**ANALYSIS PLAN**

Title: Effects of Initial SSRI Treatment on Catastrophising and Resilience in Individuals with Clinical Anxiety.

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1. **FOREWORD**

This document presents a data analysis plan for the study entitled "Effects of Initial SSRI Treatment on Catastrophising and Resilience in Individuals with Clinical Anxiety." This research project, supervised by Dr. Olivia Harrison, aims to investigate the cognitive impacts of selective serotonin reuptake inhibitors (SSRIs) specifically focusing on catastrophising behaviours and resilience in individuals who have been clinically diagnosed with anxiety disorders.

This analysis forms part of a wider research initiative, "Breathing and Anxiety Study," conducted at the University of Otago, which investigates how commonly prescribed SSRIs may alter brain-body interactions, and how these changes relate to improvements in anxiety symptoms.

Data will be utilised for analysis from up to 105 individuals who have been clinically diagnosed with an anxiety disorder and are either taking a new (n=71) or ongoing (n=34) prescribed SSRI, who have completed both an initial and follow-up session as part of the study. The purpose of this analysis plan is to provide a brief background for the proposed work, formulate the research question(s), explicitly describe planned and potential post-hoc analyses, and give the rationale for each analysis step. All code created over the course of the project will be version-controlled and documented on the internal GitHub page (https://github.com/IMAGEotago) of the IMAGE Otago research group.

1. **INTRODUCTION**

Anxiety disorders are among the most prevalent mental health conditions globally, affecting approximately 4% of the population (WHO, 2023). In Aotearoa New Zealand, anxiety affects nearly a quarter of individuals over their lifetime. Lockett et al. (2018) found a significant relationship between mental health problems and long-term physical health conditions, particularly for internalizing disorders like depression and anxiety, contributing significantly to functional impairment and healthcare burden (Oakley Browne et al., 2006). While selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed to manage anxiety, their specific cognitive effects—particularly on catastrophising and resilience—remain underexplored. Catastrophising, the tendency to expect the worst, is a maladaptive cognitive process that intensifies anxiety symptoms and interferes with recovery (Vasey & Borkovec, 1992; Hazlett-Stevens & Craske, 2004). Conversely, resilience is a protective factor associated with better treatment outcomes and improved coping under stress (Southwick et al., 2014; Rutten et al., 2013).

Despite their widespread use, SSRIs are often evaluated based on symptom reduction alone, with less attention paid to the cognitive mechanisms underlying treatment response. This project addresses that gap by assessing whether initial SSRI treatment is associated with reductions in catastrophising and improvements in resilience, and how these changes relate to anxiety reduction. The findings may inform more targeted and holistic interventions for individuals with anxiety disorders.

1. **RESEARCH QUESTIONS**

The present study is guided by the following research questions, which aim to address gaps in the literature regarding the early cognitive effects of SSRI treatment in individuals with anxiety disorders:

**Research Question 1:** Does initiating SSRI treatment reduce catastrophising behaviour in individuals with clinical anxiety over a six-week period?

* **Hypothesis 1 (H1):** Participants who begin SSRI treatment will show significant reductions in catastrophising behaviours after six weeks, relative to both their own baseline, normalising to the levels observed in the control group who are stable on an SSRI. This is based on findings that SSRIs may reduce negative cognitive biases, which are core features of catastrophising (Murphy et al., 2021; Vasey & Borkovec, 1992).

**Research Question 2:** Does SSRI treatment lead to improvements in resilience over the initial treatment period?

* **Hypothesis 2 (H2):** Participants starting on SSRIs will show significantly higher resilience scores after six weeks of treatment compared to their baseline levels, normalising to the levels observed in the control group who are stable on an SSRI. Resilience is a known protective factor in mental health and may be enhanced through SSRI-related improvements in emotional regulation (Rutten et al., 2013; Southwick et al., 2014).

**Research Question 3:** Are changes in catastrophising and resilience associated with reductions in anxiety symptoms in individuals starting SSRI treatment?

* **Hypothesis 3 (H3):** Greater reductions in catastrophising and greater improvements in resilience will correlate with larger decreases in self-reported anxiety symptoms. This hypothesis builds on evidence that both constructs are cognitively and biologically linked to anxiety severity and recovery (Hazlett-Stevens & Craske, 2004; Southwick et al., 2014).

