Post-Stroke Anxiety and Depression: The Association with Psychological Flexibility and Consideration of Time Since Stroke on Treatment Outcomes

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Thesis Portfolio Abstract

Background: Mood difficulties are prevalent in stroke survivors. Acceptance and Commitment Therapy (ACT) is a psychological intervention with a growing evidence base with stroke survivors. Psychological flexibility is a key process in ACT to support individuals manage mood difficulties. Clinical guidelines in the United Kingdom do not recommend when to provide psychological intervention for post-stroke mood difficulties. The impact of time since stroke on intervention outcomes is under-researched.

Method: A systematic review was conducted to synthesize research on psychological interventions for post-stroke depression and anxiety to explore the impact of time since stroke. A cross-sectional study recruited 206 stroke survivors, measuring impacts of stroke, psychological flexibility, depression, and anxiety. This study explored the associations between indicators of stroke impact and mood, and whether psychological flexibility moderates this relationship.

Results: A narrative synthesis of 15 studies found a greater frequency of significant improvement in depression and anxiety in intervention groups compared to controls at an earlier time since stroke. Only four studies included anxiety as an outcome. The empirical study found that psychological flexibility did not moderate the relationships between impacts of stroke, and mood. Psychological flexibility predicted depression and anxiety with a large and moderate effect size respectively.

Conclusions: Interventions were more frequently effective when provided earlier after stroke, but more evidence is needed. It is recommended that intervention randomised controlled trials for post-stroke mood routinely report time since stroke and consider recruitment of specific ranges. Psychological flexibility does not moderate the relationships between stroke impacts and mood but does predict depression and anxiety. Further research is required on psychological flexibility and mood in stroke survivors, and how it can be developed therapeutically.[1]

[1] I acknowledge that material from my ClinPsyD Thesis Proposal has been used throughout this portfolio, due to the inherent necessity to re-use material in this instance.

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Chapter 1: Introduction

Stroke is a major cause of disability worldwide with over 12 million people experiencing a stroke each year; one in four individuals aged over 25 will have a stroke in their lifetime (Feigin et al., 2021, 2022). The incidence of stroke has increased by 70% over the past 30 years and it is estimated that by 2050, there will be 200 million stroke survivors (Feigin et al., 2021). While stroke is often associated with potentially long-term changes in physical function, cognitive function, and speech difficulties (El Husseini et al., 2023; Hardie et al., 2004; Plowman et al., 2012), mood difficulties are also common after stroke.

Depression is thought to be present in 31% of stroke survivors (Hackett & Pickles, 2014) while post-stroke anxiety is prevalent in 18.7% to 24.2% of the population (Knapp et al., 2020). There is evidence to suggest that these prevalence rates of depression and anxiety can remain stable to up to 15 and 10 years respectively (Ayerbe et al., 2013a, 2014). Post-stroke depression is associated with increased mortality, poorer functional outcomes, and reduced quality of life (Ahn et al., 2015; Blöchl et al., 2019; Cai et al., 2019; Kim et al., 2018). Similarly, anxiety after stroke has been linked with worse functional status during the chronic phase of stroke, alongside lower quality of life (Lee et al., 2019; Tang et al., 2013).

The treatment for post-stroke mood is not addressed in a specific treatment guideline within the United Kingdom (National Institute for Health and Care Excellence [NICE], 2013); instead, recommendations are based on those for depression within chronic health conditions and generalised anxiety disorder (NICE, 2009, 2020). Within these guidelines cognitive behavioural therapy (CBT) is the recommended treatment in both (NICE, 2009, 2020). A recent meta-analysis suggests that CBT is an effective treatment for depression and anxiety after stroke; however, this is based on a small amount of evidence with fair to poor methodological quality, particularly regarding anxiety (Ahrens et al., 2023).

Acceptance and Commitment Therapy (ACT) is a third wave CBT approach that has shown comparative outcomes with CBT in treating anxiety and depression in the non-stroke population (Ferreira et al., 2022). ACT is based on relational frame theory and functional contextualism (Prevedini et al., 2011) and aims to support the development of psychological flexibility in order to live in line with values in the

face of inevitable human suffering (Hayes et al., 2011). In order to do this, psychological flexibility comprises of six key processes; acceptance, contacting the present moment, awareness of values, committed action, self-as-context, and cognitive defusion (Harris, 2006; Hayes et al., 2006).

Alongside CBT, ACT is a recommended treatment for post-stroke mood difficulties in the National Clinical Guideline for Stroke for the United Kingdom and Ireland (Intercollegiate Stroke Working Party, 2023) and has a growing evidence base. ACT has been found to be effective for post-stroke mood difficulties in single case, small study designs, and larger trials (Graham et al., 2015; Majumdar & Morris, 2019; Niu et al., 2022; Rauwenhoff et al., 2022). A recent multicentre randomised controlled trial (RCT) found that ACT was not more effective than psychoeducation and relaxation training for individuals with acquired brain injury; however, clinically significant change was present in long term outcomes in favour of ACT (Rauwenhoff et al., 2024).

While NICE and the Intercollegiate Stroke Working Party provide recommendations for the treatments of mood difficulties after stroke (Intercollegiate Stroke Working Party, 2023; NICE, 2009, 2020), guidelines do not suggest the optimal time to intervene. To our knowledge, only one study has directly observed the effect of time since stroke on interventions for post-stroke mood within a RCT design (Gao et al., 2017); however, the impact of time since stroke remains unclear.

Evidence suggests that post-stroke depression most often occurs within the first few months following stroke. Two thirds of stroke survivors who develop depression within the first year after stroke will do so in the initial three months (L. Liu et al., 2023). Approximately 44% will then go on to recover within the first year, representing a dynamic natural history of post-stroke depression (L. Liu et al., 2023).

L. Liu et al. (2023) suggest that there is not enough evidence to understand the natural history of post-stroke depression after one-year post-stroke. It has been suggested that prevalence remains stable over time (Ayerbe et al., 2013a); however work by Hackett and Pickles (2014) contradicts this, demonstrating a reducing prevalence rate that can be attributed to adjustment or better use of management strategies. It should be noted that Hackett and Pickles found a prevalence of post-

stroke depression of 23% at five years post-stroke which still represents a significant proportion of stroke survivors.

The longitudinal prevalence of post-stroke anxiety is similar to depression. Ayerbe et al. (2014) found that 58% of those who experienced anxiety at any point up to 10 years post-stroke, also experience post-stroke anxiety at three-months post-stroke. The prevalence rate of post-stroke anxiety is thought to be relatively stable up to 10 years post-stroke, but further research is needed (Ayerbe et al., 2014; Knapp et al., 2020).

The persistent prevalence of post-stroke mood difficulties, and the substantive recovery rates within the first year emphasise the need to understand when psychological intervention for post-stroke mood difficulties should take place. Understanding this key window of intervention may help to inform policy and resource allocation for the betterment of stroke survivors regarding their mental health.

This thesis aims to contribute to growing evidence bases and address gaps in the literature. Chapter 2 comprises a systematic review exploring whether time since stroke impacts on therapy outcomes for post-stroke depression and anxiety in randomised controlled trials. Following this, Chapter 4 investigates the associations between impacts of stroke and mood difficulties, and whether psychological flexibility moderates these relationships. Chapter 3 will act as a bridge between these studies, exploring the links between them. Finally, Chapter 5 will conclude the portfolio, bringing together the findings alongside the limitations and implications for clinical practice and future research.

Chapter 2: Systematic Review

The Consideration of Time Since Stroke on Intervention Outcomes for Post-Stroke Depression and Anxiety: A Systematic Review

The Consideration of Time Since Stroke on Intervention Outcomes for Post-Stroke Depression and Anxiety: A Systematic Review

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Abstract

Objective: This systematic review aimed to synthesise intervention randomised controlled trials (RCTs) to explore the impact of time since stroke.

Method: Four databases were searched (Medline Ultimate, APA PsychINFO, CINAHL Ultimate, and EBSCO E-Journals) from inception to October 2024. Only RCTs that explored the effect of a psychological intervention on depression or anxiety in stroke survivors were included. The Revised Joanna Briggs Institute Critical Appraisal Tool for the Assessment of Risk of Bias for Randomised Controlled Trials was used, and a narrative synthesis conducted.

Results: 15 publications were included in this review following screening and risk of bias assessment. Due to lack of reporting, heterogeneity in time since stroke, and overlapping groups, synthesis was split by maximum time since stroke recruitment of less than three months, less than four months, less than six months, and more than six months post-stroke. A greater frequency of significant improvement in depression in intervention groups compared to controls was noted at an earlier time since stroke. Only four studies included anxiety as an outcome.

Conclusions: Interventions were more frequently effective when provided earlier in time since stroke; more evidence is required to understand if there is an impact of time since stroke on intervention outcomes. The findings cannot be generalised with confidence until such evidence emerges. It is recommended that intervention RCTs on post-stroke depression and anxiety routinely report time since stroke and consider adjusting recruitment ranges to understand the effectiveness of psychological intervention in individuals who are over one-year post-stroke.

Keywords: post-stroke depression, post-stroke anxiety, intervention, time since stroke

Introduction

It is estimated that, globally, over 12 million people each year will experience a stroke (Feigin et al., 2022) with the incidence of stroke increasing by 70% over the past 30 years; should current trends continue, it is estimated that there will be more than 200 million stroke survivors by 2050 (Feigin et al., 2021).

Mood difficulties, such as anxiety and depression can follow a stroke. Anxiety and depression post-stroke have been associated with poorer functional recovery, greater length of hospital stay, and reduced quality of life (Chemerinski et al., 2001; Sugawara et al., 2015; Tang et al., 2013). Understanding psychological difficulties following stroke and how best to provide support have been recognised as leading research priorities (James Lind Alliance, 2021).

Post-stroke mood difficulties are prevalent within the stroke survivor population. Post-stroke depression is estimated to have a prevalence of 31% (Hackett & Pickles, 2014), and post-stroke anxiety is suggested to occur between 18.7% and 24.2% of stroke survivors (Knapp et al., 2020).

Many stroke survivors appear to develop depression within the first few months. A meta-analysis by L. Liu et al. (2023) suggests two thirds of stroke patients experiencing post-stroke depression within one year after their stoke are likely to develop this within the first three months after a stroke; development of depression in this time period has been regarded as early-onset post-stroke depression (Llorca et al., 2015). However, evidence suggests that 44% of these individuals recover within the first year following stroke, with new cases developing over time (L. Liu et al., 2023). The natural history of post-stroke depression, therefore, appears to be dynamic (L. Liu et al., 2023).

There is conflicting evidence regarding the wider picture of post-stroke depression prevalence. One study found that prevalence of post-stroke depression decreases over time with prevalence at one year, two to four years, and five years post-stroke being reported as 33%, 25% and 23% respectively (Hackett & Pickles, 2014). The authors suggest that a reduction in long-term prevalence of post-stroke depression may be a result of adjustment to life after stroke or better use of management strategies. Conversely, Ayerbe et al. (2013) found no significant

difference between prevalence rates less than year post-stroke, and over one year post-stroke, and that prevalence is stable over time, potentially up to 10 years, contradicting Hacket and Pickles. A dynamic natural history of post-stroke depression of up to five years is suggested, with recovery and new cases occurring over time; however, a lack of evidence mean the precise process remains unclear (Ayerbe et al., 2013; L. Liu et al., 2023).

Evidence suggests that prevalence of post-stroke anxiety remains relatively stable up to 10 years after stroke; however, it is noted that additional research is needed on prevalence rates one year post-stroke (Ayerbe et al., 2014; Knapp et al., 2020). Similar to the findings with post-stroke depression, Ayerbe et al. found that 58% of those who experienced post-stroke anxiety at any point in their 10 year range, were also anxious at the three month stage; an equal proportion of these patients experienced post-stroke depression at three months post-stroke also. These findings may suggest an early-onset for post-stroke anxiety; however, further research is needed.

There is an emerging evidence base for psychological treatments for post-stroke depression and anxiety. Cognitive behavioural therapy (CBT) is a psychological intervention that has been subject of recent meta-analysis for the treatment of post-stroke depression and anxiety. The evidence suggests that CBT is an effective therapy for the treatment of anxiety and depression post-stroke; however, more research is required, especially around post-stroke anxiety (Ahrens et al., 2023; Wang et al., 2018). Mindfulness and acceptance based interventions such as acceptance and commitment therapy and mindfulness-based stress reduction have also been employed with stroke populations with promising results; however, the evidence base is currently too small to definitively guide clinical practice (Han, 2023).

Gao et al. (2017) explored how treatments for post-stroke depression vary in effectiveness depending on time since stroke. They found that treatment, through CBT or medication, given to individuals at discharge and at three months post discharge had no significant difference in outcomes compared to controls. CBT appeared to have an impact for those recruited nine months after discharge; however, this was based on a scale of melancholia, while the Hamilton Depression Rating

Scale did not show significant differences. The impact of time since stroke on intervention outcomes remains unclear from this study.

An early review on the management of post-stroke depression suggested that research for psychological treatments should consider a variety of contextual factors, including stage of post-stroke recovery (Kneebone & Dunmore, 2000); however, there does not appear to be much literature that considers time since stroke on psychological treatment. If time since stroke impacts the outcomes of treatments it may provide insight into the best time to provide treatment; however, if it is not considered within research studies, it may lead to less effective treatments for post-stroke mood difficulties.

This review aims to explore whether time since stroke impacts on therapy outcomes for post-stroke depression and anxiety in RCTs. Clinical practice, and the guidelines that shape it, are informed by available literature. It is therefore important for research on psychological interventions for post-stroke mood difficulties to consider time since stroke to inform if there is a best time to provide treatment. Understanding this may also help to inform policy and allow better use of resource to provide better outcome for stroke survivors. This review will also explore whether time since stroke is routinely recorded, considered, and controlled as a potential variable that could impact confidence in the outcomes of treatment trials.

Methodology

The protocol for this review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) at the conception of the project on 16th April 2024 (Registration Number: CRD42024530658). Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Page et al., 2021) were followed for this review (Appendix B and C).

Search Strategy

An electronic literature search was completed across four databases (Medline Ultimate, APA PsychINFO, CINAHL Ultimate, and EBSCO E-Journals) to retrieve studies published between inception and the 18th October 2024, when the search was completed. The search terms were generated through consultation with a specialist

librarian. Search terms included “stroke”, “anxiety”, “depression”, and “RCT”, alongside their synonyms (Appendix D).

Eligibility Criteria

Studies were required to be published in a peer-reviewed journal and available in the English language. Studies were included if they were RCTs that investigated psychological treatment for a mood difficulty where a mood measure was used as a primary outcome. Pilot RCTs were included provided they had a sample size of at least 20. This size was chosen in order to include more studies to generate a better understanding of the consideration and reporting of time since stroke. This cut off also enabled studies with very small sample sizes to be excluded, as their inclusion may have impacted the outcome of the synthesis by using data where sufficient power was likely not achieved. When deciding this cut off, the limitations and impacts of inadequate power were considered.

A criterion was required to ensure that the interventions included in the synthesis were psychological therapies that focused on active change, especially given the breadth of other therapy disciplines that provide support post-stroke. For the purpose of this review, a treatment was deemed psychological if at least 50% of the processes involved in the treatment were based on a cognitive or behavioural theory that aimed to modify thoughts or behaviour. Cognitive or behavioural elements were required as this aligned with the current evidence base and National Institute for Health and Care Excellence (NICE) guidelines used for psychological intervention in post-stroke mood (NICE, 2009, 2020) A 50% figure was decided so that a substantive element of the treatment would include an element of active change where a patient was required to enact concepts from the therapy, and was based on cognitive and behavioural principles. Where possible, sessions plans were reviewed to inform this judgement. The design had to include a comparator group (passive or active) which was not a comparable psychotherapy. The participants must have been stroke survivors who were aged 18 or above. Only studies utilising primary data were included.

Feasibility RCTs were excluded unless there was a clearly defined objective that explored the outcome of the intervention, as opposed to the acceptability of the

methodology or intervention. If there was an objective on the outcome of treatment, more confidence could be placed in their methodology and conclusion regarding treatment outcome compared to those who solely explored feasibility. Feasibility RCTs also required an adequate sample (n = 20) as described above. Non-inferiority trials were also excluded. If participants were survivors of transient ischemic attacks or spinal strokes, these studies were excluded unless this data was reported separately. Studies were also excluded if they only used qualitative data and analysis.

Procedure

The primary researcher (EB) completed the search of databases and removed duplicate studies. All titles and abstracts were then independently screened for their eligibility by the primary researcher. Semi automation software, Rayyan, was used to support the screening procedure (Ouzzani et al., 2016). Studies were put forward for full text screening if they met the inclusion criteria or if further information was required to ascertain this. A second researcher (AM) independently screened 25% of the studies at each stage. At title and abstract screening percentage agreement was 94% ($k = 0.62$); disagreements were resolved without the need for the third reviewer. Percentage agreement at the full-text stage was 96% ($k = 0.90$).

Quality Assessment

Methodological quality was assessed using the Revised Joanna Briggs Institute (JBI) Critical Appraisal Tool for the Assessment of Risk of Bias for Randomised Controlled Trials, shown in Appendix E (Barker et al., 2023). This appraisal tool features 13 questions to ascertain whether study design and application have been implemented in a way to adequately minimize the risk of bias. In the revised tool, the 13 questions have been organised into specific validity constructs to better support judgements regarding risk of bias at each domain level. The authors of the assessment tool recommend that the results of the assessment tool be presented in a transparent way that allows the reader to understand the risk of bias within specific domains (Barker et al., 2023). A percentage was also calculated for the total questions where the criteria has been met regarding reducing internal validity bias; this does not include statistical conclusion validity which should be reviewed separately to internal validity bias (Barker et al., 2023). An overall score was not

provided as criteria will be weighted differently (Robertson-Malt, 2014); however, higher percentages indicate a lower risk of bias as more of the criteria have been met. Risk of bias was assessed for all studies by EB with AM reviewing 25%; disagreements were resolved between the two reviewers without the need of a third reviewer.

Data Extraction

The following data was extracted from 100% of the included studies by the primary researcher: Author, year, country, intervention type, intervention length, intervention format, intervention setting, control type, control intervention, control length, sample size at analysis, age, sex, aspect of mood targeted by intervention, outcome measure, reported time since stroke, recruitment criteria time since stroke, outcome of analysis regarding depression and anxiety. The data extraction was checked by a second reviewer (AM), who reviewed 25% of the studies; there was agreement in 100% of the studies checked.

Data Synthesis Strategy

A meta-analysis was intended at the time of pre-registration; however, the data extracted did not allow for a meta-analysis that would meaningfully answer the research question. Due to the wide ranges of time since stroke within many of the studies, the only possible separation of studies would be at the three month post-stroke stage. While this is consistent with the discrimination between early-onset and late-onset post-stroke depression (L. Liu et al., 2023), the small amount of studies that only recruited later than three month post-stroke, and the lack of formal interim analyses meant a meta-analysis was not viable in the context of the research question. In addition, the heterogeneity of the data, particularly regarding intervention type, would have made conclusions difficult to draw.

A narrative synthesis was conducted to review the effect of time since stroke within intervention RCTs. The synthesis utilised guidance by Popay et al. (2006) to explore patterns across the included studies regarding the effects of interventions in the context of time since stroke while considering other factors that may explain these patterns. It was planned that studies would be grouped based on intervention type; however, there was large heterogeneity and too few studies for this to be

possible; therefore, this aspect was dropped. Due to wide ranges, these groups were determined based on the top limit of the time since stroke recruitment criteria; up to three months, up to four months, up to six months, and over six months post-stroke. One study stratified their sample to explore the effect of time since stroke on intervention outcomes (Gao et al., 2017), this study is included in all groups for synthesis, except for up to four months. The synthesis explores depression and anxiety separately. In keeping with the guidance of Popay et al. additional factors were explored which may provide alternative explanations for the findings; risk of bias, inclusion of participants with a history of depression, and intervention setting were explored.

