed no significant associations between NA and ΔLE in the right anterior cingulum: B=1.94, p=0.59, left parahippocampal gyrus:

Table 3
Means and standard deviations per DWI measure before (T0) and after (T1) intervention.

	ACT-DL condition		TD condition			
	T0 Mean (SD)	T1 Mean (SD)	T0 Mean (SD)	T1 Mean (SD)	χ^{2*}	p-value
Fractional Anisotropy	0.58 (0.09)	0.58 (0.09)	0.58 (0.08)	0.58 (0.08)	35.39	0.50
Axial Diffusivity	0.0014 (0.00018)	0.0014 (0.00018)	0.0014 (0.00018)	0.0014 (0.00018)	34.39	0.55
Radial Diffusivity	0.00048 (0.000082)	0.00047 (0.000083)	0.00048 (0.000082)	0.00047 (0.000081)	26.12	0.89
Mean Diffusivity	0.00077 (0.000078)	0.00077 (0.000080)	0.00077 (0.000079)	0.00077 (0.000078)	22.91	0.96
Local efficiency	0.85 (0.048)	0.83 (0.022)	0.86 (0.047)	0.82 (0.019)	2.49	0.99
Clustering coefficient	0.35 (0.049)	0.33 (0.024)	0.35 (0.049)	0.33 (0.023)	5.58	0.99
Global efficiency	0.72 (0.020)	0.71 (0.024)	0.73 (0.018)	0.72 (0.022)	−0.0013	0.82

ACT-DL: Acceptance and Commitment Therapy in Daily Life, TD: Topic Discussion. χ^2 and p-values are derived from multilevel random regression analyses. * For global efficiency, the B-estimate (change per condition; TD to ACT-DL) is provided.

B=−0,58, p=0.85 and left angular gyrus: B=5.30, p=0.06 or between NA and ΔCC in the left frontal superior medial gyrus: B=0.02, p=0.99, left parahippocampal gyrus: B=−0.99, p=0.75, left angular gyrus: B=5.40, p=0.06, right paracentral lobule: B=−1.90, p=0.58 and left caudate: B=1.49, p=0.71, in the TD condition. The models for the ACT-DL condition had not enough variation in NA and ΔCC to be executed.

4. Discussion

There were no significant changes in DWI white matter parameters or network-based measures in either condition, with no significant difference between the two conditions. The randomized application of ACT-DL or TD in emerging adults with subclinical PE and or depressive symptoms yielded higher momentary PE levels after ACT-DL. The CAPE positive symptom frequency and distress scores, MADRS or daily life PE-scores showed no significant interaction with white matter microstructural changes. In the statistical model of NA several regions showed significant interactions between condition and respectively ΔLE and ΔCC. Although the stratification models per condition did not run for the ACT-DL-condition, the TD condition showed no significant associations between NA symptom levels and ΔLE and ΔCC.

4.1. ACT-DL and pre-post intervention symptom change

Results from the current study showed a small, but significant increase in the ESM subclinical PE item (comprising the items 'feeling unreal' and 'suspicious mood') after the ACT-DL intervention compared against the TD condition. Although the baseline scores of the PE items was fairly low and the relevance of a 1.55–1.82 PE score increase on a 1–7 Likert scale is questionable, the small increase in "feeling unreal/mood suspiciousness" may reflect that participants become more aware of their environment during the training (Hayes et al., 2006). In addition, minor daily life stress may be seen as an underlying factor leading to increased PE (Klippel et al., 2017), which can be a temporary effect during psychological training due to increased self-reflection/awareness. Notably, from a symptom-network perspective, feelings of suspiciousness could potentially lead to less 'down feelings' and more 'cheerful and content feelings' in individuals with psychosis and depression (Wigman et al., 2015). It can be speculated that since participants in the ACT-DL intervention may have become more aware and reflective and were able to accept their feelings better, this may have resulted in more positive experiences in daily life. While the momentary PE-score may be more sensitive to subtle changes, as compared to an interview session or questionnaire (Myin-Germeys et al., 2000), the application of ESM to investigate subclinical psychotic symptoms in the general population has not yet been fully explored. The current findings in a relatively small group of individuals with mild levels of psychopathology are tentative and warrant further investigation to provide more definite conclusions.

4.2. ACT and pre-post microstructural white matter change

No significant white matter and network-connectivity changes as a result of the ACT-DL intervention were found in individuals with mild psychopathology. Baseline and follow-up measures were rather close to each other (on average 24 weeks), although white matter plasticity may occur in a period ranging from one day to months. Nevertheless, the possibility that pre- and post-intervention time-points were temporally too close together to detect any alterations related to the ACT-DL intervention cannot be fully excluded. Another explanation for the absence of white matter change over time can be the mild psychopathology levels of this group, i.e., a mean CAPE positive distress score of three and a mean MADRS score 14. Based on the above, it can be tentatively concluded that there is no evidence for microstructural white matter changes in response to a five-week psychological training plus self-monitoring period in individuals with mild psychopathology.