1. **DATASET**

The dataset used in this project is part of the broader "Breathing and Anxiety Study" and consists of survey data collected from a total of 105 adult participants (88 minimum) between the ages of 18 and 45 years. The treatment group comprises at least 54 individuals (and up to 71) who were prescribed an SSRI for the treatment of clinical anxiety and had either not started or had been taking the medication for less than one week at the time of the first session. The control group includes at least 34 individuals who had been taking an SSRI consistently for more than three months. Participants were recruited from the Dunedin, New Zealand region through a combination of local advertisements, social media outreach, and referrals local GP practices.

**Inclusion Criteria:**

Participants were required to be between the ages of 18 and 45 and to have received a clinical diagnosis of an anxiety disorder. Treatment participants must have been prescribed an SSRI for the first time or have taken an SSRI for less than one week. Control participants must have been taking an SSRI consistently for more than three months at the time of recruitment and be stable on their medication for the duration of the study.

**Exclusion Criteria:**

Participants were excluded if they had a history of severe neurological disorders, brain injury, or recent substance abuse (within the past six months). Additional exclusion criteria included current suicidal ideation, the use of other psychotropic medications (besides SSRIs), and previous SSRI use within the past six months for those in the treatment group.

**Study Procedure:**

Participants in both the treatment and control groups completed two laboratory sessions, scheduled at least six weeks apart. During each session, participants filled out a battery of questionnaires measuring dimensions of psychopathologic symptomology, subjective interoceptive ability, and demographics. These included: the Body Sensations Questionnaire (BSQ), Pain Catastrophising Scale (PCS-Resp), and Pain Vigilance and Awareness Questionnaire (PVAQ-Resp) to measure catastrophising, the Connor-Davidson Resilience Scale (CD-RISC), Fatigue Severity Scale (FSS), and General Self-Efficacy Scale (GSE) to measure resilience, and the Generalized Anxiety Disorder 7-item scale (GAD-7), State-Trait Anxiety Inventory (STAI), and the Centre for Epidemiological Studies Depression Scale (CES-D) to measure anxiety and depression.

Each participant also took part in a larger set of procedures involving the Breathing Learning Task (Harrison et al., 2021), an Emotional Faces Task (Harmer et al., 2003), the Respiratory Resistance Sensitivity Task (RRST; Nikolova et al., 2022), and the Visual Perceptual Task (VPT; Rouault, et al., 2018); however, these tasks fall outside the scope of the current project and are not included in this analysis. Data from the questionnaire responses at both timepoints form the basis of the analyses described in this plan.

1. **EXCLUSION OF DATASETS**

Data sets with complete BSQ, PCS-RESP, PVAQ-RESP, CD-RISC, GSE, FSS, GAD-7, CES-D, and STAI data will be included in the analyses.

Data will be excluded from analysis based on several predetermined criteria to ensure quality and consistency across participants. Any participants who fail to complete both the baseline and follow-up sessions will be excluded, as change scores and repeated measures analyses require data from both timepoints.

Additionally, participants with incomplete questionnaire responses that exceed 20% of the total items for any one measure will be excluded from analyses involving that specific measure. This threshold is consistent with common standards in psychological research, where 80% item completion is often used as a benchmark for acceptable data quality (Parent, 2012). It ensures sufficient content coverage for the calculated score to retain validity, particularly when computing scores derived from standardized scales.

Any data that demonstrates implausible or outlier values based on established cutoff scores for specific questionnaires (e.g., z-scores > ±3) will be reviewed and potentially excluded following sensitivity analyses.

1. **DATA PREPROCESSING**

This section outlines the detailed statistical analysis procedures that will be undertaken to address each of the three primary research questions, as well as exploratory aims. Analyses will be conducted using STATA 18, with reproducible code documented and retained for review.

The following preprocessing steps will be undertaken for each of the nine questionnaires used in the study:

The **Body Sensations Questionnaire (BSQ-18)** will be scored in accordance with standard procedures for the 18-item version. Item responses will be summed to produce a total score ranging from 18 to 90. Higher scores reflect greater fear of and attentional focus on bodily sensations commonly associated with anxiety (Chambless et al., 1984).