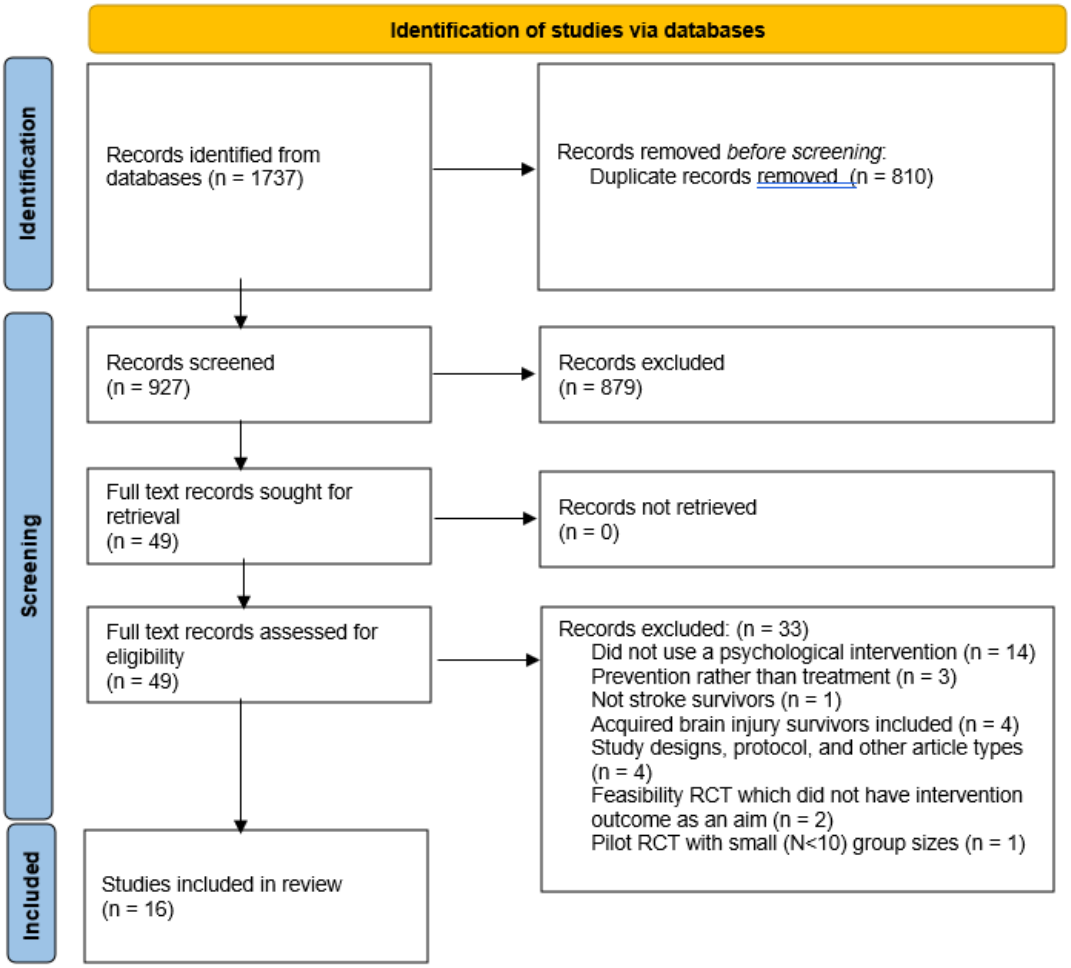
Results

Study Selection

After removing duplicates, 927 studies were screened against the inclusion and exclusion criteria. 49 studies remained after title and abstract screening, and 16 studies were included in the review following full-text screening (Figure 1).

Figure 1

PRISMA Flowchart



Risk of Bias Assessment

Table 1 below shows the outcome of each assessment question, with a percentage score for the number of criteria met within each domain. In RCTs that have multiple outcomes, i.e. depression and anxiety, no difference was observed in rating between outcomes. Therefore, the risk of bias was condensed into a single rating for each question.

Table 1

Internal validity bias assessment results using Joanna Briggs Institute guidelines

Study ID	Outcome	Internal Validity Bias Related to:														Statistical Conclusion Validity		
		Selection and Allocation				Administration of intervention/exposure				Assessment, detection, and measurement of the outcome				Participant Retention				
		1	2	3	Domain %	4	5	6	Domain %	7	8	9	Domain %	10	Domain %	Total %	11	12	13
Chow et al. (2023)	D	N	?	?	0	Y	N	?	33	Y	Y	Y	100	N	0	40	N	N	Y
Duan et al. (2023)	D	Y	?	Y	66	Y	N	Y	66	Y	Y	?	66	Y	100	70	N	N	Y
Gao et al. (2017)	D	Y	Y	?	66	Y	N	Y	66	N	Y	?	33	Y	100	60	N	N	Y
Kirkness et al. (2017)	D	Y	Y	N	66	N	N	Y	33	Y	Y	?	66	Y	100	60	N	N	Y
Kootker et al. (2017)	D and A	N	?	N	0	N	N	Y	33	Y	Y	N	66	N	0	30	?	Y	Y
Lincoln and Flannaghan (2003)	D	Y	Y	?	66	N	N	Y	33	Y	Y	N	66	N	0	50	N	Y	Y
Y. Liu et al. (2023)	D	Y	Y	Y	100	N	N	Y	33	Y	Y	Y	100	Y	100	80	N	N	Y
Mitchell et al. (2009)	D	N	?	N	0	N	N	?	0	Y	Y	?	66	N	0	20	?	N	Y
Peng et al. (2015)	D and A	Y	Y	Y	100	N	N	Y	33	Y	Y	?	66	N	0	60	N	N	Y
Sun et al. (2022)	D	Y	Y	Y	100	Y	N	Y	66	Y	Y	?	66	N	0	70	N	N	Y
Sun et al. (2024)	D	Y	Y	Y	100	N	N	?	0	Y	Y	Y	100	Y	100	70	?	N	Y
Thomas et al. (2013)	D	Y	Y	Y	100	N	N	?	0	?	Y	?	33	Y	100	50	Y	Y	Y

Study ID	Outcome	Internal Validity Bias Related to:														Statistical Conclusion Validity		
		Selection and Allocation				Administration of intervention/exposure				Assessment, detection, and measurement of the outcome				Participant Retention				
		1	2	3	Domain %	4	5	6	Domain %	7	8	9	Domain %	10	Domain %	Total %	11	12	13
Thomas et al. (2019)	D	Y	Y	N	66	N	N	?	0	Y	Y	N	66	Y	100	50	Y	Y	Y
Udvardi et al. (2024)	D and A	?	?	Y	33	N	N	Y	33	?	?	?	0	N	0	20	N	Y	N
Wang et al. (2020)	D	?	?	?	0	N	N	?	0	?	?	?	0	N	0	0	N	N	?
Wichowicz et al. (2017)	D and A	?	?	N	0	N	N	?	0	Y	Y	N	66	N	0	20	N	N	N

Note: Outcomes: Depression (D), Anxiety (A); Rating scale: Yes (Y), No (N), Unclear (?).

JBI Tool Questions:

1 = Was true randomization used for assignment of participants to treatment groups?; 2 = Was allocation to groups concealed?; 3 = Were treatment groups similar at the baseline?; 4 = Were participants blind to treatment assignment?; 5 = Were those delivering the treatment blind to treatment assignment?; 6 = Were treatment groups treated identically other than the intervention of interest?; 7 = Were outcome assessors blind to treatment assignment?; 8 = Were outcomes measured in the same way for treatment groups?; 9 = Were outcomes measured in a reliable way?; 10 = Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?; 11 = Were participants analyzed in the groups to which they were randomized?; 12 = Was appropriate statistical analysis used?; 13 = Was the trial design appropriate and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

Barker et al. (2023) disagree with the removal of studies to allow a synthesis of high-quality studies as this limits the potential for data synthesis. The guidance of Barker et al. was largely followed, including studies with a relatively high risk of bias, where only two domains were met. Barker et al. also state how removal of studies can limit the full potential of synthesis of eligible research. In light of this, the authors chose to make an exception with regards to one study (Wang et al., 2020). This study was removed from the review due to meeting none of the criteria of the risk of bias tool and the methodology they detailed provided little confidence for their inclusion and eligibility within a synthesis of RCTs. It is possible that their inclusion may have negatively impacted the synthesis through the introduction of an extremely high risk of bias, so strong that it would not weigh into consideration. The following risk of bias assessment was reported for the remaining 15 studies in the review.

The studies in the review varied in their reduction of internal validity bias. Four studies met at least 70% of the criteria pertaining to reducing internal validity bias (Duan et al., 2023; Y. Liu et al., 2023; Sun et al., 2024; Sun et al., 2022); six papers were assessed to meet between 50 and 70% of the criteria (Gao et al., 2017; Kirkness et al., 2017; Lincoln & Flannaghan, 2003; Peng et al., 2015; Thomas et al., 2013, 2019). The remaining five RCTs met less than 50% of the internal validity bias criteria (Chow et al., 2023; Kootker et al., 2017; Mitchell et al., 2009; Udvardi et al., 2024; Wichowicz et al., 2017).

Table 2 provides common reason for studies not meeting criteria across areas of randomisation, blinding and measurement. When reviewing randomisation methods, minimization was deemed appropriate with a clear description of group allocation concealment, as recommended by Cochrane (Higgins et al., 2024). No publications described blinding of interventionists. Items assessing the blinding of interventionists and participants to group allocation should be weighted within the context of research in psychological interventions where blinding of participants and interventionists is not routine or straightforward (Juul et al., 2021).

Table 2

Reasons for not meeting quality criteria within randomisation, blinding, and measurement

Area of Internal Validity Bias and Reason	Frequency (n =)	Study ID
Randomisation		
Minimization method applied without describing group allocation concealment	3	Chow et al. (2023); Kootker et al. (2017); Mitchell et al. (2009)
Randomisation method not adequately reported	2	Udvardi et al. (2024); Wichowicz et al. (2017)
Group allocation concealment method not adequately reported	6	Chow et al. (2023); Duan et al. (2023); Kootker et al. (2017); Mitchell et al. (2009); Udvardi et al. (2024); Wichowicz et al. (2017)
Blinding		
Did not blind participants to group	11	Y. Liu et al. (2023); Kootker et al. (2017); Wichowicz et al. (2017); Peng et al. (2015); Udvardi et al. (2024); Sun et al. (2024); Thomas et al. (2013); Kirkness et al. (2017); Wang et al. (2020); Thomas et al. (2019); Mitchell et al. (2009); Lincoln and Flannaghan (2003)
Did not blind assessors to group	1	Gao et al. (2017)
Assessor blinding not adequately reported	2	Thomas et al. (2013); Udvardi et al. (2024)
Measurement		

Area of Internal Validity Bias and Reason	Frequency (n =)	Study ID
Did not adequately describe steps to improve measurement reliability	8	Duan et al. (2023); Gao et al. (2017); Kirkness et al. (2017); Mitchell et al. (2009); Peng et al. (2015); Sun et al. (2022); Thomas et al. (2013); Udvardi et al. (2024)
Did not report procedure for the measurement of outcomes	1	Udvardi et al. (2024)

Statistical conclusion validity was assessed by questions 11,12, and 13. Intention to treat analysis was only completed and adequately described in two studies (Thomas et al., 2013, 2019). The appropriateness of statistical analysis was determined based on balance of several factors including evidence of power analysis, implementation of appropriate statistical tests, detail of the assumptions met for analysis method, and adequate reporting of test statistics, effect sizes and descriptive statistics. Five studies were deemed to have met the majority of this criteria (Kootker et al., 2017; Lincoln & Flannaghan, 2003; Thomas et al., 2013, 2019; Udvardi et al., 2024). Four RCTs did not report a power calculation (Y. Liu et al., 2023; Peng et al., 2015; Sun et al., 2022; Wichowicz et al., 2017), while one study implies a power calculation was performed but does not report significance or power level (Mitchell et al., 2009).

Study Characteristics

Study, sample, and intervention characteristics of the 15 included studies are presented in Tables 3 and 4. The total sample size was 1759. The mean age could be calculated across 13 studies, $M = 62.66$, range of mean age = 55.41–73.72, the remaining two publications reported age as a median (Kootker et al., 2017; Sun et al., 2024). In the 14 studies which reported gender, 62.10% of the sample were male.

The studies were conducted in a variety of countries. Six were completed in China, three in the UK, two in the USA, one in Hong Kong, the Netherlands, Poland, and Hungary respectively.

CBT was used as the intervention in four publications (26.67%), four used a CBT-based approach, either a brief intervention with CBT elements or behavioural activation (26.67%), one used behavioural therapy, and two used mindfulness-based approaches (13.33%). The remaining four studies each used a different intervention: Solution Focused Therapy, Narrative Therapy, Neurolinguistic Programming, and group Acceptance and Commitment Therapy (ACT). The wide range of interventions applied in the included studies represents a large degree of heterogeneity.

All 15 studies had depression as an outcome and was mostly (n = 8) measured using a version of the Hamilton Rating Scale for Depression (53.33%). The Hospital Anxiety and Depression Scale was used in two studies (13.33%), while the Center for Epidemiological Studies Depression Scale, Beck Depression Inventory, Stroke Aphasic Depression Questionnaire 21, Patient Health Questionnaire-9, and the Geriatric Depression Scale were each used in one study. While a common outcome measure was used in over 50% of the studies, the wide range measurement tools represent further heterogeneity within the data.

Anxiety was an outcome in only four studies (26.67%). The Hospital Anxiety and Depression Scale was used in two studies, the Hamilton Anxiety Rating Scale in one, and the Spielberger Trait Anxiety Inventory in the final study.

Table 3

Study and Sample Characteristics

Study ID	Country	Sample Size at Post-Intervention Analysis	Reported Time Since Stroke	Recruitment Criteria Time Since Stroke	Age (mean)	Sex (% male)
Y. Liu et al. (2023)	China	Intervention n = 70 Control n = 69	Not reported	Stroke diagnosis within the last 2 weeks	61.91	65.47
Duan et al. (2023)	China	Intervention n = 24 Control n = 24	Intervention 74.00 +/- 18.55 (days) Control 70.88 +/- 20.73 (days)	1 – 6 months post-stroke	55.41	81.69
Sun et al. (2024)	China	Intervention n = 118*** Control n = 119***	Not reported	2 – 36 weeks post-stroke	Unable to calculate	68.35
Sun et al. (2022)	China	Intervention n = 33 Control n = 32	Not reported	<3 months post-stroke	62.03	56.92
Peng et al. (2015)	China	Intervention n = 90 Control n = 90	Not reported	<3 months post-stroke	60.00	72.22
Kirkness et al. (2017)	USA	Intervention n = 65** Control n = 26	Not reported	Recruited post hospital discharge	60.30	50.00

Study ID	Country	Sample Size at Post-Intervention Analysis	Reported Time Since Stroke	Recruitment Criteria Time Since Stroke	Age (mean)	Sex (% male)
Gao et al. (2017)	China	Intervention n = 87 Placebo Control n = 86 Citalopram Control n = 85	Not reported	Groups stratified for discharge, discharge - 3 months post-discharge, 3 - 6 months post-discharge, and 6 - 9 months post-discharge	66.03	51.82
Lincoln and Flannaghan (2003)	UK	Intervention n = 38 Passive Control n = 38 Active Control n = *42*	Not reported	Participants recruited at 1, 3, and 6 months post-stroke	66.05	51.22
Thomas et al. (2013)	UK	Intervention n = 54* Control n = 51*	Intervention *M* = 8.7 months (4.1 – 26.1) Control *M* = 9.0 months (4.9 – 39.0)	Not reported	66.96	62.86
Thomas et al. (2019)	UK	Intervention n = 25* Control n = 23*	Intervention: 3 months – 1 year = 16 1 – 2 years = 7	Between 3 months and 5 years post-stroke	65.60	60.40

Study ID	Country	Sample Size at Post-Intervention Analysis	Reported Time Since Stroke	Recruitment Criteria Time Since Stroke	Age (mean)	Sex (% male)
			2 – 4 years = 2 Control: 3 months – 1 year=14 1 – 2 years=5 2 – 4 years=4			
Chow et al. (2023)	Hong Kong	Intervention n = 58 Control n = 50	Not reported	>2 years post-stroke	73.72	67.00
Kootker et al. (2017)	Netherlands	Intervention n = 24 Control n = 28	Intervention *Mdn* = 26 months (2 – 243) Control *Mdn* = 21.5 (2 – 138)	>3 months post-stroke	Unable to calculate	62.30
Wichowicz et al. (2017)	Poland	Intervention n = 30 Control n = 32	Not reported	Baseline measures administered at 14-days post-hospital discharge. Reported that participants left hospital after 9 +/- 2 days	54.00	Not reported

Study ID	Country	Sample Size at Post-Intervention Analysis	Reported Time Since Stroke	Recruitment Criteria Time Since Stroke	Age (mean)	Sex (% male)
Udvardi et al. (2024)	Hungary	Intervention n = 43 Control n = 37	Intervention *M* = 112.02 days *SD* = 169.60 Control *M* = 205.68 days *SD* = 504.75	Not reported	56.89	62.37
Mitchell et al. (2009)	USA	Intervention n = 45 Control n = 53	Not reported	<4 months post-stroke	57.00	60.40

Note: Sample size after data imputation (*); Intervention groups were combined for analysis (**); Loss to follow up included in analysis with unreported imputation methods (***)

Table 4

Intervention Characteristics

Study ID	Intervention	Mood Focus and Measure	Format	Intervention Setting	Control and Type	Outcome
Y. Liu et al. (2023)	Acceptance and Commitment Therapy	Depression; HAM-D 24	Group	Acute stroke inpatient unit	Passive - Usual care support within hospital	Group ACT significantly reduced symptoms of depression at post intervention and at 3 month follow up. Significant time x group interaction in favour of the intervention $\eta_p^2 = .306$.
Duan et al. (2023)	Mindfulness Based Stress Reduction (MBSR) and Sham Transcranial Magnetic Stimulation	Depression; HAMD-17	Not reported	Not reported	Active - Sham Transcranial Magnetic Stimulation and General psychological care	Significant time x group interaction. Post hoc comparisons showed significant differences after intervention and at eight week follow up between intervention and control group ($p < .001$).
Sun et al. (2024)	Cognitive Behavioural Therapy*	Depression; HAMD-17	Individual	Not reported	Active - Acupuncture combined with 5 elements music (AFEM)*	Both CBT and AFEM significantly improved symptoms of depression. significantly greater reduction in depression symptoms with AFEM

Study ID	Intervention	Mood Focus and Measure	Format	Intervention Setting	Control and Type	Outcome
						compared to CBT post-intervention and at 12 week follow up.
Sun et al. (2022)	Behavioural activation therapy	Depression; HAMD-17	Individual	Community	Passive - Standardised usual care	Significant type x group interaction at post-intervention for depression (p = .003). Decreases in the intervention group were greater than control.
Peng et al. (2015)	Neurolinguistic programming and health education	Depression; HAMD-17 Anxiety; HAM-A	Individual	Inpatient	Passive - Usual care	Significantly greater remission of depression (p = .003) and anxiety (p = .016) symptoms in the intervention group compared to control Prevalence rates of depression and anxiety were significantly reduced in the intervention group at post-intervention; intervention was a significant factor influencing both depression (p = .002) and anxiety (p = .007). Intervention had no significant difference at 6-month follow up.

Study ID	Intervention	Mood Focus and Measure	Format	Intervention Setting	Control and Type	Outcome
Kirkness et al. (2017)	Brief psychosocial behavioural intervention, two intervention groups (in-person vs telephone delivery).	Depression; HDRS	Individual	Community	Passive - Usual care	No significant difference between intervention and control
Gao et al. (2017)	Cognitive Behavioural Therapy and placebo medication.	Depression; HAMD-17	Individual	Community	Active - Placebo psychological intervention and placebo medication	No significant differences between intervention and control on HAMD-17.
Lincoln and Flannaghan (2003)	Cognitive Behavioural Therapy	Depression; BDI	Individual	Not reported	Passive - No intervention / Active - Attention placebo	No significant differences between groups at baseline, post-intervention (three months), or six months post recruitment. Discussion states significant improvement over time regardless of group but this is not reported as a statistical analysis. Medians reported suggest an improvement over time,

Study ID	Intervention	Mood Focus and Measure	Format	Intervention Setting	Control and Type	Outcome
						with no further improvement at six months post-stroke.
Thomas et al. (2013)	Behavioural Therapy	Depression; Stroke Aphasic Depression Questionnaire 21	Individual	Community	Passive - Usual care	Per protocol: At post intervention, group was a significant predictor for depression when baseline values were controlled (p = .05). At 3-month post intervention, group alone was a significant predictor for depression outcome (p = .045) and remained when adjusted for baseline values (p = .022). Intention to Treat: Only 3-month post intervention remained significant.
Thomas et al. (2019)	Behavioural Activation Therapy	Depression; PHQ-9	Individual	Community	Passive - Usual care	Formal interim analysis was not completed due to a lack of power. Clinically important difference demonstrated between groups suggesting a clinically relevant effect.

Study ID	Intervention	Mood Focus and Measure	Format	Intervention Setting	Control and Type	Outcome
Chow et al. (2023)	Narrative Therapy for survivor and caregiver dyads;	Depression; Geriatric Depression Scale	Group	Community	Passive - Treatment as usual and psychoeducation group	Intervention was not found to be a significant predictor regarding symptoms of depression. No direct significance testing was completed on depression between groups.
Kootker et al. (2017)	Augmented Cognitive Behavioural Therapy	Depression; HADS-D Anxiety; HADS-A	Individual	Community	Active - Computerised Cognitive Training	No significant differences found between groups. Significant effect of time on the HADS-D and HADS-A between pre and post-treatment; no *p* value reported.
Wichowicz et al. (2017)	Solution Focused Brief Therapy	Depression; HADS-D Anxiety; HADS-A	Individual	Community	Passive - No intervention	Mann-Whitney test showed significant differences between intervention and control group ($p < .01$).
Udvardi et al. (2024)	Mindfulness Based Cognitive Therapy (MBCT)	Depression: BDI Trait Anxiety; Spielberger	Group	Inpatient	Passive - Standard care	Significant main effects for time and group for both depression and anxiety.

Study ID	Intervention	Mood Focus and Measure	Format	Intervention Setting	Control and Type	Outcome
		Trait Anxiety Inventory				Group x time interaction non-significant for both depression and anxiety. No significant differences between groups over time.
Mitchell et al. (2009)	Brief Psychosocial Behavioural Intervention	Depression; HRSD	Individual	Community	Passive - Usual care	Significant difference in mean HDRS change at post intervention ($p < .001$) and at 12-month follow up ($p < .023$).

Data Synthesis

Reporting of Time Since Stroke

No studies which recruited participants within the first four months of stroke reported details about time since stroke within the sample demographics, but did report time since stroke as part of their recruitment criteria. Of those that recruited participants up to a maximum of six months post-stroke, only one reported the time since stroke of their sample (Duan et al., 2023); this included the mean and standard deviation.

Time since stroke was more frequently reported in those who included participants who were more than six months post-stroke, with four studies (57%) reporting time since stroke as part of their sample demographics. One study provided a breakdown of time since stroke into categories (Thomas et al., 2019) while one reported mean and standard deviation (Udvardi et al., 2024). The remaining two papers reported time since stroke as a median or mean accompanied by a range (Kootker et al., 2017; Thomas et al., 2013). The time since stroke reported in these studies suggests that participants within the sample are likely to be at different stages of post-stroke recovery.

