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Training Cognitive Control to Reduce Emotional Vulnerability in Breast Cancer

*Jessica Swainston and Nazanin Derakshan*

*Department of Psychological Sciences, Birkbeck, University of London, Malet Street,*

*London, WC1E 7HX, UK*

Address for correspondence:

Jessica Swainston or Nazanin Derakshan,

Centre for Building Resilience in Breast Cancer (BRiC),

Department of Psychological Sciences,

Birkbeck University of London,

Malet Street, London, UK.

Email: jess.swainston@gmail.com; n.derakhshan@bbk.ac.uk

**Abstract**

*Objectives*: Breast cancer enhances anxiety and depressive vulnerability, profoundly impairing the quality of life in survivors. Hinging on recent research that training attentional control can reduce emotional vulnerability, we assess how improving cognitive function could reduce emotional vulnerability in female survivors of breast cancer.

*Methods:* Participants took part in a course of adaptive dual n-back cognitive training (Training Group) or a non-adaptive active control group (Active Control) for 12 days across a two-week period. Transfer-related training gains were assessed immediately after the intervention, at a shorter one-month follow-up and at a longer follow-up time of approximately 15 months post intervention, to assess sustainability of training effects.

*Results:* Adaptive cognitive training reduced anxiety and rumination with effects evident at shorter and longer term follow-up assessments.

*Conclusions:* Our results are amongst the first to suggest that adaptive cognitive training can reduce emotional vulnerability in breast cancer, with the potential to enhance quality of life in survivorship. Our findings have profound implications for designing interventions targeting cognitive function in populations who've suffered from cancer.

Keywords: Breast Cancer, Attentional Control, Cognitive Training, Anxiety, Psycho-oncology

**Introduction**

Breast Cancer is the biggest cause of malignancy in women worldwide [1]. While medical advancements can help extend survival to 10 or more years post diagnosis [2], the psychological cost of diagnosis and treatment has shown to profoundly enhance vulnerability to anxiety and depression, psychological distress, rumination, and post-traumatic stress, greatly impairing quality of life [3]. Indeed, around 60% of patients with a breast cancer diagnosis still suffer from post-traumatic stress symptoms at one-year post diagnosis [4]. Fear of recurrence, anxieties regarding mortality, altered body image following surgery, changes in sexuality and fears regarding the impact of diagnoses on immediate families can impact societal commitments, relationships and personal and familial well-being [see, 5, for a review]. For younger breast cancer sufferers there is also loss of fertility and early menopause as a result of treatment-induced hormonal changes from chemotherapy [6].

Corroborating behavioral studies, recent neural findings investigating the effects of chemotherapy have established structural and functional changes within the central nervous system, associated with the specific cognitive impairments that breast cancer survivors describe, most notably functions of verbal working memory, attention and executive functions [see, 7, for a review]. Aromatase inhibitors and selective estrogen receptor modulators such as tamoxifen used in endocrine therapy can also contribute to cognitive decline, both alone and in combination with chemotherapy [8]. Such cognitive deficits are even found prior to adjuvant therapy, shortly after diagnosis, suggesting that the trauma associated with diagnosis can severely impact cognitive function [9].

The instrumental role of cognitive health in emotional well-being is substantiated in recent interventions that target cognitive function to improve well-being in anxiety and depression [10]. Based on recent theoretical breakthroughs in cognitive and clinical

neuroscience advocating a causal role for attentional control in the onset, maintenance, and recurrence of anxiety and depressive vulnerability, increasing evidence shows that training cognitive control can reduce and protect against anxiety and depressive vulnerability [11-14]. Attentional control is the ability to exercise and regulate attention towards relevant and away from irrelevant information, flexibly and efficiently [15], playing a vital role in everyday and complex activities. Growing evidence supports predictions from Attentional Control Theory [15] that top down attention necessary for goal achievement is disrupted by excessive negative affect reducing processing efficiency [16, 17].

Research on reducing emotional vulnerability through the exercise of attentional control using engaging computerized cognitive tasks is growing in clinical research [see, 18 for a review]. Such techniques can target key neural circuits enabling transfer related benefits to a number of related cognitive capabilities [19]. Critically, transfer effects are found on enhanced executive functioning [20] and long term improvement in verbal learning and working memory [21] in women with a breast cancer diagnosis. There are also improvements in working memory, attention and processing speed in childhood survivors of cancer [22]. Such improvements have the potential to greatly enhance quality of life in survivors through improving cognitive flexibility.