The **Pain Catastrophising Scale – Respiratory version (PCS-Resp)** is scored by summing the item responses to produce a total score ranging from 0 to 52. The PCS-Resp comprises three subscales: Rumination (e.g., persistent focus on symptoms), Magnification (e.g., exaggerating the threat of symptoms), and Helplessness (e.g., perceiving inability to manage the symptoms). Subscale scores are calculated by summing their respective item responses. A total score of over 30 is considered to reflect a clinically significant level of catastrophising. Higher scores across the total and subscale levels indicate greater catastrophising in relation to respiratory symptoms (Sullivan et al., 1995).

The **Pain Vigilance and Awareness Questionnaire – Respiratory version (PVAQ-Resp)** assesses attention to breathing-related symptoms. Item responses are summed to produce a total score ranging from 0 to 80, with higher values reflecting increased hypervigilance to respiratory sensations (McCracken, 1997).

The **Connor-Davidson Resilience Scale (CD-RISC)** will be scored by summing responses to 25 items, with total scores ranging from 0 to 100. Higher scores reflect greater resilience (Connor and Davidson, 2003).

The **Fatigue Severity Scale (FSS)** total score will be calculated as the average of item responses. Scores above 4 generally indicate clinically relevant fatigue (Krupp et al., 1989).

The **General Self-Efficacy Scale (GSS/GSE)** provides a single total score derived by summing all item responses (range: 10 to 40). Higher scores reflect greater perceived self-efficacy (Schwarzer and Jerusalem, 1995).

The **Generalized Anxiety Disorder 7-item scale (GAD-7)** will be scored in accordance with official guidelines. The final score is the sum of all item responses and ranges from 0 to 21. Scores of 0–4 indicate minimal anxiety, 5–9 mild anxiety, 10–14 moderate anxiety, and 15–21 severe anxiety (Spitzer et al., 2006).

The **State-Trait Anxiety Inventory (STAI)** includes two subscales (State and Trait), each scored separately. Each subscale yields a total score ranging from 20 to 80. For the State scale (Form Y-1) and Trait scale (Form Y-2), scores of 20–37 reflect low or no anxiety, 38–44 moderate anxiety, and 45–80 high anxiety (Spielberger, 1983).

The **Centre for Epidemiological Studies Depression Scale (CES-D)** total score ranges from 0 to 60. Scores of 0–15 suggest minimal depressive symptoms, 16–23 moderate, and 24 or higher indicate severe depressive symptomatology (Radloff, 1977).

All scores will be checked for entry accuracy, plausibility, and consistency with standardized scoring criteria before statistical analysis. Scores for each questionnaire will be calculated as per their original scoring guidelines ensuring correct reverse scoring of required entries. This will be done using MATLAB after pulling the raw data from QUALTRICS. For each construct domain (catastrophising, resilience, and the internalizing family (anxiety and depression); Caspi et al, 2020), principal component analysis (PCA) will be used to derive a composite score from the respective measures (BSQ, PCS-Resp, and PVAQ-Resp for Catastrophising; CD-RISC, FSS, and GSE for Resilience; and GAD-7, STAI, and CES-D for the internalizing family, with the internalizing family also being split into Anxiety (GAD-7 and STAI) and depression (CES-D).

1. **DATA ANALYSIS**

To confirm the effect of the intervention on anxiety and depression symptoms themselves, mixed-effects longitudinal regression models will be applied to the anxiety and depression domain scores. These models will include fixed effects for Time (baseline vs. follow-up), Group (treatment vs. control), and their interaction (Time × Group), with random intercepts specified for each participant ans significance taken at P<0.05. Separate models will also be applied to each of the individual anxiety and depression questionnaires (e.g., GAD-7, STAI, CES-D) to evaluate robustness. The interaction term will be used to test whether changes over time in anxiety and depression scores differ significantly between groups, thereby confirming the effectiveness of the intervention.