Depression

An overview of the findings regarding interventions for post-stroke depression are presented in Table 5.

Table 5

Summary of Intervention Findings for Post-Stroke Depression

Time Since Stroke Group	Study ID	Intervention	Control	Significant Intervention Effects Post-Treatment
Less than three months	Gao et al. (2017)	CBT	Placebo psychological intervention	No

Time Since Stroke Group	Study ID	Intervention	Control	Significant Intervention Effects Post-Treatment
	Kirkness et al. (2017)	Brief Psychosocial Behavioural Intervention	Treatment as usual	No
	Y. Liu et al. (2023)	Group ACT	Treatment as usual	Yes
	Peng et al. (2015)	Neurolinguistic Programming	Treatment as usual	Yes
	Sun et al. (2022)	Behavioural Activation	Treatment as usual	Yes
	Wichowicz et al. (2017)	Solution Focused Brief Therapy	Treatment as usual	Yes
Less than four months	Mitchell et al. (2009)	Brief Psychosocial Behavioural Intervention	Treatment as usual	Yes
Less than six months	Duan et al. (2023)	MBSR	General psychological care	Yes
	Lincoln and Flannaghan (2003)	CBT	Treatment as usual / Attention placebo	No
	Gao et al. (2017)	CBT	Placebo psychological intervention	No
Over six months	Chow et al. (2023)	Narrative Therapy	Treatment as usual + psychoeducation group	No
	Gao et al. (2017)	CBT	Placebo psychological intervention	No
	Kootker et al. (2017)	Augmented CBT	Computerised Cognitive Training	No
	Sun et al. (2024)	CBT*	AFEM*	No
	Thomas et al. (2013)	Behavioural Therapy	Treatment as usual	Yes**

Time Since Stroke Group	Study ID	Intervention	Control	Significant Intervention Effects Post-Treatment
	Thomas et al. (2019)	Behavioural Activation	Treatment as usual	Yes***
	Udvardi et al. (2024)	MBCT	Treatment as usual	No

Note: Intervention and control swapped for reporting (*); Intention to Treat Analysis was ns (**); Analysis utilised clinically relevant change (***)

<3 months. Six studies (40%, n = 686) recruited stroke survivors who were less than three months post-stroke. Significant improvements in depression symptoms were present in four of these studies (n = 446) when compared to controls (Peng et al., 2015; Y. Liu et al., 2023; Sun et al., 2022; Wichowicz et al., 2017).

Long-term effects of interventions provided to those less than three months post-stroke were explored by three (50%, n = 384) of these studies. The effects of group ACT and behavioural activation were maintained at a three month follow up (Y. Liu et al., 2023; Sun et al., 2022). Neurolinguistic Programming was found to have no effect at reducing depression symptoms at a six month follow up (Peng et al., 2015).

Significant within-subjects effects were reported in two studies (n = 204). This suggests that depression symptoms improved over time, regardless of intervention group (Y. Liu et al., 2023; Sun et al., 2022).

<4 months. Only one study (n = 101) allowed the recruitment of stroke survivors up to four months post-stroke (Mitchell et al., 2009), suggesting that a four month post-stroke limit is less common. A significant difference between the intervention group and a passive control in change of depression scores was exhibited at post-intervention and persisted at 12 month follow-up.

<6 months. Three RCTs (20%, n = 259) had extended time since stroke recruitment criteria to include individuals up to six months post-stroke; all allowed the recruitment of participants less than three months post-stroke (Duan et al., 2023; Gao et al., 2017; Lincoln & Flannaghan, 2003).

When treating stroke survivors with a time since stroke of up to six months, only one study (n = 71) had an intervention that significantly outperformed the control; this effect persisted at an eight-week follow-up (Duan et al., 2023). It should be noted that 68% of the sample in this study would likely have had a time since stroke between 53.4 and 94.6 days, falling within the less than three months post-stroke bracket.

Duan et al. (2023) reported a significant within-subjects effect. Lincoln and Flannaghan (2003) state that they observed a significant improvement in mood over time when discounting group allocation; however, no statistical analyses were reported to show this.

6 months+. Seven studies (47%, n = 713) recruited stroke survivors who were over six months post-stroke (Chow et al., 2023; Gao et al., 2017; Kootker et al., 2017; Sun et al., 2024; Thomas et al., 2013, 2019; Udvardi et al., 2024). All but one study recruited participants who were less than six months post-stroke, which recruited stroke survivors who had a time since stroke of at least two years (Chow et al., 2023).

Two studies (n = 153) found improvement in depressive symptoms compared to control. Thomas et al. (2013) found behavioural therapy was effective in reducing depressive symptoms when analysed on a per protocol basis; however, this became non-significant when conducting intention to treat analysis. Behavioural activation was shown to produce clinically relevant change on the PHQ-9 compared to controls; however no formal analysis of efficacy was used due to the not being powered for this type of analysis (Thomas et al., 2019).

Three studies that had no significant treatment effects for psychological therapy demonstrated that symptoms of depression reduced over time, irrespective of intervention group (Kootker at al., 2017; Sun et al., 2024; Udvardi et al., 2024). These effects may indicate that time is a factor in the reduction of depression symptoms; however, both Kootker et al. (2017) and Sun et al. (2024) utilised active control groups: computerised cognitive training, and acupuncture with five elements music therapy, respectively.

Anxiety

An overview of the findings regarding interventions for post-stroke anxiety are presented in Table 6. Only four (n = 396) of the available papers in this review had anxiety as a primary or secondary outcome. Two of these recruited participants who were less than three months post-stroke (Peng et al., 2015; Wichowicz et al., 2017), while the remaining two allowed the recruitment of those who were over six months post-stroke (Kootker et al., 2017; Udvardi et al., 2024). Kootker et al. (2017) report a wide range of time since stroke in the intervention group of 2-243 months, while Udvardi et al. (2024) report a large standard deviation relative to the mean for the intervention group; *M* = 112.02 days, *SD* = 169.06 days.

Only the two studies (n = 242) who recruited participants at less than three months post-stroke had significant intervention effects (Peng et al., 2015; Wichowicz et al., 2017). The two studies (n = 154) who widened recruitment to beyond six months post-stroke reported no significant intervention effects (Kootker et al., 2017; Uvardi et al., 2024). Both of these studies reported a significant effect for time irrespective of intervention group.

Table 6

Summary of Intervention Findings for Post-Stroke Anxiety

Time Since Stroke Group	Study ID	Intervention	Control	Significant Intervention Effects Post-Treatment
Less than three months	Peng et al. (2015)	Neurolinguistic Programming	Treatment as usual	Yes
	Wichowicz et al. (2017)	Solution Focused Brief Therapy	Treatment as usual	Yes
Over six months	Kootker et al. (2017)	Augmented CBT	Computerised Cognitive Training	No
	Udvardi et al. (2024)	MBCT	Treatment as usual	No

Additional Factors

The average risk of bias score for the 15 included studies was 50% (*SD* = 20). Risk of bias was evenly represented across groups regarding depression, with percentage scores falling within one standard deviation of the mean, (<3 months = 58%; <6 months = 60%; 6+ months = 46%) except for <4 month (20%). When exploring anxiety, risk of bias remained evenly spread; however, the percentage of criteria met was lower overall (<3 months = 40%; 6+ months = 25%).

Whether studies excluded participants with a history of depression was also explored to understand if significant results could be attributed to those with participants who only experienced depression following stroke. Participants who experienced pre-stroke depression may experience a depression that is more persistent or complex in nature, or it may suggest other factors such as reduced social support or increased life stressors within the sample (Grav et al., 2012; Plieger et al., 2015). Nine studies included participants with a history of depression which was evenly spread across the time since stroke categories (<3 months, three out of six; <6 months, two out of three; 6+ months, three out of seven). The less than four months group contained only one study which included participants with a history of depression. When considering the eight studies that observed significant intervention effects compared to controls, only two excluded participants for historic depression. Of the five studies that did not show significant group effects, two excluded participants who had a history of depression.

Intervention setting was also explored. An intervention taking place within a hospital setting may indicate more severe impairment or greater rehabilitation needs. Nine studies provided intervention to individuals within the community (60%, n = 916), while three provided interventions for patients on hospital wards (20%, n = 412). Three studies (20%) did not report intervention setting. Two studies providing intervention for patients on hospital wards were in the less than three month category (Y. Liu et al., 2023; Peng et al., 2015), while one was in the over six month category, taking place in an inpatient rehabilitation clinic (Udvardi et al., 2024). Two studies (66%, n = 319) provided interventions in a hospital setting and produced significant treatment effects, both in the less than three month category, while five of studies providing intervention within the community produced significant treatment effects

(56%, n = 381). Significant treatment effects were proportionally similar with respect to setting.

Discussion

This is the first systematic review to explore the impact of time since stroke on intervention RCTs for post-stroke depression and anxiety. It is important to understand if time since stroke has an impact on intervention outcomes. This understanding will allow clinicians to know whether there is an optimal time to provide intervention for post-stroke mood difficulties. This evidence may also help to guide clinical policy in supporting post-stroke mood difficulties and draw attention to time since stroke as a factor to consider for future research.

More studies demonstrated effective treatment for post-stroke depression when recruiting stroke survivors earlier in recovery compared to later. The narrative synthesis highlighted a greater proportion of significant outcomes for post-stroke depression when recruitment was limited to those less than three months post-stroke. As the maximum time since stroke increased, fewer articles reported significant intervention effects.

There are a number of hypotheses that may explain this finding. Firstly, fewer significant outcomes later in recovery may indicate that psychological intervention at this stage is less effective. Stronger natural recovery in earlier stages may facilitate greater therapeutic outcomes in a synergistic interaction. Hackett and Pickles (2014) highlighted that reduced prevalence of post-stroke depression may be a result of adjustment to life after stroke. Considering this, alongside the 44% recovery rate of post-stroke depression within the first year post-stroke (L. Liu et al., 2023), it may be that stroke survivors are experiencing a naturalistic recovery as adjustment and adaptation to life after stroke takes place over time. Within subjects effects were reported across time periods, suggesting that time is a factor in reducing depression symptoms, supporting the hypothesis of Hackett and Pickles regarding adjustment.

The findings may represent differences in the construct of depression being treated. It may be possible that earlier psychological interventions support adjustment related depression post-stroke, especially given the importance of psychological factors in physical and psychosocial trajectories of health related

quality of life (Van Mierlo et al., 2018). Alternatively, given the natural history of post-stroke depression within the first year, those recruited later may be more likely to be experiencing a persistent depression (L. Liu et al., 2023) which may be more difficult to treat compared to an adjustment related depression. There is evidence to suggest that a greater degree of functional disability and pre-stroke psychiatric history are risk factors for the development of persistent depression (L. Liu et al., 2023). An adjustment related depression may be more related to the impact of stroke, but when these impacts are more significant, a persistent depression is more likely to develop.

A more systemic hypothesis of the findings would suggest that stroke survivors may be more responsive to psychological input during the earlier stages of rehabilitation due to wider multi-disciplinary support they already receiving. Rehabilitation following a stroke is recommended to take place for at least three hours per day, on a minimum of five days a week (NICE, 2023). A high intensity of rehabilitation will require motivation which may support engagement within psychological interventions provided at the same time.

The findings may also represent other uncontrolled population differences. While risk of bias, inclusion of participants of pre-stroke depression, and intervention setting were found to be spread across the studies included, other variables not explored may explain the findings. For example, the heterogeneity of time since stroke in this review may suggest that individuals are being recruited at different points in stroke recovery which may also entail differences in the setting they are recruited from.

RCTs that included anxiety as an outcome displayed a similar to trend described above, whereby both studies who recruited at less than three months post-stroke demonstrated effective interventions (Peng et al., 2015; Wichowicz et al., 2017). Of the four papers which investigated post-stroke anxiety, three demonstrated the potential for a high amount of bias within their methodology, with concerns being raised regarding the reporting and methodology of two (Udvardi et al., 2024; Wichowicz et al., 2017). Due to the potential of risk of bias, and the small number of publications that investigated anxiety, the synthesis regarding post-stroke anxiety should be taken with caution.

Additional factors were explored to understand if alternative explanations could be found for the patterns demonstrated in the data. The level of risk of bias was found to be evenly spread across time since stroke groups. Studies investigating anxiety were found to be at higher risk of bias, but this was again spread evenly across the time since stroke groups. The inclusion of participants with pre-stroke depression was evenly distributed across time since stroke groups. A great proportion of studies finding effective treatments included participants with a history of depression compared to studies where non-significant treatment effects were found. Finally, intervention setting was also explored, which suggests that effective treatments were relatively equal across settings. The factors explored did not differ enough across time since stroke categories to provide an alternate explanation.

Research that allowed the recruitment of stroke survivors over six months post-stroke generally had large heterogeneity of time since stroke duration (Kootker et al., 2017; Thomas et al., 2013, 2019; Udvardi et al., 2024), with one study recruiting stroke survivors who were between two months and 20 years post-stroke. While these papers reported time since stroke within the demographic information of the sample, the high levels of heterogeneity within the samples made it difficult to explore specific groups of time since stroke. The inclusion of participants at different stages post-stroke meant that the samples of these studies could not be allocated to a more specific time category to better understand the impact of time since stroke.

The heterogeneity of time since stroke also limits conclusions that can be drawn regarding the outcomes of interventions for those who are one year post-stroke and beyond. All studies in this review included stroke survivors who were less than five months post-stroke, with the exception of one which had a minimum time since stroke criteria for recruitment of two years (Chow et al., 2023). For clinicians to be evidence led in supporting stroke survivors with mood difficulties across different stages post-stroke, research is required that uses more homogeneous samples with regards to time since stroke. The prevalence rate of post-stroke depression is thought to be stable for up to 10 years post-stroke (Ayerbe et al., 2013); therefore, this is particularly pertinent for stroke survivors who are at least one year post stroke as the evidence base does not represent this population effectively but they are likely to still experience post-stroke depression.

Limitations

Limitations were identified with this systematic review. Only 16 studies were identified from the literature search which allowed a range of methodological differences, suggesting scarcity in the overall literature of intervention RCTs for post-stroke mood difficulties. This was particularly evident for post-stroke anxiety, where only four studies were found to investigate this.

A large degree of heterogeneity was present. Differences in reporting time since stroke of the sample demographic and reporting using different measures of central tendency meant that it was not possible to pool outcomes to explore the efficacy of treatments. Heterogeneity of time since stroke was also observed within the inclusion and exclusion criteria of the studies recruitment. Studies recruiting participants who were later in their stroke recovery, also recruited participants who were less than five months post-stroke. Recruiting participants at different stages of recovery represent potential population differences and may reflect different constructs of depression, adjustment vs persistent depression, that may bias the results towards early intervention appearing more effective. Heterogeneity of intervention and control type also posed a limitation. With a wide array of interventions, the patterns observed in the data are harder to attribute to time since stroke; the differences in effective interventions may be a result of the interventions themselves. Similarly, effective treatment was discerned through comparison with control groups. Varying types of control then pose a potential for bias and influence on the pattern of findings observed.

In addition, the higher risk of bias present in five of studies would suggest that the outcome of the synthesis be approached with caution. Many studies included in this review did not provide adequate information to be confident in randomisation and group allocation concealment methodology. Most studies to not blind participants to group which is expected within the context of psychological intervention research (Juul et al., 2021). Many studies described the reliability of the outcome measures used; however, inter-rater reliability was rarely reported. Finally, intention to treat analysis was only adequately described in two studies, while 11 studies appeared to use a per-protocol analysis principles. The potential for increased

risk of bias raises concern for the reliability and confidence in the outcomes of some of the studies included in this review.

Implications and Recommendations

This review has implications for future research regarding interventions for post-stroke mood difficulties and potential implications for clinical practice. More generally, more research should investigate intervention for post-stroke anxiety which is under-represented in the evidence base. With regards to time since stroke, research should ensure that this is adequately reported for their sample, with a mean and standard deviation to better understand the distribution of the demographic. The current synthesis was also impacted by a lack of reported effect sizes within the included studies. Researchers should provide effect sizes to help readers in understanding the magnitude of findings and to better support synthesis in secondary research. Future research should narrow their inclusion/exclusion criteria regarding time since stroke based on the literature, to also allow better synthesis of evidence with regards to this factor. Introducing cut offs at pre and post 3 months after stroke to account for the early onset depression stage (L. Liu et al., 2023) and evaluating treatments on individuals who are at least 1-year post-stroke as this sample is underrepresented within the research base. In addition, further research should explicitly explore time since stroke, comparing intervention outcomes when delivered at three, six, and nine months, and one year post-stroke. This would incorporate the early and late development stages of post-stroke depression, while also accounting for the naturalistic recovery period (L. Liu et al., 2023).

This review also demonstrated deficiencies in reducing risk of bias and adequately reporting methodology. Researchers should ensure that their randomisation and group allocation concealment methods are reported to ensure confidence in the randomisation that is vital for an RCT. To reduce the impact of statistical noise in the data, differences in groups at baseline should be reviewed through sensitivity analysis. Researchers should also report the steps taken to improve the reliability of measurement within their trial by detailing whether assessors were blinded to group allocation, the number of raters used to assess outcomes, the training of raters that supports their reliability, and any steps taken to directly assess inter-rater reliability. Analysing through the intention to treat principle

deems that participants should be analysed in their assigned group irrespective of treatment completion; this analysis type provides an unbiased estimate of treatment efficacy (McCoy, 2017). Adequately reported intention to treat analysis was largely absent in this sample of studies. Stroke researchers should routinely utilise intention to treat principles in their analysis to allow more confidence in their outcomes of analysis.

In conclusion, psychological interventions were more frequently effective when provided earlier with respect to time since stroke which may suggest an important opportunity to maximise the effectiveness of psychological intervention. Further research is needed given the limitations in the current evidence base and this systematic review. It is important to note that the high heterogeneity of time since stroke meant that meta-analysis regarding this factor was not possible. Time since stroke is under reported as a demographic variable and does not appear to be considered as a potential confounding variable with large ranges in samples when including individuals who are over six months post-stroke. The quality of the studies included varied, with many not adequately reporting steps taken to reduce bias. It is recommended that future research adequately report time since stroke as a demographic and consider the factor as a potential confounding variable by narrowing their recruitment criteria or by performing sensitivity analyses.

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Chapter 3: Bridging Chapter

The systematic review presented in Chapter 2 explored whether time since stroke impacts on therapy outcomes for post-stroke depression and anxiety in randomised controlled trials. The findings suggest that earlier intervention may be more effective; however, the studies included represented a small evidence base with a high degree of heterogeneity. Of the studies included in the review, the majority utilised CBT, or CBT principles, while only one used ACT. This demonstrates the infancy of the evidence base for ACT compared to other more frequently research intervention types.

ACT has been shown to have comparable outcomes with treating anxiety and depression in the general population with CBT (Ferreira et al., 2022). The intervention has also been found to be effective for the treatment of post-stroke mood difficulties (Graham et al., 2015; Majumdar & Morris, 2019; Niu et al., 2022; Rauwenhoff et al., 2022), which would have contributed to its inclusion as an intervention within the National Clinical Guideline for Stroke for the United Kingdom and Ireland (Intercollegiate Stroke Working Party, 2023).

The theoretical mechanism for change in ACT is through the development of psychological flexibility. A construct of six key processes that help an individual to open up to their experiences, be present, and to do what is meaningful and that which brings richness to their lives (Harris, 2019). Research has found that ACT produces changes in psychological flexibility which also correlated with outcomes. Some studies have found the change in psychological flexibility to occur prior to changes in symptomology of mental health difficulties (Ciarrochi et al., 2010). Changes in psychological flexibility are not consistently reported, with a recent RCT demonstrating no change in the construct in individuals with acquired brain injury following ACT intervention (Rauwenhoff et al., 2024).

While ACT has been found to be effective for stroke survivors experiencing mood difficulties, and is recommended as an intervention (Intercollegiate Stroke Working Party, 2023), further research is required. Providing a strong theoretical basis by exploring the role of psychological flexibility on anxiety and depression in stroke survivors, may develop a foundation for additional research to build from. Therefore, Chapter 4 will investigate the associations between impacts of stroke and

mood difficulties, and whether psychological flexibility moderates these relationships, with the aim of shedding light on the role of psychological flexibility in post-stroke mood.

Chapter 4: Empirical Study

Exploring the Associations Between Impacts of Stroke, Psychological Flexibility and Post-Stroke Anxiety and Depression

Exploring the Associations Between Impacts of Stroke, Psychological Flexibility and Post-Stroke Anxiety and Depression

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Abstract

Objective: Mood difficulties are common post-stroke. Psychological flexibility is a key process in Acceptance and Commitment Therapy (ACT), a psychological intervention with growing evidence in stroke. It is hypothesised that psychological flexibility may act as a protective factor for post-stroke mood difficulties with regards to stroke severity. This study explored the associations between indicators of stroke impact and mood, and whether psychological flexibility moderates this relationship.

Method: A cross-sectional online study recruited 206 stroke survivors globally. Participants completed a series of questionnaires assessing fatigue, physical function, perceived cognitive function, psychological flexibility, depression, and anxiety.

Results: Main effects from moderation analysis indicated that fatigue, physical function, and perceived cognitive function significantly predict depression and anxiety. Pre-stroke depression predicted depression in two moderation models, while age predicted anxiety scores, and depression in one model. Psychological flexibility did not moderate these relationships but was itself a significant predictor. Multiple linear regression explored the size of effect for predictors within a larger model. While accounting for other variables, depression was predicted by psychological flexibility, perceived cognitive function, and physical function, but not fatigue, age, or pre-stroke depression. Anxiety was predicted by perceived cognitive function, psychological flexibility, and age but not fatigue, physical function, or pre-stroke depression. Psychological flexibility was associated with depression with a large effect size, while psychological flexibility and perceived cognitive function predicted anxiety with moderate effects.