The hypothesis that improvements in attentional control via engaging cognitive training tasks can attenuate negative affect was addressed in a recent systematic review [11] and in a meta-analysis [23] of cognitive control training studies, with gains in working memory improvements associated with reductions in negative affect. Adaptive cognitive training has reduced rumination in clinical depression [24] and anxious symptomatology in anxiety [13]. Sari, Koster, Pourtois & Derakshan [13] showed that a 3 week course of adaptive dual n-back training, previously shown to increase fluid intelligence [19] and processing efficiency in sub-clinically depressed individuals [25], can reduce anxiety in

highly anxious individuals. In the adaptive dual n-back training prefrontal functions of control are exercised and engaged in a systematic and adaptive manner. Other studies have reported increases in resilience in students at risk of depression [26] and reduced symptoms of burnout as part of a stress rehabilitation program in exhaustion disorder [27]. Adaptive cognitive training can regulate prefrontal – amygdala activity [12], so has the potential to modify the emotion-cognition prefrontal network crucial for emotion regulation.

**The current investigation**

Adaptive cognitive training holds the promise to help reduce emotional vulnerability by enhancing processing efficiency in breast cancer survivorship. Using the ORBIT Model [29] for developing behavioral treatments for chronic diseases (see figure b. supplementary materials) the current intervention validated the effectiveness of the adaptive dual n-back training to translate basic behavioral scientific findings to clinical application.

In a former feasibility study, which acted as a preliminary/proof of concept study for the present investigation (Phase IIa along the ORBIT pathway), we successfully determined the efficacy of the adaptive dual n-back cognitive training in improving working memory capacity and reducing anxiety related symptomatology in a small group (N = 17) of survivors of non-metastatic breast cancer who were recruited from The Breast Cancer Care (UK) charity. The current intervention extended these effects on emotional vulnerability in a larger sample of women with breast cancer (Phase IIb along the ORBIT pathway), the majority of whom had primary non-metastatic breast cancer. We predicted that training related benefits would result in reductions in anxiety vulnerability post vs pre-intervention in the adaptive training compared with the active control group, with effects sustained at shorter and longer follow-up time points. The study received ethical approval from the research ethics

committee of the Department of Psychological Sciences at Birkbeck University of London (Ref: 141511). Informed consent was obtained from participants prior to participation.

**Method**

**Participants**

The study was advertised through the [Centre for Building Psychological Resilience in Breast Cancer](#) on various social media and breast cancer support network platforms using Facebook and Twitter. In total, 79 participants (40 Control, 39 Training) were recruited for the study. Participants must have had a diagnosis of breast cancer, and be 6 months post active treatment to be eligible for participation. All participants received a fee of £100 upon testing at one month follow-up, and a £7 Amazon Voucher at the second follow-up.  For participant demographics, clinical characteristics and psychiatric history see online supplementary materials.

**Materials and Experimental Tasks**

**Training Tasks:** A standard dual n-back task was utilised, replicated from Owens et al., [25]. Participants were presented with a 3x3 grid within which a green square appeared at one of eight different positions. Concurrently, one of 8 consonants (h, l, c, q, s, r, k and t) were presented audibly.  Participants were asked to memorize the position of the green square and the letter spoken to them 'n' trials back within each trial and respond with appropriate keys on the keyboard to indicate a match or a non-match [for further details, see online supplementary materials].

**Dual N-Back Task (Training):**  Participants in the training group completed 20 blocks of 20 + n trials per day whereby 'n' was determined by the level of n-back that the participant

reached (e.g. 3-back, 20+3 = 23 trials). Participants started at the 1-back level for each training session. Difficulty level (level of n) was determined by average accuracy percentage scores for each block (hit minus false alarm rate) for each modality (auditory and visual). When accuracy on both modalities was 95% or above, level of n increased by 1, if less than 75% it decreased by 1, and if between 75% and 95%, level of n was maintained. Participants received feedback on their daily performance.

**Dual 1-back Task (Active Control):** Participants in the control group undertook a non-adaptive version of the task whereby the difficulty level remained unchanged. Participants began and remained on the 1-back level across 20 blocks per session.

**Procedure**

The design followed a pre-intervention, intervention, post-intervention, and two follow-ups, the first at one month post intervention and the second at approximately 15 months (11 – 18 months range) post intervention [see CONSORT diagram in supplementary materials]. Allocation to Training or Active Control conditions was achieved using a procedure that alternated participants sequentially to either of these conditions. Participants remained naive to the allocation to either the control or training groups and were emailed task instructions with verbal instructions over the phone. Participants accessed the task online in their homes on a secure and dedicated website, granting access only to the participant and the experimenter ensuring confidentiality. They firstly answered demographics questions on their breast cancer diagnosis, followed by the first set of questionnaires. They then continued on to the training task. Participants completed each daily training session of 30 minutes, across 12 days, within a two week period, at approximately the same time each day. Performance was

monitored by the experimenter daily. On completion of training, participants completed the questionnaires, and again at both follow-up time points.