To answer Research Question 1, linear mixed-effects models will be fitted to the PCA score for catastrophising with fixed effects for Time (baseline vs. follow-up), Group (treatment vs. control), and their interaction (Time × Group). Random intercepts will be specified for each participant to account for individual variability and significance taken at p<0.05. The key term of interest is the interaction effect, which indicates whether the change in catastrophising over time differs significantly between the two groups. Separate models will be run for each individual catastrophising questionnaire as a sensitivity check.

To address Research Question 2, the same analytical approach will be applied to the resilience domain PCA score. Fixed effects will again include Time, Group, and the Time × Group interaction, with random intercepts per participant and significance taken at p<0.05. The same separate model approach will be repeated using the resilience subscales to confirm the robustness of findings.

To address Research Question 3, bivariate Pearson correlations will be calculated between the changes in internalising family scores with changes in both catastrophising and resilience PCA scores (change calculated as follow-up minus baseline). In cases where assumptions of linearity or normality are violated, Spearman rank-order correlations will be employed instead. To control for the two comparisons within this research question, the significance threshold will be adjusted to p<0.025 using Bonferroni correction. Additionally, a full exploratory correlation matrix will be calculated, comparing the changes between all individual questionnaire score. No correction for multiple comparison will be applied, and all results will be marked as exploratory.

**Assumption checks:**

The normality of residuals will be assessed using Shapiro-Wilk tests test (with an alpha value of p<0.05 rejecting the null hypothesis of normally distributed data) and visual inspection of Q-Q plots. If residuals demonstrate substantial non-normality, model transformations such as logarithmic, square root, or Box-Cox transformations may be applied to normalize the outcome variable. If these transformations are insufficient or inappropriate, non-parametric alternatives such as the Aligned Rank Transform (ART) ANOVA may be considered to enable valid factorial interaction testing while relaxing normality assumptions.

Linearity between predictor and outcome variables will be assessed using residual plots. Any evidence of non-linear relationships may warrant transformations or alternative modelling approaches.

Homoscedasticity will also be assessed via residual vs. fitted value plots. Unequal variance patterns may lead to the use of robust standard errors, to adjust the standard error estimates accounting for non-constant variance and ensure more reliable p-values and confidence intervals.

1. **REVISIONS**

**Version Date: 19/05/25**

This is version one of the analysis plan.

1. **REFERENCES**

Caspi A, Houts RM, Ambler A, et al. Longitudinal Assessment of Mental Health Disorders and Comorbidities Across 4 Decades Among Participants in the Dunedin Birth Cohort Study. *JAMA Netw Open.* 2020;3(4):e203221. doi:10.1001/jamanetworkopen.2020.3221

Chambless, D. L., Caputo, G. C., Bright, P. & Gallagher, R. (1984). Assessment of fear of fear in agoraphobics. Journal of Consulting and Clinical Psychology, 52 (6), 1090- 1097.

Connor, K. M., & Davidson, J. R. T. (2003). Development of a new resilience scale: The Connor-Davidson Resilience Scale (CD-RISC). Depression and Anxiety, 18(2), 76–82. <https://doi.org/10.1002/da.10113>

Harmer, C. J., Hill, S. A., Taylor, M. J., Cowen, P. J., & Goodwin, G. M. (2003). Toward a neuropsychological theory of antidepressant drug action: Increase in positive emotional bias after potentiation of norepinephrine activity. American Journal of Psychiatry, 160 (5), 990–992. DOI: 10.1176/appi.ajp.160.5.990

Harrison, O., K¨ochli, L., Marino, S., Luechinger, R., Hennel, F., Brand, K., Hess, A. J., Fr¨assle, S., Iglesias, S., Vinckier, F., Petzschner, F. H., Harrison, S. J., & Stephan, K. E. (2021). Interoception of breathing and its relationship with anxiety. Neuron, 109 (24), 4080–4093.e8. DOI: 10. 1016/j.neuron.2021.09.045

Hazlett-Stevens, H., & Craske, M. G. (2004). The catastrophizing worry process in generalized anxiety disorder: A preliminary investigation of an analog population. Behavioural and Cognitive Psychotherapy, 31(3), 387–401. <https://doi.org/10.1017/S1352465803004016>

Krupp, L. B., LaRocca, N. G., Muir-Nash, J., & Steinberg, A. D. (1989). The fatigue severity scale: Application to patients with multiple sclerosis and systemic lupus erythematosus. Archives of Neurology, 46(10), 1121–1123. <https://doi.org/10.1001/archneur.1989.00520460115022>

Lockett, H., Jury, A., Tuason, C., Lai, J., & Fergusson, D. (2018). Comorbidities between mental and physical health problems: An analysis of the New Zealand Health Survey data. New Zealand Journal of Psychology, 47(3), 5-11.