Conclusions: Psychological flexibility does not moderate the relationships between impacts of stroke and mood difficulties, but does predict depression and anxiety, producing large and medium effect sizes respectively. Further research should explore how psychological flexibility impacts mental health outcomes in stroke survivors and how this could be developed in practice.

Keywords: post-stroke depression, post-stroke anxiety, psychological flexibility, fatigue, cognition, physical function

Introduction

Stroke, or cerebrovascular accident, is estimated to occur in 100,000 individuals each year, with currently 1.3 million stroke survivors in the United Kingdom alone (National Institute for Health and Care Excellence [NICE], 2023a). Globally, it is estimated that one in four individuals aged over 25 will have a stroke in their lifetime (Feigin et al., 2022). The prevalence and impact of stroke has increased over the past 30 years which has been linked to population growth and ageing, alongside a breadth of other health factors (Feigin et al., 2021).

Surviving a stroke can bring a number of long-term difficulties including fatigue, cognitive changes, physical impairments, and sensory loss, with varying degrees of prevalence (Cumming et al., 2016; El Husseini et al., 2023; Hardie et al., 2004; Jönsson et al., 2014). These difficulties can impact a person's functional independence.

Mood difficulties are common after stroke. A recent meta-analysis suggests that 27% of stroke survivors experience post-stroke depression, which frequently develops within the first three months post-stroke (Liu et al., 2023). Longitudinal research has suggested that this rate of post-stroke depression can persist, with 30% of stroke survivors experience depression 15 years post-stroke (Ayerbe et al., 2013a). Anxiety is also prevalent, with prevalence rates estimated to be between 18.7% and 24.2% based on clinical interview or psychometric measure (Knapp et al., 2020). While more research is needed, the available evidence suggests that prevalence of post-stroke anxiety is relatively stable up to 10 years post-stroke (Ayerbe et al., 2014; Knapp et al., 2020).

Although anxiety and depression appear to impact a relatively large proportion of stroke survivors, mood measures are infrequently used within clinical stroke research (Lees et al., 2012). Clinical research is also thought to favour post-stroke depression, whereas post-stroke anxiety has been insufficiently researched, often with randomised controlled trials (RCT) being completed on concurrent anxiety and depression (Ayerbe et al., 2014; Tang et al., 2013).

Various impacts of stroke have been linked with mood difficulties; however, the evidence has been variable. Evidence of the associations between post-stroke

fatigue and anxiety and depression is inconsistent (Nadarajah & Goh, 2015). Anxiety is associated with post-stroke fatigue when measured between one and 18 months following stroke; however, several studies have not demonstrated this association (Ponchel et al., 2015). Although significant associations have been found (Galligan et al., 2016; Snaphaan et al., 2011), there is not enough evidence to ascertain the direction of the relationship.

A systematic review of observational studies identified consistent associations between cognitive impairment and post-stroke anxiety (Menlove et al., 2015). Other studies suggest a non-significant association when controlling for post-stroke depression, or when measured prior to five years post-stroke (Ayerbe et al., 2014; Williams & Demeyere, 2020). The evidence with respect to post-stroke depression is more consistent, with reviews and a large-scale research paper suggesting consistent associations (Ayerbe et al., 2011; Hackett & Anderson, 2005).

The evidence of association between physical functioning and post-stroke anxiety is inconsistent. Evidence suggests a significant association with post-stroke anxiety, both during the rehabilitation stage and more longitudinally up to three years post-stroke (Åström, 1996; Roomruangwong & Thavichachart, 2005). A review of observational studies by Menlove et al. (2015) did not find consistent evidence of a significant association.

Reduced physical functioning is more consistently associated with post-stroke depression. Functional dependence has been regarded as the best predictor of post-stroke depression at a year since the cerebral event (Appelros & Viitanen, 2004). Systematic reviews have also found that physical disability can be a risk factor for post-stroke depression (Kutlubaev & Hackett, 2014; Shi et al., 2017).

It is important that interventions consider the impact of stroke as a risk factor for mood difficulties; reducing their impact may support the reduction of anxiety and depression symptomology. Yet current treatment guidelines in the United Kingdom do not provide recommendations for treating mood difficulties within the context of stroke specifically (NICE, 2023b). Recommendations instead are based on those for depression with chronic health conditions and generalised anxiety disorder; with Cognitive Behavioural Therapy (CBT) recommended for both (NICE, 2009, 2020).

Meta-analyses of available RCTs suggest that CBT can improve symptomology in both post-stroke anxiety and depression; however, relatively small pooled sample sizes and low-quality studies in the studies reviewed pose limitations. Additionally, there is little evidence on the long-term effectiveness of CBT for post-stroke depression and anxiety (Ahrens et al., 2023; Wang et al., 2018).

While recent meta-analyses suggest that CBT may be effective for treating mood difficulties post-stroke (Ahrens et al., 2023; Wang et al., 2018), Acceptance and Commitment Therapy (ACT) has shown comparative outcomes with CBT in reducing symptoms of anxiety and depression in the non-stroke population (Ferreira et al., 2022). ACT has also been recommended as a treatment for post-stroke mood difficulties in the National Clinical Guideline for Stroke for the United Kingdom and Ireland (Intercollegiate Stroke Working Party, 2023).

ACT is a third-wave CBT approach that was developed around relational frame theory (RFT) and functional contextualism (Prevedini et al., 2011). ACT aims to help individuals live a life that is more aligned to their values, alongside unavoidable human suffering through the development of psychological flexibility (Kangas & McDonald, 2011). Psychological flexibility comprises of six key processes; acceptance, contacting the present moment, awareness of values, committed action, self-as-context, and cognitive defusion (Harris, 2006; Hayes et al., 2006). Considering this, ACT may be well placed to support stroke survivors to live in line with their values within the context of the long-term impact of their stroke.

Evidence suggests that changes in psychological flexibility is a potential mechanism to change within ACT intervention research. ACT has been found to support improvements in psychological flexibility, while also correlating with outcomes. While this relationship is not causal, other studies have found that changes in psychological flexibility occurred prior to changes in symptomology (Ciarrochi et al., 2010).

ACT has been found to be effective with individuals experiencing chronic pain in reducing depression alongside other outcomes. Pain-related functioning, linked with acceptance of pain sensations, was the outcome of ACT that produced the largest effect size in a recent meta-analysis (Ma et al., 2023). This is in line with

the ACT model and demonstrates how developing acceptance, an aspect of psychological flexibility, reduce the interference of physical health difficulties in everyday life.

The evidence base for the use of ACT with a stroke population is in its infancy but growing. Group based ACT significantly reduce depression scores and may also be a preventative measure for depression in stroke survivors (Majumdar & Morris, 2019; Niu et al., 2022), while single case studies and smaller designs have also shown ACT to be effective (Graham et al., 2015; Rauwenhoff et al., 2022). Qualitative research suggests that group based ACT may also support adjustment after stroke (Large et al., 2020). Conversely, a recent multicentre RCT suggests that individual ACT for people with acquired brain injury was not more effective than psychoeducation combined with relaxation training at reducing depression and anxiety symptoms. Depression and anxiety were found to decrease over time, while psychological flexibility increased, but these did not differ between ACT and the control (Rauwenhoff et al., 2024).

Based on the links between the impacts of stroke and mood difficulties, we hypothesise that psychological flexibility could act as a moderator within these relationships. Should this be demonstrated, ACT would be validated as a model of intervention for stroke survivors within the context of severity of stroke impact. Therefore, we will seek to answer the following research questions:

1. Are post-stroke fatigue, physical functioning and perceived cognitive functioning associated with anxiety and depression after stroke?
2. If significant, does psychological flexibility moderate the associations between the impacts of stroke, and anxiety and depression

Methodology

Design

A cross-sectional design was used to gather information on psychological flexibility, anxiety and depression, and measures of stroke impact (fatigue, perceived cognitive function, and physical function). Alongside their associations in the literature, the three impacts of stroke included in the study were chosen for two

reasons. Firstly, they are common difficulties that individuals may experience following a stroke, as previously described. Secondly, they are difficulties which are likely to have a functional impact on the individual and may interfere with accessing pre-stroke valued action. A self-report battery of questionnaires was created using an online platform, JISC Online Surveys (https://app.onlinesurveys.jisc.ac.uk) and distributed via social media and through consenting charitable organisations between May and November 2024.

Participants

Two hundred and six people completed the survey with 191 participants included in the analysis. The sample was predominantly female (77%), with an average age of 48.03 (*SD* = 12.22). The average time since stroke of participants was 3.86 years (*SD* = 3.86). Most participants lived in the USA or UK, with 85 (44.5%) and 81 (42.4%) living in these countries respectively.

Eligible participants were stroke survivors over the age of 18 and at least six months post-stroke, meaning they were no longer in the acute or subacute phase after which difficulties are more stable (Grefkes & Fink, 2020). This research sought to understand the role of psychological flexibility following the immediate adjustment and recovery, with more stable impacts of stroke. In addition, the validity of the concept of depression and anxiety within the first 6 months of stroke could be questioned, as this is a time that is likely dominated by initial adjustment and emotional reactions to a traumatic health event. After six months, depression and anxiety are more likely to be related to their supposed constructs. Participants were also required to speak English and able to provide their own answers; practical assistance to complete the measures was encouraged. Individuals were not able to take part if their stroke was a spinal stroke, transient ischaemic attack, or subarachnoid haemorrhage, or if they had experienced a brain injury prior to their stroke. The required sample size for power is detailed in Appendix F.

Measures

Information was collected on age, sex, country of residence, nationality, ethnicity, time since stroke, premorbid anxiety and depression, whether the

participant had undergone talking therapy, or taken medication for anxiety or depression prior to their stroke.

Fatigue Severity Scale

The Fatigue Severity Scale (FSS) is a validated measure of fatigue with stroke survivors (Krupp et al., 1989). The FSS is a nine-item measure where participants rate their agreement with items on a seven-point Likert scale. The measure is reported to have good internal consistency and reliability ($\alpha = 0.93$) (Valko et al., 2008). The FSS has been found to be a valid measure of fatigue for a stroke population (Ozyemisci-Taskiran et al., 2019).

Stroke Impact Scale 3.0 (SIS) Memory and Thinking Subscale

The Memory and Thinking subscale of the SIS (Duncan et al., 2003a) allows the measurement of perception of cognition through the lens of a quality-of-life measure. The SIS 3.0 was developed from the SIS 2.0 and has excellent reliability and internal consistency ($\alpha = 0.92$), and is validated for use with stroke survivors (Duncan et al., 2003a; Jenkinson et al., 2013; Richardson et al., 2016). Although not an actual measure of cognitive performance, Almalki et al. (2019) found that the measure could identify cognitive difficulties in stroke survivors that may have been missed in a clinical setting.

The SIS-16 Stroke Impact Scale Version 3.0

The Stroke Impact Scale 16 (SIS-16) is a 16-item measure that assesses physical functioning following stroke, measuring areas of activities of daily living, mobility, and hand function utilising a five-point Likert scale (Duncan et al., 2003b). The SIS-16 was developed and validated with a stroke population and was designed to capture a wide range of physical difficulties following stroke. It is sensitive to difficulties that arise from mild strokes and is found to have excellent reliability (person separation reliability = .94) (Duncan et al., 2003b).

Patient Health Questionnaire

The Patient Health Questionnaire (PHQ-9) is a nine-item measure of depression symptomology, where participants respond using a four-point Likert scale

(Kroenke et al., 2001). It is regarded as an appropriate measure of depression symptomology following stroke with good internal consistency (α = 0.82) (Meader et al., 2014; Turner et al., 2012). The PHQ-9 has also been validated within the stroke population (Prisnie et al., 2016; Williams et al., 2005).

Generalised Anxiety Disorder Assessment

The Generalised Anxiety Disorder Assessment (GAD-7) is a screening tool measuring generalised anxiety symptom severity containing seven items scored on a four-point Likert scale (Spitzer et al., 2006). When used within a primary care setting, Spitzer and colleagues found the measure to have excellent internal consistency (α = 0.92). Although the tool has not been validated with a stroke population, the measure has been used in post-stroke anxiety research (Beauchamp et al., 2020).

Multidimensional Psychological Flexibility Inventory

Psychological flexibility was measured using the Multidimensional Psychological Flexibility Inventory (MPFI). While the Acceptance and Action Questionnaire (AAQ-II) is commonly used in brain injury research to measure psychological flexibility, there has been some debate regarding its discriminant validity where is may be a greater measure of psychological distress (Wolgast, 2014). Landi et al., 2021 suggest the MPFI has a greater discriminant validity in the assessment of psychological flexibility compared to the AAQ-II.

The MPFI is a 60-item measure, scored on a six-point Likert scale, containing two 30-item measures of psychological flexibility and inflexibility. Each measure includes six subscales which map on to the six core aspects of psychological flexibility, has excellent reliability when used with the general population (Rolffs et al., 2018). The measure is not yet validated in a stroke population; however, it is set to be used in a multicentre RCT with individuals with multiple sclerosis (Giovannetti et al., 2022). Due to concerns about questionnaire length for stroke survivors, only the 30-item flexibility measure was used as part of this study.

Procedure

Ethical approval [Approval Number ETH2324-2765] was obtained by the Faculty of Medicine and Health Sciences Research and Ethics Committee at the University of East Anglia (Appendix G). Data collected was non-identifiable to allow for anonymity and confidentiality. Research data was stored in line with the University of East Anglia Research Data Management Policy (2022).

Participants were recruited through advertisements distributed on social media (e.g. Facebook, X) and by consenting stroke charities, utilising snowball sampling. Adverts contained a link which took participants to the survey platform. Participants were presented with an information sheet (Appendix H) and consent form (Appendix I). Consenting participants subsequently completed the demographic questions and the measures previously described. Following completion of the survey, a debrief form was presented, providing information about further support regarding stroke and mental health in the UK, USA, and Australia (Appendix J).

To mitigate against possible fatigue, break pages were provided between questionnaires to provide a break and to warn participants of changes in the response scales. Participants were also advised that they could pause the survey and return later to help reduce fatigue.

Analysis Plan

Data Cleaning

The process of data cleaning and identification of potential outliers is discussed further in Appendix K.

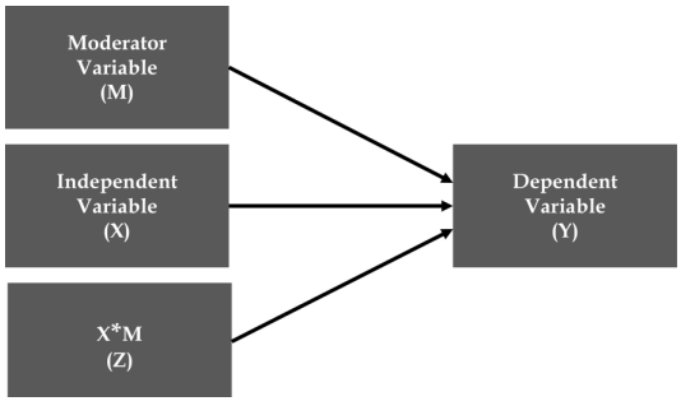
Due to human error, only six questions of the GAD-7 were coded into the online survey platform. The missing score was imputed through the mean of the other items in line with guidance on the GAD-7 form. Imputing via the mean score can distort the distribution and underestimate the variance (Lodder, 2013). Therefore, analyses were performed with both the six items collected and with the imputed data to identify any effect of imputation. No differences were found in the outcome of the models; therefore, the scores from the six items administered was used for the final analysis.

Models for Analysis

A moderation analysis was used to explore the two initial research questions. The main effects within each analysis model explored whether post-stroke fatigue, physical functioning, and perceived cognitive functioning were associated with anxiety and depression. The moderation models also included an interaction term which is the combination of an impact of stroke and psychological flexibility. The outcome of the interaction term in the moderation model demonstrated whether psychological flexibility moderated the relationship between the impact of stroke with depression and anxiety. An illustration of the moderation statistical model can be found below (Figure 1). The analysis was completed on IBM SPSS Statistics (Version 29) using the PROCESS tool developed by Hayes (2022). Only 190 participants were included within the moderation analysis due to one participant having missing data for age; the PROCESS tool only allows for listwise deletion of missing data.

Figure 1

Visual Representation of the Moderation Statistical Model (Memon et al., 2019)



Six moderation models were created, each with an independent variable (fatigue, physical function, perceived cognitive function), the moderator (psychological flexibility), and an interaction term (e.g. fatigue x psychological flexibility). Depression was the outcome variable for three models, and anxiety the remaining three.

Covariates

Potential covariates from demographic questions were checked by analysing associations with the outcome variables. Potential covariates that were continuous (age and time since stroke) were analysed using correlations. Dichotomous covariates (presence of pre-stroke depression, pre-stroke anxiety, undergone psychological therapy, taking medication for mood) were analysed using a factorial ANOVA. Age was significantly correlated with anxiety $r = .24$, $p = .001$ and was included as a covariate. Depression scores significantly varied between pre-stroke depression groups, $F(1,175) = 4.12$, $p = .044$, $\eta_p^2 = .023$. Age and pre-stroke depression were included as covariates in all models to allow comparability.

Results

Descriptive statistics for each measure in presented in Table 1. Demographic information for the sample analysed can be found in Appendix L.

Table 1

Mean and Standard Deviation of Variables

Measurement Tool	*M*	*SD*
Fatigue Severity Scale	48.91	(11.67)
Stroke Impact Scale-16	63.51	(12.36)
Stroke Impact Scale 3.0 Memory and Thinking Subscale	24.47	(6.92)
Multidimensional Psychological Flexibility Inventory	107.68	(25.86)
Patient Hospital Questionnaire-9	11.90	(6.62)
Generalised Anxiety Disorder-7 (6 items only)	8.41	(5.08)

To understand whether fatigue, physical function, and perceived cognitive function are significant predictors of depression and anxiety, the main effects of the moderation models can be interpreted. The results of the moderation model for depression are outlined in Table 2. All depression models were significant, explaining between 37% and 47% of the variance in depression scores. Fatigue, physical functioning and perceived cognitive functioning all significantly predicted

depression where higher levels of physical functioning and perceived cognitive functioning, and lower levels of fatigue, predicted lower depression scores. Pre-stroke depression was a significant predictor of depression in models exploring fatigue and physical functioning but not perceived cognitive function. Age was a significant predictor of depression in the physical functioning model.

Psychological flexibility was found to be a significant predictor of depression across all three moderation models, with higher psychological flexibility being associated with lower depression scores. To determine if psychological flexibility was a significant moderator for the relationship between the stroke impact and depression, the interaction term (stroke impact x psychological flexibility) can be interpreted. None of the interaction terms were significant, suggesting that psychological flexibility does not moderate the relationships between the measured impacts of stroke and depression.

Table 2

Moderation Analysis: Impacts of Stroke and Psychological Flexibility scores on Depression scores

Effect	Model R^2	*b*	*SE*	95% CI *LL*	95% CI *UL*	*t*	*p*
Fatigue and Psychological Flexibility scores on Depression scores							
Constant	.371*	13.21	1.60	10.01	16.33	8.19	<.001*
Fatigue[a]		0.18	0.04	0.11	0.28	3.99	<.001*
Psychological Flexibility[a]		-0.10	0.02	-0.14	-0.07	-5.34	<.001*
Fatigue x Psychological Flexibility		0.001	0.002	-0.002	0.005	0.55	.581
Pre-Stroke Depression[b]		2.17	0.93	0.31	3.97	2.25	.026*
Age		-0.04	0.03	-0.10	0.03	-1.14	.255
Physical Function and Psychological Flexibility scores on Depression scores							
Constant	.408*	15.58	1.61	12.43	18.72	9.37	<.001*

Effect	Model R^2	*b*	*SE*	95% CI *LL*	95% CI *UL*	*t*	*p*
Physical Function[a]		-0.20	0.03	-0.26	-0.14	-6.46	<.001*
Psychological Flexibility[a]		-0.10	0.02	-0.13	-0.07	-6.15	<.001*
Physical Function x Psychological Flexibility		-0.002	0.001	-0.004	0.001	-1.28	.204
Pre-Stroke Depression[b]		2.66	0.89	0.87	4.36	2.90	.004*
Age		-0.09	0.03	-0.15	-0.03	-2.73	.007*
Perceived Cognitive Function and Psychological Flexibility scores on Depression scores							
Constant	.472*	11.43	1.48	8.46	14.29	7.54	<.001*
Perceived Cognitive Function[a]		-0.46	0.06	-0.56	-0.34	-7.55	<.001*
Psychological Flexibility[a]		-0.08	0.02	-0.11	-0.05	-5.14	<.001*
Perceived Cognitive Function x Psychological Flexibility		0.002	0.002	-0.001	0.007	1.14	.258
Pre-Stroke Depression[b]		1.72	0.91	0.03	3.55	1.80	.067
Age		-0.002	0.03	-0.06	0.06	-0.07	.946

Note: CI = Confidence interval; *LL* = lower limit; *UL* = upper limit. *SE* and CI derived from bootstrapping.

[a] Variable mean centred, [b] 0 = no, 1 = yes.