**Outcome Measures**

**Primary Outcome:** *Anxious symptomatology* was assessed by a composite score derived from the anxious and distress related subscales (Anxious Arousal, General Distress) of the Mood and Anxiety Scale Questionnaire (MASQ) [30], a 30-item inventory in which frequency of symptoms are indicated on a Likert scale ranging from 1 ('not at all') to 5 ('extremely'), as well as the anxious subscale (Hyperarousal) of the Cancer Impact of Events Scale (IOE) [31] a 22-item inventory, whereby frequency of symptoms are indicated on a Likert scale ranging from 0 ('not at all') to 4 ('extremely'). Higher scores indicated higher anxiety. The scales demonstrated good reliability in the current study: all Cronbach's alphas >.75.

**Secondary Outcomes:** *Rumination,* a key predictor of depression, was assessed by the Ruminative Response Scale [32], a 22-item scale with a Likert scale ranging from 1 ('almost never' to 4 ('almost always)', with higher score indicating higher levels of rumination. *Depression symptomatology* was assessed using the anhedonic depression subscale of the MASQ. *Worry* was assessed by the Penn State Worry Questionnaire [33], measuring trait worrying on a Likert scale ranging from 1 ('not typical of me') to 5 ('very typical of me') with higher scores indicating greater pathological worry. *Resilience* was assessed by the Connor Davidson Resilience Scale (CD-RISC) [34], on a Likert scale ranging from 1 ('not true at all') to 5 ('true nearly all the time'), with higher scores indicating higher levels of resilience. All scales showed good reliability, all Cronbach alphas > .92.

**Statistical methods**

Data were analysed using IBM SPSS Statistics, Version 22.0. Chi-square tests were used to compare group demographics. T-tests were used to assess working memory improvement from pre- to post-intervention. 2 (Group: Active Control, Training) X 4 (Time: Pre-intervention, Post-intervention, 1st Follow-up, 2nd Follow-up) Linear Mixed Effect Models (MLMs) were used to compare groups on self-reported emotional vulnerability measures over time. Fixed effects were specified for Group (Active Control, Training), Time (Pre-intervention, Post-intervention, 1st Follow-up, 2nd Follow-up), and a Group x Time interaction. Data were analysed according to the intention-to-treat (ITT) principle whereby the initial sample's ($n = 79$) data were analysed, irrespective of whether participants were compliant to the entire intervention. Models were estimated with the maximum likelihood method. Effect sizes were calculated by Cohen's $d$ which was derived from the $F$- test and calculated as $d = 2*\sqrt{(F / \mathrm{df})}$. In addition, MLMs were conducted on a per protocol (PP) sample which included only the participants who completed the study in its entirety (Control, $n = 28$, Training, $n = 32$). Post hoc power analysis for the initial sample of 79, and the intended MLM analyses with a significance level of 0.05 (alpha), a small to moderate effect size of .3d), with three time point measurements (pre, post, and first follow-up) was .83, and for the final sample of 60, with four time point measurements (pre, post, first and second follow-ups), with the same specifications as above, the desired power was .79.

**Results**

**Dual n-Back Performance**

**1-back Control Group:** There was a good average level of accuracy across the 12 days of training sessions ($M$ = 96.28 %, $SD$ = 7.03). **N-back Training Group**: Figure 1 shows that working memory functioning, as measured by increasing levels of N, improved from Day 1 ($M$ = 1.49, $SD$ = 7.03) to Day 12 ($M$ = 2.78, $SD$ = .62), $t(31)$ = 14.27, $p$ < .001. The slope of this improvement was significantly different from zero $t(38)$ = 8.60, $p$ <.001.

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Insert Figure 1 here

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**Changes in Emotional Vulnerability**

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Insert Table 1 here

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Mean self-reported symptomatology for each group at each time point is presented in Table 1.[1] The groups did not differ significantly at pre-intervention on any of the measures, all $t's$ < .95, NS.