McCracken, L. M. (1997). Pain Vigilance and Awareness Questionnaire (PVAQ). APA PsycTests. <https://doi.org/10.1037/t14777-000>

Murphy, S. E., Capitão, L. P., Giles, S. L. C., Cowen, P. J., Stringaris, A., & Harmer, C. J. (2021). The knowns and unknowns of SSRI treatment in young people with depression and anxiety: Efficacy, predictors, and mechanisms of action. The Lancet Psychiatry, 8(9), 824–835. https://doi.org/10.1016/S2215-0366(21)00154- 1

Nikolova, N., Harrison, O., Toohey, S., Brændholt, M., Legrand, N., Correa, C., Vejlø, M., Jensen, M. S., Fardo, F., & Allen, M. (2022). The respiratory resistance sensitivity task: An automated method for quantifying respiratory interoception and metacognition. Biological Psychology, 170, 108325. DOI: 10.1016/j.biopsycho.2022.108325

Oakley Browne, M. A., Wells, J. E., Scott, K. M., & McGee, M. A. (2006). Lifetime prevalence and projected lifetime risk of DSM-IV disorders in Te Rau Hinengaro: The New Zealand Mental Health Survey. Australian and New Zealand Journal of Psychiatry, 40(10), 865-874. <https://doi.org/10.1080/j.1440-1614.2006.01905.x>

Parent, M. C. (2012). Handling item-level missing data: Simpler is just as good. *The Counseling Psychologist, 41*(4), 568–600. <https://doi.org/10.1177/0011000012445176>

Radloff, L. (1977). The CES-D Scale: A self-report depression scale for research in the general population. 1 (3), 385–401.

Rouault, M., Seow, T., Gillan, C. M., & Fleming, S. M. (2018). Psychiatric symptom dimensions are associated with dissociable shifts in metacognition but not task performance. Biological Psychiatry, 84 (6), 443–451. DOI: 10. 1016/j.biopsych.2017.12.017

Rutten, B. P. F., Hammels, C., Geschwind, N., Menne-Lothmann, C., Pishva, E., Schruers, K., van den Hove, D., Kenis, G., van Os, J., & Wichers, M. (2013). Resilience in mental health: Linking psychological and neurobiological perspectives. Acta Psychiatrica Scandinavica, 128(1), 3–20. <https://doi.org/10.1111/acps.12095>

Schwarzer, R., & Jerusalem, M. (1995). Generalized Self-Efficacy scale. In J. Weinman, S. Wright, & M. Johnston, Measures in health psychology: A user’s portfolio. Causal and control beliefs (pp. 35-37). Windsor, UK: NFER-NELSON.

Spielberger, C. D. (1983). State-Trait Anxiety Inventory for Adults.

Spitzer, R. L., Kroenke, K., Williams, J. B. W., & Lowe, B. (2006). A brief measure for assessing generalized anxiety disorder: The GAD-7. Archives of Internal Medicine, 166 (10), 1092–1097.

Southwick, S. M., Bonanno, G. A., Masten, A. S., Panter-Brick, C., & Yehuda, R. (2014). Resilience definitions, theory, and challenges: Interdisciplinary perspectives. European Journal of Psychotraumatology, 5, 25338. <https://doi.org/10.3402/ejpt.v5.25338>

Sullivan, M. J., Bishop, S. R., & Pivik, J. (1995). The Pain Catastrophising Scale. Psychological Assessment, 7 (4), 524-532. doi: 10.1037/1040- 3590.7.4.524

Vasey, M. W., & Borkovec, T. D. (1992). A catastrophizing assessment of worrisome thoughts. Cognitive Therapy and Research, 16(5), 505-520.

World Health Organization. (2023, September 27). Anxiety disorders. Retrieved from https://www.who.int/news-room/fact-sheets/detail/anxiety-disorders.