* *p* value significant at .05

Table 3 shows the moderation models for anxiety. Similar to depression, all models were found to be significant, but explained less variance in the outcome score; between 24% and 32% of the variance in anxiety scores could be explained by

the model. Consistent with the depression models, fatigue, physical functioning, perceived cognitive functioning and psychological flexibility were all significant predictors of anxiety scores. Higher levels of physical functioning, perceived cognitive functioning, and psychological flexibility, alongside lower levels of fatigue, predicted lower anxiety scores. Pre-stroke depression did not significantly predict anxiety scores; however, age was a significant predictor of anxiety across the models. No interaction terms were significant which suggests that psychological flexibility does not moderate the associations between the impacts of stroke measures, and anxiety.

Table 3

Moderation Analysis: Impacts of Stroke and Psychological Flexibility scores on Anxiety scores

Effect	Model R^2	*b*	*SE*	95% CI *LL*	95% CI *UL*	*t*	*p*
Fatigue and Psychological Flexibility scores on Anxiety scores							
Constant	.235*	12.14	1.29	9.67	14.78	9.33	<.001*
Fatigue[a]		0.11	0.03	0.05	0.17	3.21	.002*
Psychological Flexibility[a]		-0.06	0.01	-0.08	-0.03	-4.17	<.001*
Fatigue x Psychological Flexibility		0.0006	0.001	-0.002	0.003	0.45	.655
Pre-Stroke Depression[b]		0.61	0.80	-0.96	2.14	0.75	.454
Age		-0.08	0.03	-0.13	-0.03	-3.10	.002*
Physical Function and Psychological Flexibility scores on Anxiety scores							
Constant	.235*	13.29	1.33	10.68	15.94	9.69	<.001*
Physical Function[a]		-0.09	0.03	-0.15	-0.04	-3.29	.001*
Psychological Flexibility[a]		-0.06	0.01	-0.08	-0.03	-4.35	<.001*

Effect	Model R^2	*b*	*SE*	95% CI *LL*	95% CI *UL*	*t*	*p*
Physical Function x Psychological Flexibility		-0.001	0.001	-0.003	0.0005	-1.19	.234
Pre-Stroke Depression[b]		0.98	0.77	-0.56	2.42	1.25	.213
Age		-0.11	0.03	-0.16	-0.06	-3.98	<.001*
Perceived Cognitive Function and Psychological Flexibility scores on Anxiety scores							
Constant	.323*	11.11	1.28	8.67	13.65	8.53	<.001*
Perceived Cognitive Function[a]		-0.30	0.05	-0.39	-0.19	-5.87	<.001*
Psychological Flexibility[a]		-0.04	0.01	-0.07	-0.02	-3.44	.001*
Perceived Cognitive Function x Psychological Flexibility		0.001	0.002	-0.003	0.004	0.34	.735
Pre-Stroke Depression[b]		0.31	0.77	-1.20	1.83	0.41	.686
Age		-0.06	0.03	-0.11	-0.01	-2.32	.022*

Note: CI = Confidence interval; *LL* = lower limit; *UL* = upper limit. *SE* and CI derived from bootstrapping.

[a] Variable mean centred, [b] 0 = no, 1 = yes.

* *p* value significant at .05

While psychological flexibility was not found to be a significant moderator, the analysis shows that it does significantly predict depression and anxiety after stroke. The significant main effects, and lack of interaction effects, of the moderation models are presented graphically in Figures 2 to 7. The categorisation of low, average, and high, were based on mean and one standard deviation above and below the mean for each variable. Within each graph, it can be observed that the gradients

of each line showing anxiety or depression scores, by level of impact of stroke, do not change significantly at different levels of psychological flexibility, demonstrating the absence of moderation. However, the graphs demonstrate that higher levels of psychological flexibility are linked with lower depression and anxiety scores across different impacts of stroke.

Figure 2

Mean Depression Scores Across Levels of Fatigue and Psychological Flexibility

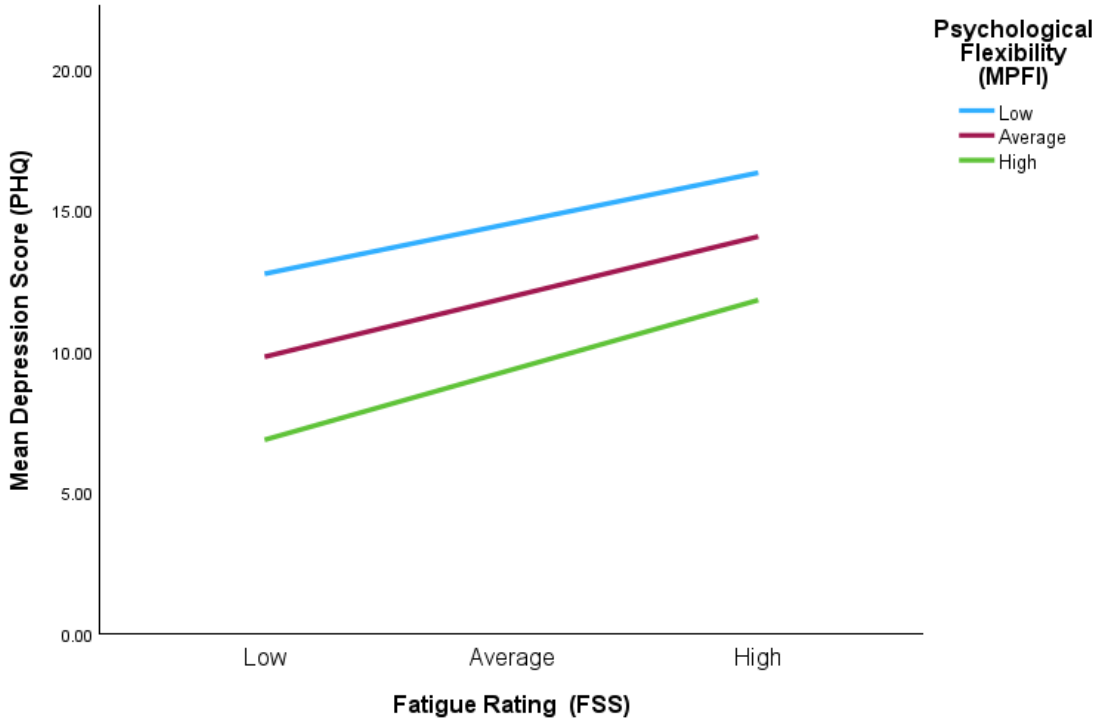


Figure 3

Mean Depression Scores Across Levels of Physical Function and Psychological Flexibility

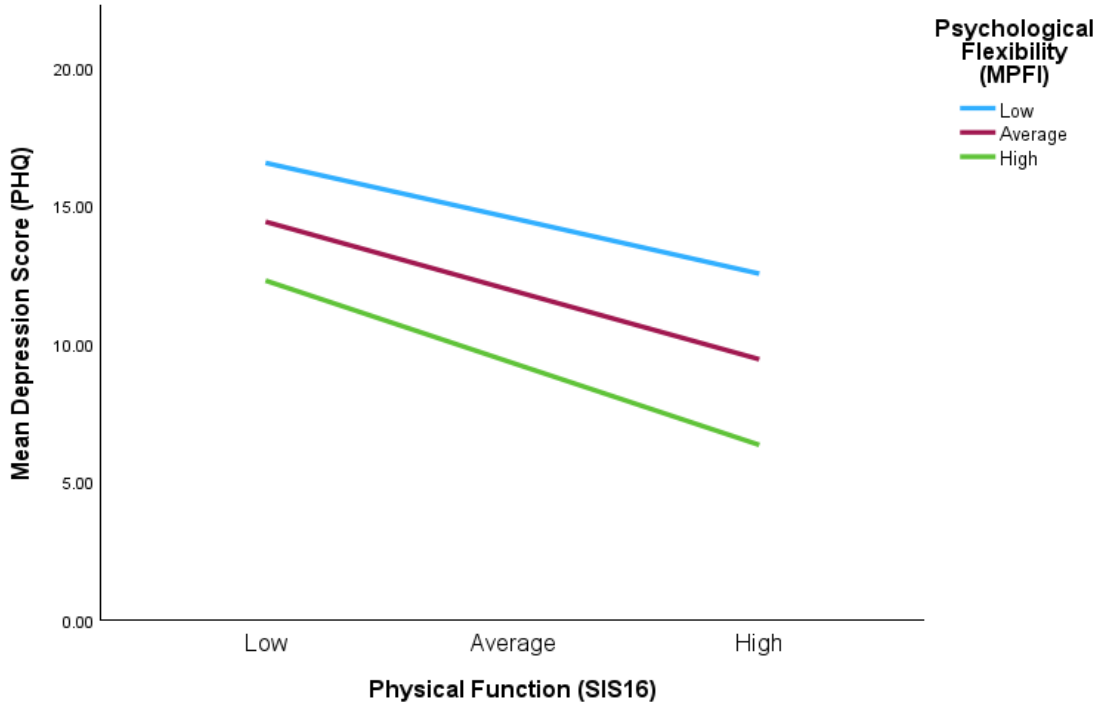


Figure 4

Mean Depression Scores Across Levels of Perceived Cognitive Function and Psychological Flexibility

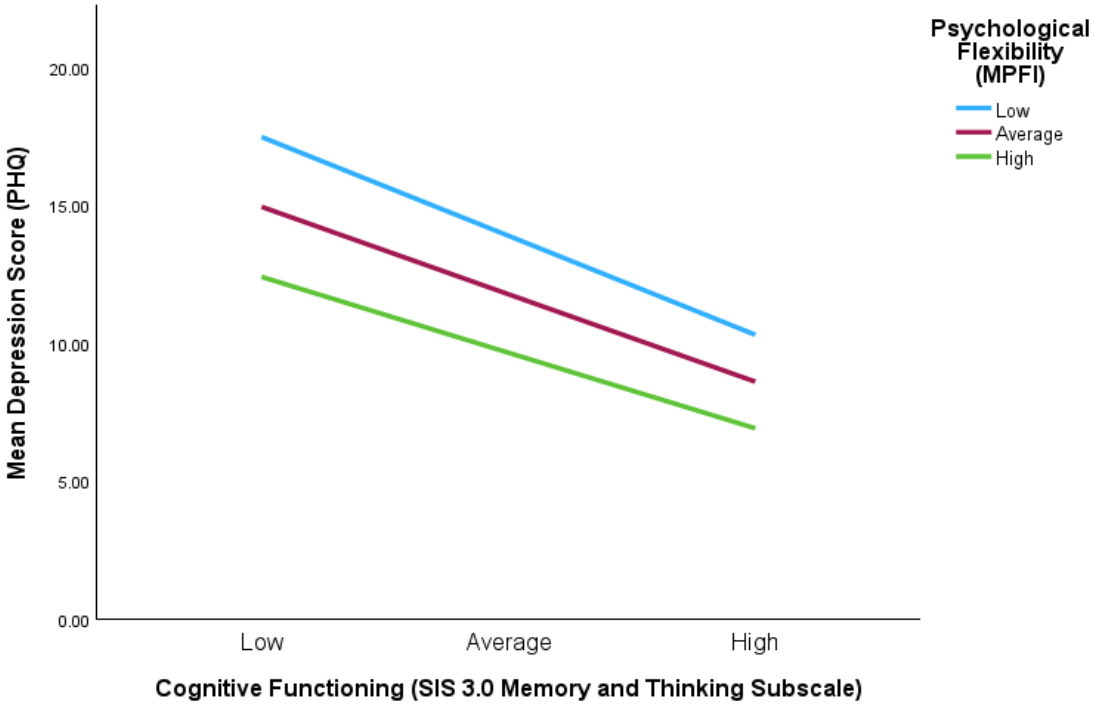


Figure 5

Mean Anxiety Scores Across Levels of Fatigue and Psychological Flexibility

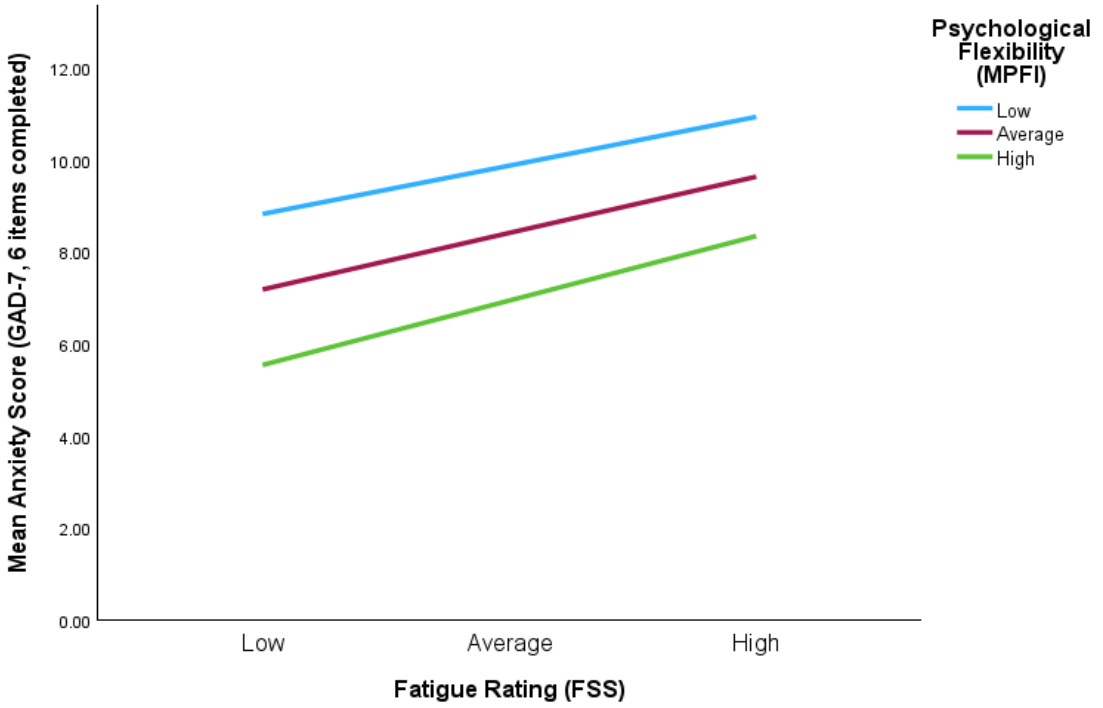


Figure 6

Mean Anxiety Scores Across Levels of Physical Function and Psychological Flexibility

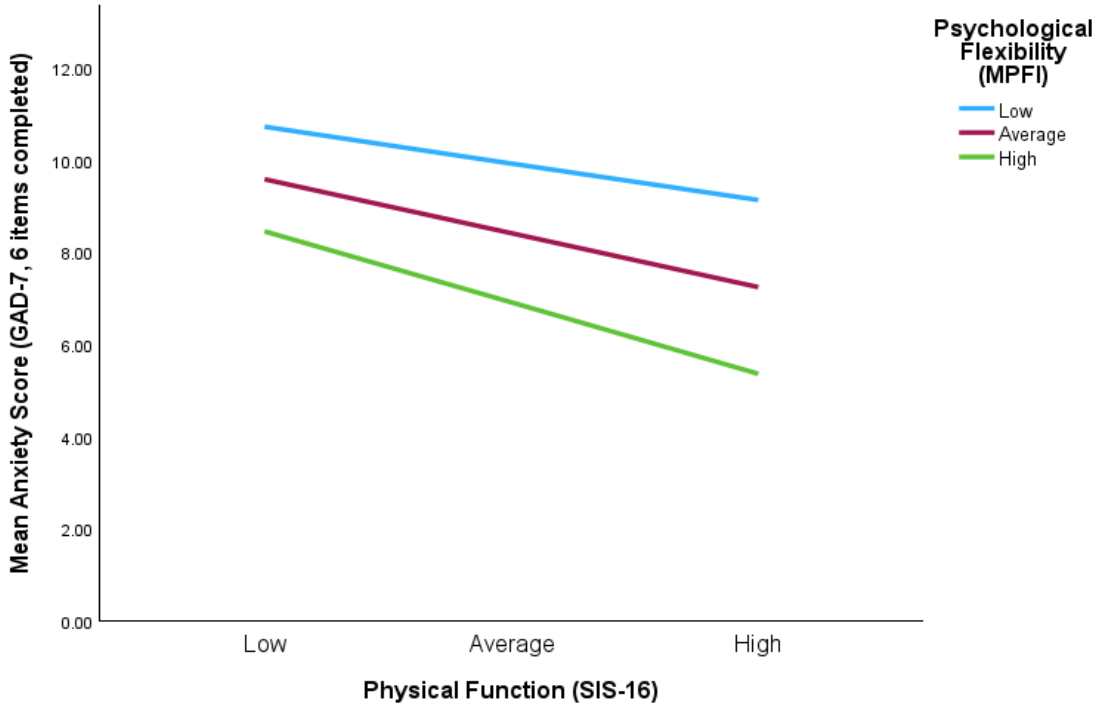
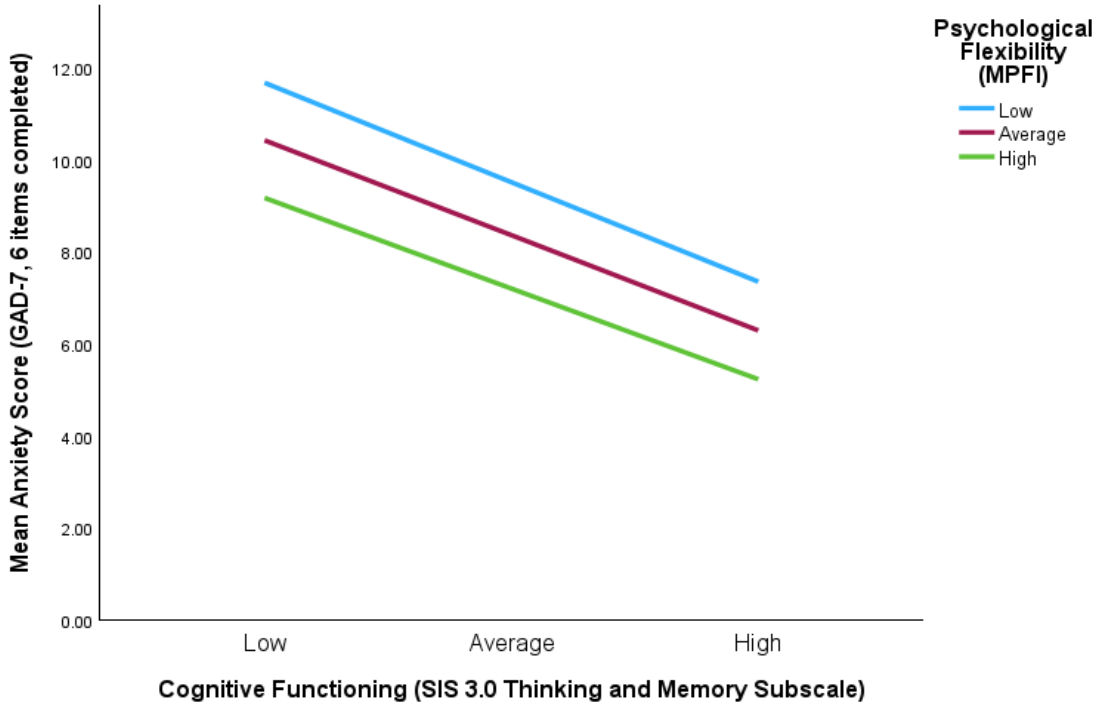


Figure 7

Mean Anxiety Scores Across Levels of Perceived Cognitive Function and Psychological Flexibility



Additional Exploratory Analysis

The PROCESS macro used for the main moderation analysis did not produce effect sizes or the information required to calculate them. Effect sizes were important to understand the magnitude of the associations between the impacts of stroke and psychological flexibility, with post-stroke depression and anxiety, and when relevant to the research are fundamental within psychological studies (Pek & Flora, 2018). An additional analysis was conducted to calculate effect sizes. As all measures of stroke impact and psychological flexibility were significant predictors of depression and anxiety, all factors were loaded as individual predictors into multiple linear regression models. This allowed for effect sizes to be calculated while accounting for the shared variance between impacts of stroke. Pre-stroke depression and age were also included as they were found to be significant co-variates in the main analysis.

Partial eta squared was derived as an effect size as it provides a measure of effect while accounting for the effects of other variables, generating a measure of the

unique effect of each predictor. Assumptions of normality, linearity, and homoscedasticity were deemed to be met through visual inspection of plots. As this analysis was not pre-planned and does not fall under the initial hypotheses, a Bonferroni correction was applied to reduce the type 1 error rate of the analysis. The original alpha value was divided by four, representing the number of hypotheses tested in each model, providing a corrected alpha value of $\alpha = .0125$.

The results of the regression analysis for depression and anxiety are detailed in Table 4. The measured impacts of stroke, psychological flexibility, age, and pre-stroke depression explained 52.6% of the variance in depression scores, $R^2 = .526$, $F(6,183) = 33.91$, $p < .001$. Physical function, perceived cognitive function, and psychological flexibility were found to be significant predictors of post-stroke depression scores. Fatigue was not a significant predictor of depression with a Bonferroni correction applied. The effect sizes suggest that psychological flexibility had the greatest effect on depression with a large effect. Perceived cognitive functioning and physical function demonstrated a medium sized effect.

Only 33.7% of the variance in anxiety scores were explained by the predictors in the model, $R^2 = .337$, $F(6,183) = 15.48$, $p < .001$. While this suggests that the measured impacts of stroke and psychological flexibility account for less variability for anxiety than depression, the size of effects of both models are in the substantial range. Only perceived cognitive function, psychological flexibility and age were found to be significant predictors of anxiety scores. The largest effect was produced by perceived cognitive function, followed by psychological flexibility, with both producing medium sized effects.