**Effects on primary outcome**

*Anxiety symptomatology*:

Composite scores were used in order to specifically test the primary outcome of anxiety and to protect against the risk of a false positive [35]. These were determined using a factor analysis, whereby each subscale (Anxious Arousal, General Distress and Hyperarousal) showed consistently high correlations with each other (>.6) across all time points. Figure 2 shows that participants in the Training group showed marked and sustained reductions in anxiety symptomaotology relative to the Control group. The MLM confirmed this observation with a significant Group X Time interaction, $F(3, 68.43) = 2.81$, $p$ .04, Cohen's $d = 0.41$, (ITT); $F(3, 63.48) = 3.07$, $p = .03$, Cohen's $d = 0.44$ (PP).[2]

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Insert Figure 2 here

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**Effects on secondary outcomes**

***Rumination:*** Figure 3 shows that the Training group's scores decrease at follow-up times, but the Control group's scores remain consistent across time. This observation was supported by a Group X Time interaction, $F(3, 82.51) = 2.81$, $p = .04$, Cohen's $d = .39$ (ITT); $F(3, 75.54) = 2.82$, $p = .04$, Cohen's $d = .39$ (PP). ***Depression symptomatology and Resilience:*** No significant interactions were found, $Fs < 1$, NS. ***Worry:*** There was no significant interaction, $F(3, 74.48) = 1.21$, $p = .24$, Cohen's $d = .25$ (ITT); $F(3, 64.05) = 1.21$, $p = .32$, Cohen's $d = .27$ (PP).

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Insert Figure 3 here

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**Further Analyses**

Table a. [supplementary materials] indicates group characteristics on demographic variables for the initial sample of 79. Group differences were found for age at diagnosis (Training: $M = 47$, $SD = 6.43$, Control: $M = 44$, $SD = 6.94$), $t(77) = 2.02$, $p = .05$) and number of participants taking psychiatric medication for anxiety and/or depression, $X^2 (1) = 3.93$, $p = .05$ (ITT), however these differences were not apparent in the final per protocol sample, (Age at diagnosis, Training: $M = 47$, $SD = 6.84$, Control: $M = 45$, $SD = 6.54$), $t(58) = 1.23$, $p = .22$; Psychiatric medication, $X^2 (1) = 2.64$, $p = .1$). No significant correlations were found between any demographic or medical variables and the slope of the primary and secondary outcome measures, (all $r$'s < .26, all $p$'s > .06).

**Additional responses**

Without elicitation, numerous participants expressed the positive impact of training on them. Participants spoke of how they would *'miss the daily challenge'* and how it had prompted them to give the *'brain a bit more of a workout on a regular basis'* because of the *'improvement in my memory'. Others commented* that it *'helped me in a funny way to stay concentrated on one thing', 'made me feel empowered and confident', and 'was just what I needed'.* Overall, participants enjoyed the training with improvement and completion igniting a sense of achievement and empowerment.

**Discussion**

We investigated how adaptive cognitive training via the dual n-back training, previously shown to enhance cognitive efficiency and reduce emotional vulnerability in anxiety and depression, compared with an active control training, can help increase cognitive flexibility and reduce emotional vulnerability in breast cancer survivorship. As predicted, working memory performance improved in the training group pre to post intervention. Importantly, training-related benefits resulted in reductions in anxiety-related symptomatology as well as in rumination. Critically, these reductions were sustained across time to one month follow-up and the longer period of 11 − 18 months follow-up testing intervals.

Transfer related gains on anxiety vulnerability imply a significant beneficial impact of training on physiological arousal symptoms such as anger and irritability, and difficulty concentrating due to cancer related traumatic experiences. Given the numerous physiological long-term side effects associated with breast cancer treatment (e.g., lymphedema, peripheral neuropathy, menopausal symptoms as well as fatigue and insomnia [36, 37]) this finding is particularly pertinent. Thus through remediating anxiety-related symptoms, there is potential for cognitive training to attenuate the distress caused by long term side effects that breast cancer survivors experience. These results have implications for better regulation of emotion and attenuation of cancer related thoughts, especially fear of recurrence, that frequently interrupt daily functioning [38].

Significant reductions in rumination in the training compared with the control group extend previous findings [20, 23] of reduced ruminative thinking in major depression.

Rumination is a key cognitive risk factor for depression [16] that involves top-down processes which can benefit from training related gains as a result of brain neuroplasticity. By reducing rumination through improved cognitive control capabilities, it is possible to protect against depression. Rumination has also been linked to a delay in seeking diagnosis for breast cancer symptoms and motivational deficits that inhibit individuals from taking required action to solve problems [39]. Our current finding is thus key to this population who must remain vigilant for symptoms of recurrence and attend follow up appointments with medical practitioners.

