1 Statistical analysis plan (SAP) for PSY21-0451R

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4 **A Randomized Controlled Trial of the Effectiveness of Cognitive-Behavioral Therapy vs.**
5 **Mindfulness-Based Stress Reduction in Adults with Social Anxiety Disorder**

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7 **Project Description**
8 While several previous studies have investigated the individual effectiveness of cognitive
9 behavioral therapy and mindfulness-based stress reduction in social anxiety disorder (SAD), and
10 have compared their efficacy in other clinical conditions, this is the first direct comparison of
11 these two treatments for SAD. This preregistration contains a description of the project and a
12 detailed analysis plan pertaining to the fMRI and in-scanner behavioral data.

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14 **fMRI Preprocessing Steps**
15 All brain imaging data will be preprocessed using the FSL version 5.0.9 statistical software
16 package (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL). Pre-statistical processing steps will include
17 high-pass temporal filtering (72s = 0.0167 Hz), motion correction using the MCFLIRT linear
18 registration algorithm [Jenkinson et al., 2002], BET brain extraction, and spatial smoothing with
19 a 5-mm cubed full-width, half-maximum Gaussian kernel. The functional scans for each
20 participant will be registered to their high-resolution T1 images using FSL's boundary-based
21 registration (BBR). These images will then be normalized to the 2mm composite MNI-152
22 standard space brain. The first four volumes per scan will also be removed since steady-state
23 magnetic stabilization was being achieved during that time. The motion correction parameters
24 will also be kept in order to be applied as confound regressors in the GLM.

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26 **Planned Analyses**
27 To test changes in cognitive reappraisal (CR) vs. attention regulation (AR) pre-to-post CBT vs.
28 MBSR vs. waitlist (WL) control groups, we will conduct standard MRI preprocessing and
29 individual statistical analyses to:

30

31 [1] create contrasts of react vs. neutral statements, CR vs. neutral statements, AR vs. neutral
32 statement and then compute within and between group t-tests on change from pre-to-post
33 treatment/WL.

34

35 [2] All event files, contrasts, and general linear models (GLM) will be generated using FSL's
36 FEAT tool. All explanatory variables (regressors) within each condition will be convolved with a
37 double gamma hemodynamic response function. Second-level parametric maps will be produced
38 according to a random-effects model and corrected for multiple comparisons using FSL's
39 threshold-free cluster enhancement tool (TFCE).

40

41 We will conduct planned comparisons to assess change within-group and between-groups.
42 Specifically, for behavioral responses, we will conduct a 2 Group (CBT+MBSR, WL) x 2 Time
43 (pre, post) repeated measures analysis of variance (ANOVA) for negative emotion ratings during
44 attention regulation (acceptance) and cognitive reappraisal. We will implement linear regressions
45 controlling for baseline values to test whether post-CBT and post-MBSR behavioral responses,
46 separately, predict baseline residualized SAD symptoms at 1-year post-treatment completion.

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48 To test for changes in brain responses within the pre-defined search volumes, we will conduct
49 within-group pre vs post paired t-tests on fMRI BOLD signal intensity within each search
50 volume with the TFCE correction applied for attention regulation, and also for cognitive
51 reappraisal. To test for the differential effect of treatment on brain responses during attention
52 regulation and during reappraisal, we will conduct between-group t-tests on the pre-to-post
53 differences in fMRI BOLD signal within search volumes with the TFCE correction applied. This
54 will be done first for CBT+MBSR vs. waitlist to determine the effect of treatment vs. no
55 treatment. Second, we will directly compare CBT vs. MBSR brain responses within search
56 volumes. If there are significant CBT vs MBSR brain activation clusters, then we will extract the
57 mean BOLD signal per cluster and visualize the results as bar charts showing pre vs post for
58 CBT vs MBSR.
59
60 **Analysis of fMRI BOLD signal temporal dynamics**
61 We will further examine the BOLD signal temporal dynamics of significant clusters of CBT vs.
62 MBSR results by extracting the time series during attention regulation and during reappraisal
63 (each versus neutral) at pre and post treatment. To test whether pre-to-post-treatment brain
64 changes predict decreases in the severity of social anxiety symptoms at 12 months post-treatment
65 completion, we will use the pre-to-post CBT/MBSR change in fMRI BOLD signal within each
66 search volume as predictor of baseline residualized 1-year post-treatment completion social
67 anxiety symptoms measured on the Liebowitz Social Anxiety Scale - self-report version.
68
69 **Pre-statistical masking**
70 An *a priori* search region mask was created from a combination of brain regions identified by the
71 Neurosynth forward inference meta-analysis for "Attentional Control" and "Reappraisal", as well
72 as brain regions identified in the meta-analysis of cognitive reappraisal to down-regulate
73 negative emotions (Buhle et al., 2014), and a meta-analysis of open monitoring meditation (Fox
74 et al., 2016). This single mask file will be used as a composite search volume for analyses of
75 both cognitive reappraisal and attention regulation (i.e., decentering-acceptance) strategies. For
76 each contrast, we will use threshold free cluster enhancement (FSL) to correct for multiple
77 comparisons and to identify significant clusters of brain activation at baseline and post-
78 treatment/waitlist. This method is preferable to applying abritrary or pre-defined cluster or voxel
79 activation thresholds.

80 The mask creation steps are as follows:

81 [1] The forward inference maps for "reappraisal" and "attentional control" were downloaded
82 from Neurosynth in the MNI T1-152 2mm composite brain space.

83 [2] Separately, the MNI coordinates reported as the peaks related to cognitive reappraisal and
84 open monitoring meditation from the Buhle and Fox meta-analyses, respectively, were recorded.

85 [3] These coordinates were then manually checked to ensure that they were in grey matter
86 regions, and then translated from MNI peaks into FSL voxel coordinates.

87 [3] Spheres were then drawn around these peaks, with an 8mm radius for all spheres.

88 [4] A composite map, and then masks, were then created that included spheres from both meta-
89 analyses.

90   [5] The meta-analysis map was then combined with the two Neurosynth maps.

91   [6] A gray matter mask for the FSL MNI brain was created using a converted nifti file version of
92   the 152 T1 grey average image.

93   [7] This grey matter mask was then used to remove voxels outside the brain and in the CSF and
94   white matter of the combination mask.

95   [8] The resulting map was then binarized and is available for download here.

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