Table 4

Multiple Linear Regression: Impacts of Stroke and Psychological Flexibility on Depression and Anxiety Scores

Effect	R^2 Block	*b*	*SE*	95% CI		*t*	*p*	η_p^2
				LL	*UL*			
Impacts of Stroke and Psychological Flexibility scores on Depression scores								

Effect	R^2 Block	*b*	*SE*	95% CI		*t*	*p*	η_p^2
				LL	*UL*			
Step 1								
Constant	.087*	13.86	1.92	10.05	17.52	7.17	<. 001*	-
Pre-Stroke Depression[a]		3.93	1.11	1.77	6.11	3.72	<.001*	-
Age		-0.06	0.04	-0.14	0.02	-1.64	.099	-
Step 2								
Constant	.526*	33.30	4.12	24.71	41.01	8.96	<.001*	.305
Pre-Stroke Depression[a]		1.45	0.82	-0.14	3.06	1.82	.080	.018
Age		-0.04	0.03	-0.10	0.02	-1.35	.196	.010
Fatigue		0.08	0.04	0.01	0.16	2.41	.030	.031
Physical Function		-0.12	0.03	-0.18	-0.05	-3.73	<.001*	.071
Perceived Cognitive Function		-0.32	0.07	-0.45	-0.18	-5.34	<.001*	.135
Psychological Flexibility		-0.08	0.01	-0.11	-0.05	-5.97	<.001*	.163
Impacts of Stroke and Psychological Flexibility scores on Anxiety scores								
Step 1								
Constant	.078*	12.52	1.39	9.69	15.13	8.42	<.001*	-
Pre-Stroke Depression[a]		1.63	0.84	-0.03	3.25	2.01	.054	-
Age		-0.10	0.03	-0.15	-0.04	-3.25	.001*	-
Step 2								
Constant	.337*	22.56	3.42	16.03	29.30	6.71	<.001*	.197
Pre-Stroke Depression[a]		0.16	0.75	-1.31	1.63	0.22	.837	<.001
Age		-0.07	0.03	-0.12	-0.02	-2.62	.007*	.036
Fatigue		0.04	0.03	-0.02	0.11	1.36	.213	.010
Physical Function		-0.03	0.03	-0.09	0.02	-1.21	.224	.008

Effect	R^2 Block	*b*	*SE*	95% CI		*t*	*p*	η_p^2
				LL	*UL*			
Perceived Cognitive Function		-0.25	0.06	-0.36	-0.13	-4.54	<.001*	.101
Psychological Flexibility		-0.04	0.01	-0.07	-0.02	-3.60	<.001*	.065

Note: CI = Confidence interval; *LL* = lower limit; *UL* = upper limit. *SE*, CI and *p* values derived from bootstrapping.

[a] 0 = no, 1 = yes.

* *p* value significant at corrected alpha (α = .0125)

η_p^2 effect size: small = .01; medium = .06; large = .14

Discussion

This cross-sectional study aimed to explore the associations between indicators of stroke impact and depression and anxiety, and to understand whether psychological flexibility moderated these relationships. The analysis found that fatigue, physical functioning, and perceived cognitive functioning were significant predictors of depression and anxiety. However, when analysing these predictors through a larger exploratory mode, that controlled for the shared variance between predictors, fatigue was no longer a significant predictor of post-stroke depression or anxiety, and physical functioning no longer significantly predicted post-stroke anxiety. Psychological flexibility did not moderate the relationships between the indicators of stroke impact and depression and anxiety but was a significant predictor for both mood difficulties.

Fatigue was found to be a significant predictor of anxiety and depression within moderation models, but in larger models was found to be non-significant. This may be due to shared variance between fatigue and other predictors being accounted for within the model, or through the conservative alpha level through Bonferroni adjustment. There is lack of agreement regarding the associations between post-stroke fatigue and mood difficulties. Galligan et al. (2016) found that fatigue was significantly associated with and stroke specific anxiety, but not

generalised anxiety, which constituted the measurement of anxiety in this study. The authors did find significant associations between fatigue and post-stroke depression; however, this outcome has not been consistently replicated (Ponchel et al., 2015). The inconsistent associations between fatigue and mood difficulties were replicated in this study.

Physical function was a significant predictor of depression but inconsistently predicted anxiety. These results mirror the evidence base. Physical functioning is inconsistently associated with post-stroke anxiety. Ayerbe et al. (2014) only found a significant association between disability and post-stroke anxiety at three months and three years after stroke, while Menlove et al. (2015) found no significant associations across observational studies. Physical function is more consistently associated with post-stroke depression (Kutlubaev & Hackett, 2014; Shi et al., 2017), which has been further evidenced in this study. Reduced physical function may result in a loss of meaningful and valued activity in ways that were accessed prior to a stroke. This may be similar to the perpetuating factor of withdrawal and reduced activity in the maintenance of depression symptomology that is addressed with behavioural activation (Veale, 2008).

Perceived cognitive functioning was consistently associated with both post-stroke anxiety and depression symptomology in this study. These findings appear to be consistent with the literature, linking cognitive impairment to mood disorders (Ayerbe et al., 2011; Menlove et al., 2015). However, the current findings are based only on self-reported cognitive difficulties, which may not fully align with objectively measured cognitive functioning. For example, people's perception of their cognition may be influenced by various biopsychosocial biases and those with mood disorders may be more prone to negative self-assessments. While the findings do not speak to the link between objective cognitive functioning and mood disorders, they do highlight that perceptions of impairment are indeed associated with mood difficulties.

Psychological flexibility was not a significant moderator within all moderation analyses. The moderation models provide some insight into the role of psychological flexibility in post-stoke depression and anxiety. We found that increasing psychological flexibility does not change the relationship between the

three measured stroke impacts and mood difficulties; in other words, individuals with high levels of psychological flexibility and fatigue are likely to experience more depressive symptoms than those with high flexibility and low levels of fatigue.

Although not a significant moderator, psychological flexibility appeared to negatively predicted anxiety and depression. While depression and anxiety scores are likely to increase as post-stroke impacts worsen, higher psychological flexibility is associated with overall lower anxiety and depression scores compared with lower psychological flexibility. This suggests that, if keeping stroke impacts constant, increasing psychological flexibility through a psychological intervention could reduce depression and anxiety symptomology.

The results of this analysis did not find evidence that psychological flexibility is a key process in reducing the impact of a stroke on people's mood and wellbeing; however, it was linked with reducing mood difficulties more generally. One hypothesis is that psychological flexibility predicts lower anxiety and depression scores through the response to private events (i.e. thoughts and feelings) in isolation of the impacts of stroke that were measured. As such, the role of psychological flexibility in depression and anxiety is not linked specifically with a response to stroke severity but may instead be applied to general life stimuli that result in unwanted private events. This would also be consistent with the transdiagnostic application of ACT (Hayes et al., 2011).

It is also possible that psychological flexibility as a global construct does not moderate the relationship between impacts of stroke and depression and anxiety, but certain aspects of flexibility may. Within migraine research, general acceptance and pain acceptance have been found to account for more variance in depression compared to committed action (Almarzooqi et al., 2017). Different processes of psychological flexibility may have different associations with the variables and may present a moderating relationship that the analysis in this study has been unable to detect.

While strong associations have been demonstrated between psychological flexibility and post-stroke mood, the analysis is unable to establish a causal relationship. An explanation for the lack of moderation, but significant association

may be the ambiguity in the direction of the relationship. Lower levels of distress are likely to make it easier to sit with unwanted private events and to take action in line with values when compared to higher levels of distress; therefore, lower anxiety and depression scores may result in lower scores of psychological flexibility. The sampled group is one that has not been exposed to a specific intervention that develops psychological flexibility to be used in response to distressing experiences; therefore, it is possible that within an untrained sample, the causal direction may flow in the opposite direction. This could be tested within future research through specific skill development within psychological flexibility and to measure the effect on mood when it is consciously applied.

The exploratory analysis identified different strength of associations between the predictors and post-stroke mood. Psychological flexibility was found to have the strongest association with post-stroke depression, producing a large effect size. For the anxiety model, perceived cognitive functioning produced the largest effect, while psychological flexibility was the second strongest, both with medium effect sizes. This may suggest that psychological flexibility better predicts post-stroke depression than fatigue, physical function or perceived cognitive function, and may have a greater effect on anxiety than fatigue or physical functioning; however additional research and direct significance testing is needed for more certainty around this hypothesis.

The Memory and Thinking subscale of the SIS 3.0 significantly predicted anxiety and depression with medium effect sizes; however, the measure does not assess cognition objectively. Although research has suggested the scale may be sensitive to cognitive difficulties not noted in a clinical setting (Almalki et al., 2019), it is unclear whether the scale accurately measures cognitive function. In addition, there may be some overlap between the constructs measured by the Memory and Thinking subscale and anxiety, with one question asking “How difficult was it to concentrate?” which can be a prominent difficulty associated with anxiety (Hallion et al., 2018). Difficulty in concentration may also impact other constructs the questionnaire explores such as thinking quickly and problem solving.

The mean age of the sample included in this study should be noted (M=48.03). This lower than expected age may reflect the sampling and data

collection methods employed whereby utilising an online survey that is distributed through social media may be more likely to reach a younger cohort of participants. This poses the question of how generalisable the outcomes are to the wider stroke population, especially those who were unable to access the study materials through an online platform. In addition, stroke has historically been considered a disease of the elderly; however, stroke is increasing in frequency in individuals aged 55 years and younger (Li et al., 2022). The lower average age of the sample may also reflect this.

Limitations

There are several limitations within the current study. Unfortunately, this study did not record or differentiate between ischaemic and haemorrhagic stroke. Research suggests those who experience haemorrhagic stroke are more likely to have had a more severe stroke, slower recovery during rehabilitation, and a more unfavourable outcomes (Andersen et al., 2009; Bilic et al., 2009; Schepers et al., 2008), creating the potential for different groups within the sample. While utilising a self-report online survey allowed the recruitment of a large number of stroke survivors, the sample may be biased in a number of ways. For example, the study may have recruited those who had an interest in participating in research or were able to access social media and the online study materials. This may introduce a bias in the sample around accessibility. While practical support was encouraged, the sample is likely skewed towards those who have experienced a milder stroke as they would have found it easier to participate. Equally, the use of online dissemination may have skewed the sample towards a younger population. These factors likely limit the generalisability of the findings. In addition, the use of a self-report online survey would have made it difficult for stroke survivors with higher levels of aphasia to participate, meaning this sample is likely missing an important group within the stroke survivor population.

Self-report measures have the potential to introduce bias into the data. A large number of people engaged with the survey materials and during recruitment, many stroke survivors shared the study advert within their networks. The motivation to participate in research and contribute to potential advancements in support for stroke survivors may have resulted in demand characteristics. This may have introduced a

bias where participants were not providing a true representation of themselves on the measures. Self-report measures also rely on the measurement tool providing an accurate measure of the desired construct, and to be easily understood in lay terms. With this in mind, the SIS 3.0 Memory and Thinking subscale and the MPFI carry potential limitations. The study design did not allow the use of an objective measure of cognition, rather the impact of cognitive difficulties on quality of life. Therefore, the use of the SIS 3.0 Memory and Thinking subscale does not allow the findings to be generalised and compared with cognition that has been assessed in a more detailed and structured way. The MPFI is a verbose assessment of an abstract concept which participants have had difficulty understanding. In combination with the potential for variability in the accessibility of language within a stroke population, some participants may have had difficulty with the measure and may not have been able to provide an accurate response. Alternatively, psychological flexibility could have been assessed in person through a collaborative interview, which would have allowed abstract concepts to be explained and explored directly with the individual participant. Unfortunately, this methodology was beyond the scope of this study.

Human error which led to only six items from the GAD-7 to be included in the survey poses a risk to the validity and reliability of the anxiety outcomes and analysis. The missing item was the second question of the GAD-7, which represents a core anxiety symptom and is used on the short-form version, the GAD-2 (Kroenke et al., 2007); therefore potentially impacting the construct and content validity of the measure. The internal consistency of the measure may also have been impacted by the exclusion of the second item.

Implications and Recommendations

The results of this study have implications for future research and clinical practice. While psychological flexibility did not moderate the relationship between Impacts of stroke and mood, it was significantly associated with lower depression and anxiety scores, producing a large effect with the former. This would imply that clinicians could use therapeutic approaches that develop psychological flexibility, such as ACT, to support stroke survivors with depression and anxiety. This is consistent with evidence from RCTs and single case studies demonstrating changes

in post-stroke anxiety and depression following an ACT intervention (Graham et al., 2015; Majumdar & Morris, 2019; Niu et al., 2022; Rauwenhoff et al., 2022). Higher psychological flexibility was linked with lower depression and anxiety independent of severity of stroke impact. This suggests that stroke severity should not be a limiting factor when deciding who may benefit from an intervention that develops psychological flexibility in the context of anxiety or depression. Additionally, clinicians could undertake assessments of psychological flexibility at point of hospital discharge, as a lower psychological flexibility may suggest an increased likelihood of experiencing depression and anxiety; however, further research is needed to confirm this.

To further understand the role of psychological flexibility within the context of anxiety and depression in stroke survivors, researchers should investigate the impact of psychological flexibility when it has been specifically trained and consciously applied, rather than it being a more passive construct. Researchers should also investigate the role of individual processes of psychological flexibility (Hayes et al., 2006). Doing so would allow a more detailed investigation of the mechanism of psychological flexibility for stroke survivors. For example, there may be a key process that does moderate the relationship with impacts of stroke that was not revealed through analysis of the global construct. In addition, understanding the strength of association of different processes of psychological flexibility may support the delivery and development of ACT interventions with stroke survivors. Understanding the differential effectiveness of these six process may support the development of briefer, more targeted process-specific interventions, especially in contexts where resources for longer courses of therapy are less available (Moskow et al., 2023). Researchers should continue to directly investigate the impact of ACT on anxiety and depression in stroke survivors to expand the findings of this study into a clinical application. Finally, investigations into the role of psychological flexibility require an accurate measure of the construct. Further research should aim to directly assess the validity of the MPFI within a stroke population.

In conclusion, psychological flexibility was not found to moderate the relationship between measures of the impact of stroke and mood difficulties; however, psychological flexibility was significantly associated with lower depression

and anxiety scores, producing large and medium effect sizes respectively. While psychological flexibility is not protective against stroke severity with respect to mood, it does predict anxiety and depression within stroke survivors. Although previous research has suggested that improvements in flexibility precede changes in ACT intervention outcomes, causation cannot be established for the associations in this study. The association of psychological flexibility with lower post-stroke depression and anxiety in stroke survivors warrants further research into how psychological flexibility may be developed therapeutically with stroke survivors and how this impacts mental health outcomes.

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Chapter 5: Discussion and Critical Evaluation

This thesis portfolio aimed to explore different aspects of support for mood difficulties post-stroke. The systematic review aimed to understand if there is a key window in providing psychological intervention for post-stroke depression and anxiety to support better clinical outcomes and allocation of resource. The empirical paper aimed to explore the role of psychological flexibility in post-stroke mood difficulties by understanding whether it acts as a moderator in the relationships between measures of stroke impact and mood difficulties. This chapter will initially provide an overview of the findings of both papers, followed by a discussion of the strength and limitations. Finally, directions for future research, and the clinical and theoretical implications of the findings are discussed.

Overview of Findings

Systematic Review: The Consideration of Time Since Stroke on Intervention Outcomes for Post-Stroke Depression and Anxiety: A Systematic Review

There is evidence to suggest that prevalence of post-stroke mood difficulties can be stable up to 10 years following stroke (Ayerbe et al., 2013b, 2014); however, there is no guideline to suggest the ideal time in recovery to provide psychological intervention. To our knowledge, this is the first systematic review to explore the impact of time since stroke on psychological intervention outcomes in randomised controlled trials (RCTs) for post-stroke mood difficulties. A systematic search was completed on four electronic data bases (Medline Ultimate, APA PsychINFO, CINAHL Ultimate, and EBSCO E-Journals) between inception to October 2024. Fifteen studies, involving 1759 stroke survivors, were analysed using a narrative synthesis.

The results suggest that interventions provided at an earlier time since stroke were more frequently effective than those provided later. Taken at face value this may represent an opportunity to maximise the effectiveness of psychological intervention; however, the findings may also represent different constructs of depression present within the population. The synthesis also indicated that time since stroke is under reported as a demographic factor and is not considered as a potential confounding factor for intervention outcomes. This was particularly relevant where a

large heterogeneity of time since stroke was present in studies which broadened recruitment to participants who were over six months post-stroke.

Empirical Study: Exploring the Associations Between Impacts of Stroke, Psychological Flexibility and Post-Stroke Anxiety and Depression

Acceptance and Commitment Therapy (ACT) is a third wave approach that aims to develop psychological flexibility to help individuals open up to their experiences, be present in the moment, and to take action in line with what is meaningful for them (Harris, 2019; Hayes et al., 2011). The empirical study aimed to explore whether psychological flexibility moderated the relationship between impacts of stroke with depression and anxiety. Understanding this would potentially provide insight into the mechanism of psychological flexibility in supporting mood and act as a foundation for research for the intervention with a stroke population.

The initial results suggest that fatigue, physical function, and perceived cognitive function after stroke are significantly associated with depression and anxiety; however, psychological flexibility did not moderate this relationship. While psychological flexibility is not protective against stroke severity with respect to mood, it was found to be a significant negative predictor of depression and anxiety. An additional exploratory analysis was completed to understand the level of effect of each predictor on anxiety and depression. When in a larger model, fatigue was no longer a significant predictor of anxiety or depression, and physical function did not continue to predict anxiety. Psychological flexibility was the strongest predictor of post-stroke depression, producing a large effect size ($\eta_p^2 = .163$), and produced a moderate effect size for predicting anxiety ($\eta_p^2 = .065$). The results suggest that a psychological intervention that develops psychological flexibility may reduce symptomology of anxiety and depression.

Strengths and Limitations

This section will explore the strengths and limitations of each study within the thesis, and those identified in the portfolio as a whole. A key strength of the portfolio is the contribution it has made to under-researched areas. The systematic review represented the first review of RCTs of post-stroke mood interventions that explored the impact of time since stroke, while the empirical study contributed to an

evidence base that is growing but still in its infancy. In particular, both studies explored post-stroke anxiety which has been insufficiently researched, with the wider evidence base focusing on post-stroke depression (Ayerbe et al., 2014; Tang et al., 2013). Within the systematic review, a number of databases were searched which provided studies from across continents and cultures, potentially reducing western bias. The empirical paper attempted to reduce western bias by recruiting globally. While the majority of participants were from western countries, there was some representation from other continents, for example Oceania.

There were a number of limitations within each study of this portfolio. The results of both studies should be taken with caution when informing clinical application. While the systematic review identified that early intervention was more effective, there are other factors that may explain this, such as the construct of depression the intervention is treating, or the large degree of heterogeneity within a small sample. Psychological flexibility was found to be a significant predictor of anxiety and depression in stroke survivors; however, the direction of this relationship cannot be assumed. While the clinical implications should be approached with caution, the studies within this portfolio represent first steps in a longer journey of evidence building around interventions for post-stroke mood.

For the systematic review specifically, three key limitations were identified. A high degree of heterogeneity was identified across different characteristics of the included studies. Perhaps most impactful to the synthesis of data with regards to time since stroke was the degree of reporting of time since stroke, the use of different measures of central tendency, and wide ranges of time since stroke of participants included in individual studies. These factors meant that it was not possible to pool the outcomes of studies to understand the efficacy of treatments at different stages of stroke recovery. In addition, the wide ranges of time since stroke within individual studies may also introduce different populations within the sample if depression at different stages of post-stroke recovery are seen as different constructs, i.e. adjustment vs persistent depression. Finally, heterogeneity within intervention and control types made it more difficult to attribute patterns in the data to time since stroke as opposed to methodological differences.

It should be held in mind that the evidence included in the systematic review varied in quality. Five studies were regarded as having a higher risk of bias, representing a third of studies included in the review. An absence of methodological reporting was observed across a number of areas included randomisation and group allocation concealment, and assessor blinding and reliability. Intention to treat analysis is considered an effective way of producing an unbiased estimate of treatment efficacy (McCoy, 2017); however, 11 of the studies in this review used a per-protocol analysis. The high risk of bias within the included studies has implications for the confidence in the findings of the systematic review.

Limitations were also identified in the empirical study. The use of a self-report online survey brings into question how generalisable the findings are to the wider stroke survivor population. Although the sampling method allowed a large sample to be recruited, caution should be applied as to what population that sample represents. Additionally, the use of an online survey meant that a subjective measure of cognition was required as it was not feasible within the scope of this study to administer a more objective assessment. This should be held in mind when considering the findings regarding cognitive function. The measure of psychological flexibility used was verbose and measured an abstract concept which may have made it more difficult to complete by those with difficulty in accessing language. While the study included anxiety as a main outcome measure, this was hampered by human error within the creation of the online survey, whereby the administered measure was incomplete for all participants.

Participants could only take part if they were at least six months post-stroke. This was to ensure that participants were not in the acute phase following their stroke where the constructs measured were likely to be more stable (Grefkes & Fink, 2020). This, however, means that the data may not be generalisable to those who are earlier in their recovery following stroke.

Finally, only using the score for global psychological flexibility within the analysis means that detail regarding individual processes may have been missed. It may be possible that a key process within psychological flexibility acts as a moderator or explains a greater proportion of variance in anxiety and depression scores. Therefore, the results of this study can only comment on the role of

psychological flexibility as an amalgamation of the six processes (Hayes et al., 2006).