Reductions in negative affective symptomatology in the adaptive training versus control group were not only apparent at post intervention, but were sustained at one month as well as the longer time follow-up of an average of 15 months (11 – 18 month range) post intervention. This finding is of key importance because it shows that not only can adaptive training be of immediate benefit to reductions in emotional vulnerability in survivors of breast cancer, but through its effects on neuroplasticity can encourage engagement with behaviors that can help sustain these effects at longer time periods. This demonstrates that attentional control processes remain plastic and can be targeted post treatment and has important implications for cognitive health post diagnosis. Given the plethora of evidence on treatment induced cognitive decline in breast cancer survivors [7], adaptive cognitive training can increase and sustain cognitive efficiency instrumental to cognitive health and psychological well-being in breast cancer survivorship.

Training related gains did not significantly correlate with any demographic variables such as age, age at diagnosis or time elapsed since diagnosis suggesting that training is beneficial for a wider population, irrespective of particular demographic variables relating to both age and breast cancer diagnosis. Having said this, future work should systematically

manipulate factors such as age at diagnosis and time since diagnosis to fully explore the modulating role of such individual difference variables.

Participants' positive responses indicated that they felt psychologically empowered. With increases in cognitive efficiency, individuals are better equipped and empowered to manage and reduce the impact of intrusive and troublesome anxieties through interventions that can pose less risk than current pharmaceutical treatments for psychopathology [40].

**Limitations**

The current study has a number of limitations. Participants were recruited via social media platforms and therefore may not be representative of the wider population of breast cancer survivors. While such recruitment methods can access large numbers of participants, they do not provide data on reasons for refusing participation, and clinical characteristics of the sample. Future research should extend the current intervention using a registered RCT that fully randomizes group allocation of participants and identifies primary and secondary outcome measures of interest as well as including measures of cognitive vulnerability and participant demographics such as education. The current study did not measure cognitive transfer effects and further research should clarify the specific (cognitive) mechanisms underlying these beneficial emotional transfer effects of cognitive training. Finally, future research should systematically investigate the benefits of training in women with secondary and metastatic breast cancer, given that research in secondary breast cancer is sparse, this seems highly pertinent.

**Clinical Implications**

Attentional control training is a prosperous new technique targeting specific cognitive, behavioural and neural networks that play a crucial role in anxiety, stress and

rumination [18]. Improved processing efficiency via adaptive cognitive training and its longer term effects in sustaining reduced emotional vulnerability has the potential to increase the efficacy of therapies such as CBT and mindfulness that can be available on the NHS in breast cancer survivorship. The adaptive dual n-back training was recently shown to increase mindfulness meditation effects on reductions in worry over time, through its effects on processing efficiency [14]. In a recent Cochrane review of 28 studies [28], group Cognitive Behavioural Therapy helped reduce emotional vulnerability in non-metastatic breast cancer. CBT and mindfulness meditation effectiveness rely on processing efficiency, and as such the adaptive dual n-back can help sustain and enhance their effects if used in combination.

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Table 1. Mean self-report symptomatology scores for each group (Training and Control) at pre, post and follow up time points.

| | Pre-Test | | | | Post-Test | | | | Follow-Up 1 | | | | Follow-Up 2 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Training | | Control | | Training | | Control | | Training | | Control | | Training | | Control | |
| Rumination | 41.46 | (11.78) | 41.53 | (12.07) | 40.13 | (9.23) | 40.64 | (11.59) | 36.94 | (8.54) | 40.21 | (12.66) | 35.72 | (9.55) | 41.28 | (13.51) |
| Anxiety Symptomatology | 6.11 | (1.88) | 6.28 | (2.36) | 5.09 | (1.54) | 6.12 | (2.64) | 5.03 | (1.56) | 6.1 | (2.76) | 5.11 | (2.05) | 6.01 | (2.72) |
| Depression Symptomatology | 3.19 | (.83) | 3.41 | (.87) | 3.05 | (.83) | 3.26 | (.93) | 3.12 | (.87) | 3.33 | (.88) | 3.0 | (.83) | 2.64 | (.90) |
| Resilience | 68.21 | (12.60) | 62.71 | (18.71) | 68.84 | (11.83) | 63.39 | (15.13) | 69.38 | (13.21) | 62.54 | (18.22) | 66.56 | (14.99) | 61.96 | (18.13) |
| Worry | 49.0 | (16.11) | 51.04 | (15.19) | 46.69 | (15.55) | 48.14 | (13.76) | 46.34 | (15.37) | 50.39 | (17.41) | 45.91 | (16.27) | 51.21 | (16.27) |

*Note. Standard deviations are in parentheses*.

Footnotes

[1] Mean emotional vulnerability scores reflect the per protocol population for all tables and graphs.

[2] Analyses on the subscales of intrusion and avoidance (Impact of Events) revealed no significant effects (all $F$'s < 1, NS).