4.3. DWI parameter-symptom associations conditional on intervention and brain region

4.3.1. Subclinical depressive symptoms and DWI/network connectivity

A main effect of condition on white matter changes over time was absent and no significant interactions between condition and white matter measures in the MADRS and NA models were found. Previous literature showed lower FA (compared to healthy controls) in the cingulum bundle, anterior thalamic radiation, posterior limb of the internal capsule and the superior and posterior corona radiata in patients with major depressive disorder (MDD) and suicidal thoughts (Taylor et al., 2015). In addition, decreased FA in the ALIC has been identified in patients with MDD compared to healthy controls (Zhang et al., 2013). The current sample consisted of young individuals with rather mild depressive symptoms as compared to the above mentioned studies. The null findings in the MADRS and NA symptom models from the current study may be explained by the lack of overall changes in ΔFA and rather small effect sizes. Additionally, the NA models had a smaller sample as a result of missing items. This may have resulted in limited variance and replication in a larger sample is required.

The change in network connectivity parameters showed no significant interactions with condition in the models of MADRS. There was some indication for differential associations between NA and local network measures in the two conditions. However, the models stratified per condition did not run for the ACT condition, which precludes adequate interpretation of the significant interactions between condition and network measures in models of NA.

4.3.2. Subclinical psychotic symptoms and DWI/network connectivity

There was no significant interaction between change in DWI measure over time and condition in the models of CAPE positive symptom frequency/distress change. Contrarily, in cross-sectional early stage schizophrenia research, an increase in PANSS disorganized thoughts has been related to an increased RAD and decreased FA located in the corpus callosum (Hummer et al., 2016), while another study showed a positive association between positive schizotypy symptoms and FA (Grazioplene et al., 2016). It needs to be noted that these studies involved participants with higher subclinical symptoms as compared to the current study. Furthermore, the current study aimed at changing the interaction between white matter measures and subclinical symptoms as a result of an ACT-DL intervention. As this is the first time that DWI-symptom associations in relation to psychological training in individuals with emerging psychopathology was investigated, a direct comparison with similar studies was not feasible.

There were no significant interactions between the white matter changes (ΔFA, ΔAXD, ΔRAD and ΔMD) and condition in the model of PE-score change. It was the first time ever to explore the interaction between brain white matter measures and an ACT-DL intervention in models of PE. The absence of findings may be explained due to the small, non-significant, white matter changes that may not have been detectable in relation to PE change. Further work on the relationship between white matter measurements and daily life subclinical psychotic symptoms should aim at a larger sample size and longer term interventions to investigate plasticity, as compared to the current study (24 weeks). Similarly, the network-connectivity parameters showed no significant interactions with condition in the symptom models (CAPE symptom frequency/distress score and PE-score). It is important to note that the network-based analyses depends on the fiber tractography algorithm that is used (Zalesky et al., 2011). The current study applied deterministic tractography and perhaps probabilistic tractography was more valid to obtain more detailed white matter networks.

4.4. Methodological considerations

While the carefully designed RCT is a strength of the study, some limitations need to be taken in consideration. First, the study was based

a rather small sample (n=45) and therefore the study might be underpowered for detecting a difference between the two conditions (n=20 versus n=25) and needs replication. Furthermore, participants did know about which training they received, as it was not possible to blind the intervention for them. The ACT-DL condition was very different from the TD condition in a practical matter, since the ACT-DL condition had exercises embedded in the ESM.

As the expected effect size was largely unknown, the tentative results from this study can be seen as a start for further hypotheses-generating. The sample comprised young people with mild symptomatology at the milder end of the psychosis-continuum and therefore are not directly comparable with individuals with At-Risk Mental State or Ultra-High-Risk samples.

Moreover, it needs to be noted that most models to analyse the associations between NA and ΔLE/ΔCC per ROI within the ACT-DL condition (after a significant interaction between condition and ΔLE/ΔCC in the NA models) did not converge. This can be explained by the missing values for NA items (7 missing in the ACT-DL condition and 8 in the TD condition). The sample of 13 participants in the ACT-DL condition reduced the variance in ΔLE/ΔCC and therefore the NA models did not converge, while the models with 20 participants in the TD condition did converge.

The use of tract-based spatial statistics limits the number of voxels to the white matter skeleton. This reduces the error term, but also limits analyses to the strongest structural connections only. Also, arbitrary borders have been used based on the Johns Hopkins University International Consortium for Brain Mapping (JHU ICBM)-DTI-81 atlas labels. Regions can be closely located next to each other, but are separated due to the borders in the atlas. This limits interpretation to the available atlas labels.

The current study applied deterministic tractography (Zalesky et al., 2011). Deterministic tractography allows to inspect specific regions (as based on the AAL), while probabilistic requires to set thresholds to do the same. Removal of small fibers, as based on FA<0.2, may have resulted in removal of important information for the network-based analyses, possibly explaining part of the absence of findings.

5. Conclusion

This RCT in youngsters with mild psychopathology showed no effect of ACT-DL on microstructural white matter or network-connectivity parameters. There was an indication for differential associations between change in network connectivity and NA as a result of the ACT-DL intervention, but the current sample did not allow for complete stratified analyses.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynirp.2023.100190.

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