Implications for Future Research

The findings of the systematic review indicate considerations for the direction of future research. Firstly, researchers should ensure that time since stroke is reported for their sample as demographic information. Including a mean and standard deviation will allow the reader to understand the distribution of time since stroke within the sample and will support future synthesis around time since stroke. Research should also directly investigate the impact of time since stroke within psychological intervention RCTs. Particular attention should be paid to stroke survivors who are at least one year post-stroke, as this was an under-represented population within the review. Comparisons may also be made with outcomes at three, six, and nine months post-stroke. This would allow the impact of the one year naturalistic recovery period to be better understood (L. Liu et al., 2023). Besides comparing specific time frames, RCTs should aim to have tighter inclusion and criteria around time since stroke as current variance in the demographic can be too large. It is suggested that when recruiting stroke survivors within the first year post-stroke, studies should not recruit participants who are more than one year post-stroke.

Additional RCTs are required for post-stroke mood interventions, particularly with regards to post-stroke anxiety; only four RCTs investigated anxiety within this review. Expanding the evidence base will provide more opportunities for synthesis with reduced heterogeneity, for example, only focusing on a specific intervention type. Finally, researchers should endeavour to adequately report their methodology, particularly within the context of randomisation and group allocation concealment. Intention to treat analysis was infrequently used in the included studies; adopting intention to treat principles would allow for a less biased estimate of treatment efficacy (McCoy, 2017).

Result from the empirical paper suggest psychological flexibility predicts anxiety and depression scores in stroke survivors, and future research can expand on these findings in a number of ways. The study could be replicated with stroke survivors who are in an earlier stage post-stroke to understand whether the role of

psychological flexibility varies when adjustment is less likely to have taken place. Breaking down the measure of psychological flexibility into the key processes will allow an understanding of whether certain aspects of the model act as a moderator, or if there are certain processes which better predict anxiety and depression. Understanding this would support the development of therapeutic interventions for stroke survivors which can lean into processes which better predict mood difficulties post-stroke.

Implications for Clinical Practice and Theory

The findings from the systematic review suggest that earlier psychological interventions are more effective in the treatment of depression and anxiety after stroke. A more frequent response to treatment in earlier stages of stroke recovery may represent a synergistic effect with the naturalistic recovery of depression that occurs with the first year following stroke (L. Liu et al., 2023). While this may indicate a key window for psychological intervention, it may also allude to different constructs of depression being present within the stroke-survivor population. Those being treated earlier may be more likely to experience a depression associated with adjustment to life changes following stroke, while those later in their recovery may be experiencing a persistent depression. This is consistent with Hackett and Pickles (2014) who suggested lower long-term prevalence rates of depression may be associated with adjustment to life after stroke. It is possible that different constructs of depression may require a different focus of intervention; however, at this point it is unclear. Additional research is required to better evidence the potential clinical applications of the findings of the systematic review; however, the review does highlight the convoluted picture of the impact of time since stroke, especially with the degree of heterogeneity within the evidence base.

The empirical study found that psychological flexibility does not protect against the impact of stroke severity with respect to post-stroke mood by moderating the relationships between impacts of stroke and mood. However, the findings did highlight a strong effect of psychological flexibility in its association with post-stroke depression and anxiety. This would suggest that interventions that develop this construct could be helpful in the treatment of anxiety and depression after stroke, regardless of the severity of impact of stroke. Improving psychological flexibility has

been correlated with mental health outcomes, and has been documented as changing prior to mental health outcomes following ACT interventions (Ciarrochi et al., 2010).

A recent RCT on individuals with acquired brain injury (ABI) indicated that ACT did not improve psychological flexibility, or anxiety and depression, to a greater extent than a psycho-education and relaxation control; however, both groups experienced an increase in flexibility and a decrease in anxiety and depression over time (Rauwenhoff et al., 2024). The authors suggest that their measures of psychological flexibility may not have accurately captured the processes that ACT aims to improve, thus making it difficult to differentiate between the effect of ACT and the control group. It should be noted that study was underpowered which means that differences between ACT and the control group may have been harder to detect. While previous RCTs have found ACT to be effective in a stroke population, these have utilised a passive control group (Majumdar & Morris, 2019; Niu et al., 2022), the difference when comparing to an active control suggested by Rauwenhoff et al. (2024) warrants additional research.

Psychological flexibility was found to best predict depression compared to the measured impacts of stroke in this study, including pre-stroke depression. While this study used a sample outside of the acute stage of stroke, this relationship could be applied clinically by screening psychological flexibility at discharge from hospital when patients show no symptomology of depression. Individuals with low psychological flexibility may be more likely to experience depression which should be considered in post-discharge care. Further research on psychological flexibility with stroke-survivors in the acute stage would allow more confidence in this recommendation.

Conclusions

In conclusion, this thesis portfolio found that a key window for psychological intervention for mood difficulties post-stroke may be earlier in recovery. However, large heterogeneity and problems with the quality and quantity of the data mean conclusions should be approached with caution. Studies do not routinely report time since stroke within their demographics or use a comment central tendency measure to support better synthesis of data. Future research should directly investigate the impact of time since stroke, particularly during and after the first year post-stoke.

Intervention RCTs should also routinely report time since stroke as a demographic and be mindful of reporting methodological rigour. The thesis also demonstrated that psychological flexibility is a significant predictor of post-stroke depression and anxiety, producing a greater effect on the former compared to other impacts of stroke. Psychological flexibility did not moderate the relationships between the measured impacts of stroke, and anxiety and depression. The results indicate that a psychological intervention which develops psychological flexibility may be effective in supporting stroke survivors with anxiety and depression. The significant association warrants future research regarding psychological flexibility and its development through psychological interventions with the stroke survivor population.

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Appendices

Appendix A - The Clinical Neuropsychologist Journal Requirements

Instructions for authors

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2. Should contain a structured abstract of 250 words.

A structured abstract should cover (in the following order):

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Method: A summary of the participants as well as descriptions of the study design, procedures, and specific key measures, to the extent that space allows.

Results: A summary of the key findings.

Conclusions: Clinical and theoretical implications of the findings.

NOTE: If your manuscript is a critical review or a commentary, you can omit the Results portion of the abstract. However, retain that portion for systematic reviews and meta-analyses. Read tips on writing your abstract.

Read tips on writing your abstract.

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14. **Units.** Please use SI units (non-italicized).

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Appendix B – PRISMA 2020 Abstract Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	No
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	No
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	No
Registration	12	Provide the register name and registration number.	No

Appendix C – PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	10
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	139
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	14
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	14
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	15 & 17
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	14
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	143
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	15
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	15 & 16
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	16
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	16
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	16
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	N/A
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	17
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A

Section and Topic	Item #	Checklist item	Location where item is reported
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	N/A
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	17
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	18
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	18
Study characteristics	17	Cite each included study and present its characteristics.	25 – 28
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	19 & 20
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	29 – 39
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	18 – 24
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	40 – 45
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	45 – 48
	23b	Discuss any limitations of the evidence included in the review.	48 & 49
	23c	Discuss any limitations of the review processes used.	48 & 49

Section and Topic	Item #	Checklist item	Location where item is reported
	23d	Discuss implications of the results for practice, policy, and future research.	49 & 50
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	14
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	N/A
Competing interests	26	Declare any competing interests of review authors.	N/A
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Risk of bias tool: 144

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

Appendix D – Search Strategy

The following search terms were used for each database searched:

Search Terms: (Stroke OR "cerebrovascular accident" OR cva OR post-stroke OR thrombosis) AND (mood OR anxiety OR depress*) AND ("randomi* control* trial" OR RCT)

Appendix E – Joanna Briggs Institute Critical Appraisal Tool for Assessment of Risk of Bias for Randomised Controlled Trials Checklist and Guidance

Introduction

JBI is a global organisation promoting and supporting evidence-based decisions that improve health and health service delivery.

JBI offers a unique range of solutions to access, appraise and apply the best available evidence.

JBI's approach to evidence-based healthcare is unique. JBI considers evidence-based healthcare as decision making that considers the feasibility, appropriateness, meaningfulness and effectiveness (FAME) of healthcare practice.

JBI Systematic Reviews

The core of evidence synthesis is the systematic review of literature of a particular intervention, condition or issue. The systematic review is essentially an analysis of the available evidence and a judgment of the effectiveness or otherwise of a practice, involving a series of complex steps. JBI take a particular view on what counts as evidence and the methods utilized to synthesize those different types of evidence. In line with this broader view of evidence, JBI has developed theories, methodologies and rigorous processes for the critical appraisal and synthesis of these diverse forms of evidence in order to aid in clinical decision-making in health care. Guidance now exists for conducting reviews of effectiveness research, qualitative research, prevalence/incidence, etiology/risk, economic evaluations, text/opinion, diagnostic test accuracy, mixed-methods, umbrella reviews and scoping reviews. Further information regarding JBI systematic reviews can be found in the JBI Manual for Evidence Synthesis.

JBI Critical Appraisal Tools

All systematic reviews incorporate a process of critique or appraisal of the research evidence. The purpose of this appraisal for quantitative evidence is to determine the extent to which a study has addressed the possibility of bias in its design, conduct and analysis. All papers selected for inclusion in the systematic review (that is – those that meet the inclusion criteria described in the protocol) need to be subjected to rigorous appraisal by two critical appraisers. The results of this appraisal can then

be used to inform synthesis and interpretation of the results of the study. Although designed for use in systematic reviews, JBI critical appraisal tools can also be used when creating Critically Appraised Topics (CATs), in journal clubs and as an educational tool.

How were these tools developed?

JBI critical appraisal tools have been developed by JBI and collaborators. The particular iteration of this tool was developed by the JBI Effectiveness Methods Group following oversight by the JBI Scientific Committee.

Like the previous versions of these tools, this version presents signalling questions to prompt reviewers to identify whether certain safeguards of bias have been met, in the primary literature under review. However, unlike previous iterations of this tool, this version has separated questions into whether they provide an answer relating to internal, external or statistical conclusion validity. For questions related to internal validity, these have been further separated to identify what domain of bias they are referring. Finally, this tool has also been structured to facilitate judgments related to bias at different levels (e.g. bias at the outcome level or bias at the result level) where appropriate.

These tools have been approved following extensive peer review by the JBI Scientific Committee.

How to cite: Barker TH, Stone JC, Sears K, Klugar M, Tufanaru C, Leonardi-Bee J, Aromataris E, Munn Z. The revised JBI critical appraisal tool for the assessment of risk of bias for randomized controlled trials. JBI Evidence Synthesis. 2023;21(3):494-506

Assessor:	**Date of Appraisal:**	**Record Number:**
Study Author:	**Study Title:**	**Study Year:**

Internal Validity		**Choice - Comments/Justification**	**Yes**	**No**	**Unclear**	**N/A**
Bias related to selection and allocation						
1	**Was true randomization used for assignment of participants to treatment groups?**		☐	☐	☐	☐
2	**Was allocation to treatment groups concealed?**		☐	☐	☐	☐
3	**Were treatment groups similar at the baseline?**		☐	☐	☐	☐
Bias related to administration of intervention/exposure						
4	**Were participants blind to treatment assignment?**		☐	☐	☐	☐
5	**Were those delivering the treatment blind to treatment assignment?**		☐	☐	☐	☐
6	**Were treatment groups treated identically other than the intervention of interest?**		☐	☐	☐	☐
Bias related to assessment, detection and measurement of the outcome						

7	**Were outcome assessors blind to treatment assignment?**		**Yes**	**No**	**Unclear**	**N/A**
	Outcome 1		☐	☐	☐	☐
	Outcome 2		☐	☐	☐	☐
	Outcome 3		☐	☐	☐	☐
	Outcome 4		☐	☐	☐	☐
	Outcome 5		☐	☐	☐	☐
	Outcome 6		☐	☐	☐	☐
	Outcome 7		☐	☐	☐	☐

8	**Were outcomes measured in the same way for treatment groups?**		**Yes**	**No**	**Unclear**	**N/A**
	Outcome 1		☐	☐	☐	☐
	Outcome 2		☐	☐	☐	☐
	Outcome 3		☐	☐	☐	☐
	Outcome 4		☐	☐	☐	☐

	Outcome 5		☐	☐	☐	☐
	Outcome 6		☐	☐	☐	☐
	Outcome 7		☐	☐	☐	☐

9	**Were outcomes measured in a reliable way**		**Yes**	**No**	**Unclear**	**N/A**
	Outcome 1		☐	☐	☐	☐
	Outcome 2		☐	☐	☐	☐
	Outcome 3		☐	☐	☐	☐
	Outcome 4		☐	☐	☐	☐
	Outcome 5		☐	☐	☐	☐
	Outcome 6		☐	☐	☐	☐
	Outcome 7		☐	☐	☐	☐

Bias related to participant retention

10	**Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?**					
	Outcome 1		**Yes**	**No**	**Unclear**	**N/A**
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 2		**Yes**	**No**	**Unclear**	**N/A**
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 3		**Yes**	**No**	**Unclear**	**N/A**
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 4		**Yes**	**No**	**Unclear**	**N/A**

Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 5		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 6		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 7		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐

Statistical Conclusion Validity

11	**Were participants analysed in the groups to which they were randomized?**					
	Outcome 1		**Yes**	**No**	**Unclear**	**N/A**
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 2		**Yes**	**No**	**Unclear**	**N/A**
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 3		**Yes**	**No**	**Unclear**	**N/A**
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐

Outcome 4		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 5		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 6		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 7		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐

	Result 3		☐	☐	☐	☐

12	**Was appropriate statistical analysis used?**					
	Outcome 1		**Yes**	**No**	**Unclear**	**N/A**
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 2		**Yes**	**No**	**Unclear**	**N/A**
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐
	Outcome 3		**Yes**	**No**	**Unclear**	**N/A**
	Result 1		☐	☐	☐	☐
	Result 2		☐	☐	☐	☐
	Result 3		☐	☐	☐	☐

Outcome 4		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 5		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 6		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐
Result 3		☐	☐	☐	☐
Outcome 7		**Yes**	**No**	**Unclear**	**N/A**
Result 1		☐	☐	☐	☐
Result 2		☐	☐	☐	☐

	Result 3		☐	☐	☐	☐

			Yes	No	Unclear	N/A
13	**Was the trial design appropriate and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?**		☐	☐	☐	☐

Overall appraisal: **Include:** ☐ **Exclude:** ☐ **Seek Further Info:** ☐

Comments:

Table 3 – The JBI Critical Appraisal Tool for RCTs

Question Guidance

How to use the JBI Tools for the Assessment of Risk of Bias

Each question presented in a JBI tool for the assessment of risk of bias for quantitative study designs answers a question related to certain *categories of validity* and *domains of bias*. The concept of validity is often used when referring to the soundness or rigour in which a study was conducted, and whether the results of the study are likely to be true and generalizable. At JBI we have broken this down to include three separate categories that constitute *validity*, these include internal validity, external validity, statistical conclusion validity. In addition, we have also included comprehensiveness of reporting.

Questions categorised as "Internal Validity" are then further organised to specific domains of bias in which they relate. The domains of bias that are used as an indicator of internal validity include bias related to selection and allocation, bias related to administration of the intervention/exposure, bias related to assessment, detection and measurement of the outcome, bias related to participant retention, bias related to temporal precedence, bias related to classification of the exposure, bias related to confounding factors and bias related to selective reporting and/or publication bias.

For more information, please see Barker et al. 2022

Question 1: Was true randomization used for assignment of participants to treatment groups?

Category: Internal validity

Domain: Bias related to selection and allocation

Appraisal: Study level

If participants are not allocated to treatment and control groups by random assignment there is a risk that this assignment to groups can be influenced by the known characteristics of the participants themselves. These known characteristics of the participants may distort the comparability of the groups (i.e. does the intervention group contain more people over the age of 65 as compared to the control?). A true random assignment of participants to the groups means that a procedure is used that allocates the participants to groups purely based on chance, not influenced by any known characteristics of the participants. Reviewers should check the details about

the randomization procedure used for allocation of the participants to study groups. Was a true chance (random) procedure used? For example, was a list of random numbers used? Was a computer-generated list of random numbers used? Was a statistician, external to the research team consulted for the randomization sequence generation? Additionally, reviewers should check that the authors are not stating they have used random approaches when they have instead used systematic approaches (such as allocating by days of the week).

Question 2: Was allocation to groups concealed?

Category: Internal validity

Domain: Bias related to selection and allocation

Appraisal: Study level

If those allocating participants to the compared groups are aware of which group is next in the allocation process, (i.e., the treatment or control group) there is a risk that they may deliberately and purposefully intervene in the allocation of patients. This may result in the preferential allocation of patients to the treatment group or to the control group. This may directly distort the results of the study, as participants no longer have an equal and random chance to belong to each group compared. Concealment of allocation refers to procedures that prevent those allocating patients from knowing before allocation which treatment or control is next in the allocation process. Reviewers should check the details about the procedure used for allocation concealment. Was an appropriate allocation concealment procedure used? For example, was central randomization used? Were sequentially numbered, opaque and sealed envelopes used? Were coded drug packs used?

Question 3: Were treatment groups similar at the baseline?

Category: Internal validity

Domain: Bias related to selection and allocation

Appraisal: Study level

As with question 1, any differences between the known characteristics of participants included in compared groups constitutes a threat to internal validity. If differences in these characteristics do exist, then there is potential that the ‘effect’ cannot be attributed to the potential ‘cause’ (the examined intervention or treatment). This is because the ‘effect’ may be explained by the differences between participant

characteristics and not due to the intervention/treatment of interest. Reviewers should check the characteristics reported for participants. Are the participants from the compared groups similar with regards to the characteristics that may explain the effect even in the absence of the 'cause', for example, age, severity of the disease, stage of the disease, co-existing conditions and so on? Reviewers should check the proportions of participants with specific relevant characteristics in the compared groups. [Note: **Do NOT** only consider the P-value for the statistical testing of the differences between groups with regards to the baseline characteristics.]

Question 4: Were participants blind to treatment assignment?

Category: Internal validity

Domain: Bias related to administration of intervention/exposure

Appraisal: Study level

Participants that are aware of their allocation to either the treatment or the control may behave, respond, or react differently to their assigned treatment (or control) than compared to participants that remain unaware of their allocation. Blinding of participants is a technique used to minimize this risk. Blinding refers to procedures that prevent participants from knowing which group they are allocated. If blinding has been followed, participants are not aware if they are in the group receiving the treatment of interest or if they are in any other group receiving the control interventions. Reviewers should check the details reported in the article about the blinding of participants with regards to treatment assignment. Was an appropriate blinding procedure used? For example, were identical capsules or syringes used? Were identical devices used? Be aware of different terms used, blinding is sometimes also called masking.

Question 5: Were those delivering the treatment blind to treatment assignment?

Category: Internal validity

Domain: Bias related to administration of intervention/exposure

Appraisal: Study level

Like question 4, those delivering the treatment that are aware of participant allocation to either treatment or control, may treat participants differently than compared to those that remain unaware of participant allocation. There is the risk that any potential change in behaviour may influence the implementation of the

compared treatments and the results of the study may be distorted. Blinding of those delivering treatment is used to minimize this risk. When this level of blinding has been achieved, those delivering the treatment are not aware if they are treating the group receiving the treatment of interest or if they are treating any other group receiving the control interventions. Reviewers should check the details reported in the article about the blinding of those delivering treatment with regards to treatment assignment. Is there any information in the article about those delivering the treatment? Were those delivering the treatment unaware of the assignments of participants to the compared groups?

Question 6: Were treatment groups treated identically other than the intervention of interest?

Category: Internal validity

Domain: Bias related to administration of intervention/exposure

Appraisal: Study level

To attribute the 'effect' to the 'cause', (assuming no bias related to selection and allocation) there should be no other difference between the groups in terms of treatment or care received, other than the treatment or intervention controlled by the researchers. If there are other exposures or treatments occurring at the same time with the 'cause' (the treatment or intervention of interest), then the 'effect' can potentially not be attributed to the examined 'cause' (the investigated treatment). This is because it is plausible that the 'effect' may be explained by these other exposures or treatments that occurred at the same time with the 'cause'. Reviewers should check the reported exposures or interventions received by the compared groups. Are there other exposures or treatments occurring at the same time with the 'cause'? Is it plausible that the 'effect' may be explained by other exposures or treatments occurring at the same time with the 'cause'? Is it clear that there is no other difference between the groups in terms of treatment or care received, other than the treatment or intervention of interest?

Question 7: Were outcome assessors blind to treatment assignment?

Category: Internal validity

Domain: Bias related to assessment, detection and measurement of the outcome

Appraisal: Outcome level

Like question 4 and 5, those assessing the outcomes that are aware of participant allocation to either treatment or control, may treat participants differently than compared to those that remain unaware of participant allocation. Therefore, there is a risk that the measurement of the outcomes between groups may be distorted, and the results of the study may themselves be distorted. Blinding of outcomes assessors is used in order to minimize this risk. Reviewers should check the details reported in the article about the blinding of outcomes assessors with regards to treatment assignment. Is there any information in the article about outcomes assessors? Were those assessing the treatment's effects on outcomes unaware of the assignments of participants to the compared groups?

Question 8: Were outcomes measured in the same way for treatment groups?

Category: Internal validity

Domain: Bias related to assessment, detection and measurement of the outcome

Appraisal: Outcome level

If the outcome is not measured in the same way in the compared groups, there is a threat to the internal validity of a study. Any differences in outcome measurements may be due to the method of measurement employed between the two groups, and not due to the intervention/treatment of interest. Reviewers should check if the outcomes were measured in the same way. Same instrument or scale used? Same measurement timing? Same measurement procedures and instructions?

Question 9: Were outcomes measured in a reliable way?

Category: Internal validity

Domain: Bias related to assessment, detection and measurement of the outcome

Appraisal: Outcome level

Unreliability of outcome measurements is one threat that weakens the validity of inferences about the statistical relationship between the 'cause' and the 'effect' estimated in a study exploring causal effects. Unreliability of outcome measurements is one of the different plausible explanations for errors of statistical inference with regards to the existence and the magnitude of the effect determined by the treatment ('cause'). Reviewers should check the details about the reliability of the measurement used, such as the number of raters, training of raters, the intra-rater and the inter-raters reliability within the study (not as reported in external sources). This

question is about the reliability of the measurement performed in the study, it is not about the validity of the measurement instruments/scales used in the study. Finally, some outcomes may not rely on instruments or scales (e.g. death) and reliability of the measurements may need to be assessed in the context of the study being reviewed. [Note: Two other important threats that weaken the validity of inferences about the statistical relationship between the 'cause' and the 'effect' are low statistical power and the violation of the assumptions of statistical tests. These other two threats are explored within Question 12).]

Question 10: Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?

Category: Internal validity

Domain: Bias related to participant retention

Appraisal: Result level

For this question, follow up refers to the period from the moment of randomization to any point in which the groups are compared during the trial. This question asks if there is complete knowledge (measurements, observations etc.) for the entire duration of the trial for all randomly allocated participants. If there is incomplete follow up from all randomly allocated participants, this is known as post-assignment attrition. As RCTs are not perfect, there is almost always post-assignment attrition, and the focus of this question is on the appropriate exploration of post-assignment attrition. If differences do exist with regards to the post-assignment attrition between the compared groups of an RCT, then there is a threat to the internal validity of that study. This is because these differences may provide a plausible alternative explanation for the observed 'effect' even in the absence of the 'cause' (the treatment or intervention of interest). It is important to note that with regards post-assignment attrition, it is not enough to know the number of participants and the proportions of participants with incomplete data; the reasons for loss to follow up are essential in the analysis of risk of bias.

Reviewers should check if there were differences with regards to the loss to follow up between the compared groups. If follow up was incomplete (incomplete information on all participants), examine the reported details about the strategies used to address incomplete follow up. This can include descriptions of loss to follow up (absolute numbers; proportions; reasons for loss to follow up) and impact

analyses (the analyses of the impact of loss to follow up on results). Was there a description of the incomplete follow up including the number of participants and the specific reasons for loss to follow up? Even if follow up was incomplete, but balanced between groups, if the reasons for loss to follow up are different (e.g., side effects caused by the intervention of interest), these may impose a risk of bias if not appropriately explored in the analysis. If there are differences between groups with regards to the loss to follow up (numbers/proportions and reasons), was there an analysis of patterns of loss to follow up? If there are differences between the groups with regards to the loss to follow up, was there an analysis of the impact of the loss to follow up on the results? [Note: Question 10 is NOT about intention-to-treat (ITT) analysis; question 11 is about ITT analysis.]

Question 11: Were participants analysed in the groups to which they were randomized?

Category: Statistical conclusion validity

Appraisal: Result level

This question is about the intention-to-treat (ITT) analysis. There are different statistical analysis strategies available for the analysis of data from RCTs, such as intention-to-treat analysis (known also as intent to treat; abbreviated, ITT), per-protocol analysis, and as-treated analysis. In the ITT analysis the participants are analysed in the groups to which they were randomized. This means that regardless of whether participants received the intervention or control as assigned, were complaint with their planned assignment or participated for the entire study duration, they are still included in the analysis. The ITT analysis compares the outcomes for participants from the initial groups created by the initial random allocation of participants to those groups. Reviewers should check if an ITT analysis was reported; check the details of the ITT. Were participants analysed in the groups to which they were initially randomized, regardless of whether they participated in those groups, and regardless of whether they received the planned interventions? [Note: The ITT analysis is a type of statistical analysis recommended in the Consolidated Standards of Reporting Trials (CONSORT) statement on best practices in trials reporting, and it is considered a marker of good methodological quality of the analysis of results of a randomized trial. The ITT is estimating the effect of offering the intervention, that is, the effect of instructing the participants to use or

take the intervention; the ITT it is not estimating the effect of receiving the intervention of interest.]

Question 12: Was appropriate statistical analysis used?

Category: Statistical conclusion validity

Appraisal: Result level

Inappropriate statistical analysis may cause errors of statistical inference with regards to the existence and the magnitude of the effect determined by the treatment ('cause'). Low statistical power and the violation of the assumptions of statistical tests are two important threats that weaken the validity of inferences about the statistical relationship between the 'cause' and the 'effect'. Reviewers should check the following aspects: were the assumptions of the statistical tests were respected; if appropriate statistical power analysis was performed; if appropriate effect sizes were used; if appropriate statistical methods were used given the nature of the data and the objectives of statistical analysis (association between variables; prediction; survival analysis etc.).

Question 13: Was the trial design appropriate and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

Category: Statistical conclusion validity

Appraisal: Study level

The typical, parallel group RCT may not always be appropriate depending on the nature of the question being asked. Therefore, some additional RCT designs may have been employed that each come with their own additional considerations.
Crossover trials should only be conducted in people with a chronic, stable condition, where the intervention produces a short-term effect (i.e. relief in symptoms). Crossover trials should ensure there is an appropriate period of washout between treatments. This may also be considered under question 6.
Cluster RCTs randomize groups individuals or groups (e.g. communities, wards etc.) , forming 'clusters.' When we are assessing outcomes on an individual level in cluster trials, there are unit-of-analysis issues, as individuals within a cluster are correlated. This should be considered by the study authors when conducting analysis,

and ideally authors will report the intra-cluster correlation coefficient. This may also be considered under question 12.

Stepped wedge RCTs may be appropriate to establish when and how a beneficial intervention may be best implemented within a defined setting, or due to logistical, practical, or financial considerations in the roll out of a new treatment/intervention. Data analysis in these trials should be conducted appropriately, considering the effects of time. This may also be considered under question 12.

Appendix F – Required Sample Size

The sample size for the moderation analysis was calculated prior to recruitment using G*Power. The calculation was based on a linear multiple regression with a medium effect size of 0.15, an alpha value of 0.05, and a power value of 0.8. The analysis was done based on nine predictors in the model, this would account for the three terms for the moderation analysis and six potential covariates. 114 participants were required.

Appendix G – Ethical Approval

University of East Anglia
Norwich Research Park
Norwich. NR4 7TJ

Email: ethicsmonitor@uea.ac.uk
Web: www.uea.ac.uk

Study title: Exploring the associations between post-stroke consequences, psychological flexibility, and post stroke depression and anxiety

Application ID: ETH2324-1326

Dear Ellis,

Your application was considered on 22nd April 2024 by the FMH S-REC (Faculty of Medicine and Health Sciences Research Ethics Subcommittee).

The decision is: **approved**.

You are therefore able to start your project subject to any other necessary approvals being given.

If your study involves NHS staff and facilities, you will require Health Research Authority (HRA) governance approval before you can start this project (even though you did not require NHS-REC ethics approval). Please consult the HRA webpage about the application required, which is submitted through the IRAS system.

This approval will expire on **31st December 2025**.

Please note that your project is granted ethics approval only for the length of time identified above. Any extension to a project must obtain ethics approval by the FMH S-REC (Faculty of Medicine and Health Sciences Research Ethics Subcommittee) before continuing.

It is a requirement of this ethics approval that you should report any adverse events which occur during your project to the FMH S-REC (Faculty of Medicine and Health Sciences Research Ethics Subcommittee) as soon as possible. An adverse event is one which was not anticipated in the research design, and which could potentially cause risk or harm to the participants or the researcher, or which reveals potential risks in the treatment under evaluation. For research involving animals, it may be the unintended death of an animal after trapping or carrying out a procedure.

Any amendments to your submitted project in terms of design, sample, data collection, focus etc. should be notified to the FMH S-REC (Faculty of Medicine and Health Sciences Research Ethics Subcommittee) in advance to ensure ethical compliance. If the amendments are substantial a new application may be required.

Approval by the FMH S-REC (Faculty of Medicine and Health Sciences Research Ethics Subcommittee) should not be taken as evidence that your study is compliant with the UK General Data Protection Regulation (UK GDPR) and the Data Protection Act 2018. If you need guidance on how to make your study UK GDPR compliant, please contact the UEA Data Protection Officer (dataprotection@uea.ac.uk).

Please can you send your report once your project is completed to the FMH S-REC (fmh.ethics@uea.ac.uk).

I would like to wish you every success with your project.

On behalf of the FMH S-REC (Faculty of Medicine and Health Sciences Research Ethics Subcommittee)

Yours sincerely,

Dr Paul Linsley

Appendix H – Participant Information Sheet

University of East Anglia

Participant Information Sheet – Version 4 (22/04/24)

Thank you for considering to take part in this study. Before you decide to complete the study, it is important for you to understand why the research is being conducted and what participation will involve. Please take some time to read the following information carefully and raise any questions you may have with our researchers (Ellis Blyth: e.blyth@uea.ac.uk or Dr. Jinnie Ooi: jinnie.ooi@uea.ac.uk).

(1) What is this study about?

Anxiety and depression after stroke have been found to be linked with a number of common difficulties that occur as a result of a stroke (e.g. fatigue, changes in physical ability, changes in thinking ability). A talking therapy called Acceptance and Commitment therapy has recently been included in guidelines to support people after a stroke. Acceptance and Commitment therapy focuses on increasing our 'psychological flexibility' – this is the name given to a set of skills that help us to not get hooked on difficult thoughts and feelings, and to live a fulfilling life alongside them. This study will explore how psychological flexibility is linked with anxiety and depression after stroke and whether it changes the relationship between these mental health difficulties and other common experiences after stroke.

(2) Why have I been invited?

You have been invited to take part as a survivor of stroke.

To take part:

- You must be 18 years old or older,
- There must have been at least six months since your stroke,
- You must be able to speak English,
- You must be able to provide your own answers. If you need practical help to fill in the questionnaire, then this is encouraged.

You will not be able to take part if:

- Your stroke was a spinal stroke, a 'mini-stroke' (transient ischaemic attack), or a sub-arachnoid haemorrhage.

- You have experienced a brain injury prior to your stroke.

(3) What will the study involve for me?
You will be asked to complete a questionnaire with 6 parts. It will take no longer than 30 minutes to complete. You can stop and come back later by clicking “finish later” at the bottom of the web page and following the instructions.

This information is designed to provide you with information to help you decide if you wish to take part in the research or not. You are not required to take part if you do not want to.

If you decide to take part, you can withdraw from the study at any time prior to submitting your data, by exiting the questionnaire and your answers will not be recorded or included in the study.

(4) Are there any risks and/or disadvantages with participating in this study?
Completing a long questionnaire may leave you feeling tired or fatigued. Please take breaks when you feel it is necessary.

Answering questions about mood or the potential consequences of stroke may be difficult for some people. Most questions will be multiple choice and you will not be asked to describe any details regarding your mood or potential consequences of your stroke. Details about national support that is available for mental health or stroke are available at the end of the questionnaire for the United Kingdom, United States of America, and Australia.

(5) Are there any benefits associated with being in the study?
There is no direct personal benefit to completing this study. This study gives you the opportunity to be part of developing our understanding of anxiety and depression after stroke and how it may link with psychological flexibility.

(6) What will happen to information about me that is collected during the study?
Only non-identifiable information will be recorded, so you will be completely anonymous throughout. Once you have clicked “submit”, it will not be possible to delete your data. The information collected will be kept strictly confidential on a secure university storage system. After the study, data will be stored securely for a minimum 10 years within a secure university storage system, complying with the University of East Anglia Research Data Management Policy (2022). Your anonymous data may also be used in future research.

(7) Will I be told the results of the study?

The results of the study will be written up into a doctoral thesis in 2025, presented at stroke conferences and submitted to a relevant journal. A lay summary of the results will be shared with stroke organisations that have promoted the research.

(8) What if I would like further information, a complaint or concerns about the study?

If you require more information about this research study, please do contact me at e.blyth@uea.ac.uk.

If you are concerned about the way this study is being conducted or you wish to make a complaint to someone independent from the study, please contact Professor Sian Coker (Deputy Head of Department of Clinical Psychology and Psychological Therapies) via email at s.coker@uea.ac.uk.

(9) Who is running the study?

This research is being conducted by Ellis Blyth, Postgraduate Researcher in the Doctorate in Clinical Psychology Programme (ClinPsyD) at Norwich Medical School, UEA. The research is carried out under the supervision of Dr Jinnie Ooi and Dr Joshua Blake. The research has been reviewed by the University of East Anglia Faculty of Medicine and Health Sciences Research Ethics Committee.

Appendix I – Consent Form

Consent Form – Version 2 (18/01/24)

Please read the following statements carefully:

I confirm that I have read and understand the Participant Information Sheet and I have had the opportunity to ask any questions that I have about the study, and I am happy with the answers received.

I understand the purpose, procedure and any benefits or risks involved with the study.

I understand that no personal information or identifiable data will be collected during this research.

I agree that my data gathered in this study will be stored anonymously and securely and may be used for future research.

I understand that my participation is voluntary and that I am free to withdraw without giving a reason.

I understand that once I have submitted my data by clicking “submit”, I will no longer be able to withdraw from the study.

I understand that this research can be audited by the University of East Anglia or the regulatory authorities. I therefore give permission for these organisations to access my anonymous data.

I understand and agree with the statements above and I agree to take part in this study. YES / NO

Appendix J – Debrief Page

University of East Anglia

Debrief Page – Version 4 (22/04/24)

Dear participant,

Thank you for taking part in this study; your time and participation are very much appreciated. This page provides further information about the study and sources of support based in the UK, Australia and the USA. When you are ready, you can close this webpage.

What was the aim?

The aim of this study was to better understand how anxiety and depression after a stroke is linked to other symptoms of stroke such as fatigue, difficulties in thinking, and level of dependence in day-to-day life. This study also aimed to understand whether "psychological flexibility" changed these links.

Why is it important?

The current research priority for stroke is about the psychological impact of having a stroke. This includes ways to prevent anxiety and depression from developing, or ways to treat them. A talking therapy called Acceptance and Commitment Therapy looks to build psychological flexibility to help us live meaningfully alongside difficult thoughts, feelings, and situations. The findings of this study could inform future research investigating Acceptance and Commitment Therapy for use with stroke survivors.

What if I want to know more?

We understand that this topic and the questions answered may have been difficult for you. If you have felt emotionally impacted by the topics discussed

within the research or if you are interested in learning more, please explore the resources below.

The results will be written up into a doctoral thesis in 2025, presented at stroke conferences and submitted to a relevant journal. A lay summary of the results will be shared with stroke organisations that have promoted the research.

Should you wish to contact a member of the research team regarding this study, please feel free to contact Ellis Blyth (primary researcher: e.blyth@uea.ac.uk) or Dr Jinnie Ooi (primary supervisor: jinnie.ooi@uea.ac.uk). If you wish to contact someone independent from the study, please contact Professor Sian Coker (Deputy Head of Department of Clinical Psychology and Psychological Therapies: s.coker@uea.ac.uk).

Thank you again.

Sources of Support:

UK

Stroke Association

A UK charity that provides support, funds important research and campaigns so that people impacted by stroke can access the best quality care and support.

Stroke Helpline: 0303 3033 100
Website: https://www.stroke.org.uk

Different Strokes

A UK charity that is run by young stroke survivors, for young stroke survivors. They provide information, support, and advice for young stroke survivors.

Information Line: 0345 1307 172

Website: https://differentstrokes.co.uk/

Mental Health Services Through the NHS

The NHS provide a variety of services to support mental health which will vary based on location. If you feel that you would benefit from accessing a service your GP may be a good starting point. Alternatively, the website below provides more information on finding your local service.

Website: https://www.nhs.uk/nhs-services/mental-health-services/how-to-find-local-mental-health-services/

Crisis Support – UK

If you feel that you are in a crisis and need help now you can find your local NHS urgent mental health helpline using the following link: https://www.nhs.uk/service-search/mental-health/find-an-urgent-mental-health-helpline. Alternatively, call 999 for an ambulance or go to A&E. You can also access listening services below:

The Samaritans are available 24/7 to talk about anything that is upsetting you. Call 116 123 or email jo@samaritans.org.

National Suicide Prevention Helpline UK can be reached 6pm to midnight every day on 0800 689 5652.

Australia

Stroke Foundation

An Australian charity that works to improve treatment for stroke and provide support to people who have had a stroke and their families. They aim to improve life after stroke for survivors and advocate for initiatives to prevent, treat, and beat stroke.

Website: https://strokefoundation.org.au/

Stroke Recovery Association New South Wales

An Australian association that was set up to support individuals recovering from stroke, their families/carers, and the community. They have a number of

stroke recovery groups and online support to help survivors and carers throughout New South Wales.
Website: https://strokensw.org.au/

Mental Health Services

To access mental health services in your local area, you may be best seeing your General Practitioner (GP) first. In rural or remote areas, your general practice may be where your nearest mental health service is accessible.

MindSpot

MindSpot is a free telephone and online service to support people with anxiety, stress, low mood, or depression. You can access it using the website below or by calling 1800 61 44 34. Please note this is not an emergency or instant response service.
Website: https://www.mindspot.org.au/

Crisis Support – Australia

If you feel that you are in crisis and need help now, please call 000. You can also call Lifeline on 13 11 14 – available 24 hours a day, 7 days a week.

USA

American Stroke Association

This charity offers information and advice to support life after stroke for survivors, families, care givers, and professionals.
Website: https://www.stroke.org/en/

Mental Health America

An American non-profit that aims to promote mental health, well-being, and illness prevention. They provide advice on living mentally health and can provide information on how to find local mental health support which can be found using the link below.
Website: https://www.mhanational.org/im-looking-mental-health-help-myself

Crisis Support – America

If you feel that you are in a crisis please seek help. Call or text 988, or visit 988lifeline.org. You can also text MHA to 741741 to connect with a trained Crisis Counsellor from Crisis Text Line. Alternatively, call 911 or go to the nearest emergency room.

Appendix K – Data Cleaning and Outlier Identification

Responses were checked for the potential of bot involvement. Demographic questions that asked for age, time since stroke, and age at time of stroke were cross referenced. Survey response times were reviewed in cases where these demographic questions were not in agreement (n = 11). These response times were all appropriate in length (>7.5 minutes).

Fourteen participants were removed due to their last stroke occurring less than six months before the completion of the survey. Two additional participants were removed due to evidence of straight-lining in their responses towards the end of the survey battery, possibly as a result of fatigue.

With the exception of the GAD-7 there were no missing data regarding variables. Time since stroke was collected in different measures of time; these were converted into years to support analysis. Due to demographic information being collected as a free text response, some data was missing.

The data was analysed for outliers and high influence points using standardized and studentized residuals, Cook's Distance, Centred Leverage Values, and standardised difference in betas, to review the impact of data points in a variety of contexts. As these provide values based on impact regarding the regression model, calculations were applied to the data after grand mean centering to be representative of the data used for the final models. Only one data point exceeded a studentized residual of 3; outcomes did not differ when his point was excluded from analysis and so the data point was retained. The impact of stroke can vary greatly between individuals; therefore, a wide range in observations were expected. While cut off scores for other measures were met for some data points, they did not do so across measures, or meet less conservative cut off points, for example Cooks Distance > 1, to raise concern within the context of the population being sampled.

Assumptions for using a parametric model within the main analysis were assessed on the data without grand mean centering. The assumption of linearity was met between the outcome variables and individual predictors, including the moderator, in addition to the combination of predictors on the outcome variables.

Errors were deemed to be independent after reviewing scatterplots plotting standardised residuals and predicted values while P-P plots showed normal distribution of errors for each model. No multicollinearity was observed between predictors. Stronger correlations occur when exploring moderation due to the introduction of an interaction effect. Grand mean centering has been shown to reduce multicollinearity between interaction terms and the predictors that constitute them (Dalal & Zickar, 2012). There was evidence of heteroscedasticity present in some of the models; however, the analysis utilised heteroscedasticity-consistent standard errors using the Davidson-Mackinnon estimator to correct for this, as suggested by Hayes & Cai (2007). The sample was bootstrapped 5000 times for each analysis to produce more robust confidence intervals.

References

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Appendix L – Demographic Information Table

	N	%	M	SD
Country of Residence *n* =191				
United States of America	85	(44.5)		
United Kingdom	81	(42.4)		
Australia	8	(4.2)		
Bermuda	1	(0.5)		
Canada	6	(3.1)		
Croatia	1	(0.5)		
Ireland	2	(1.0)		
Malaysia	1	(0.5)		
Netherlands	1	(0.5)		
New Zealand	2	(1.0)		
Philippines	1	(0.5)		
Romania	1	(0.5)		
South Africa	1	(0.5)		
Nationality *n* = 170				
American	56	(32.9)		
Asian American	1	(0.6)		
Australian	7	(4.1)		
British	59	(34.7)		
British Indian	1	(0.6)		
Canadian	6	(3.5)		
Croatian	1	(0.6)		
Dutch	1	(0.6)		
English	17	(10.0)		
Filipino	1	(0.6)		
German	2	(1.2)		
Irish	4	(2.4)		
Italian	3	(1.8)		
Malaysian	1	(0.6)		
New Zealander	2	(1.2)		

	N	%	M	SD
Romanian	1	(0.6)		
Scottish	5	(2.9)		
South African	1	(0.6)		
Zimbabwean Australian	1	(0.6)		
Ethnicity *n* = 173				
White	159	(91.9)		
Black	3	(1.7)		
Asian	6	(3.5)		
Mixed or Multiple Ethnicity	1	(0.6)		
Other	4	(2.3)		
Gender *n* = 191				
Male	44	(23.0)		
Female	147	(77.0)		
Previous depression *n* = 191				
Yes	51	(26.7)		
No	140	(73.3)		
Age (Years) *n* = 190			48.03	(12.22)
Time Since Stroke (Years) *n* = 189			3.86	(3.86)