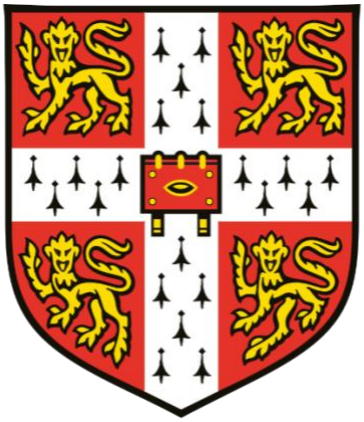
Apathy after stroke: clinical characteristics, association with functional outcome and effect on carer burden



Claudia Pallucca

Murray Edwards College

Department of Clinical Neurosciences
University of Cambridge

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Declaration

This thesis is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in the preface and specified in the text.

It is not substantially the same as any work that has already been submitted before for any degree or other qualification except as declared in the preface and specified in the text.

It does not exceed the prescribed word limit for the Clinical Medicine and Veterinary Medicine Degree Committee.

Summary

Apathy after stroke: clinical characteristics, association with functional outcome and effect on carer burden

Claudia Pallucca

Apathy is a multidimensional syndrome that frequently presents in stroke survivors and is characterised by a loss in motivation and initiative, reduced social interactions, and neutral emotionality. Apathy affects cognitive functioning, everyday activity including social life, and functional recovery. Despite the prevalence of apathy among the sequelae of stroke, an understanding of this symptom trajectory and its effect on patient and carer's quality of life needs to be clarified.

The research presented in this thesis mainly focuses on a prospective longitudinal study conducted in three acute stroke services in the East of England, UK. The main goal of the study was to evaluate the prevalence of *post*-stroke apathy and its association with outcome, mood, and cognition. Findings show that overall apathy tends to increase over one year after stroke and that different groups of patients present with different symptom trajectories. Moreover, the study results show that *post*-stroke apathy presents with specific patterns of impaired dimensions, which may vary depending on the measurement technique used, including method of scoring.

After analysing the relationship between apathy, disability, and quality of life, my findings suggest that depression, more than apathy, might play an important role in determining functional outcome and recovery. The investigation of neurobiological bases of apathy found an association with white matter pathology, reinforcing the idea that chronic ischaemia coupled with acute lesions might set up a cascade of events leading to apathy. A new study was then set up to investigate the effects of apathy on carers of patients with small vessel disease and found that apathy is associated with higher care burden and distress. The results of this study pave the way for targeted intervention approaches.

Overall, this thesis suggests that apathy is a symptom or syndrome presenting in about 20% of stroke patients and affecting patient and carer lives alike. A comprehensive characterisation of apathy holds clinical relevance and encourages the further development of new apathy treatments.

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I have personally collected the data in Chapter 8, part of the data in Chapter 3 to 7, designed and conducted the statistical and imaging analyses.

Dedication

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Abbreviations

AD	Alzheimer's Disease
AES	Apathy Evaluation Scale
BDI	Beck's Depression Inventory
BIC	Bayesian information criterion
BMET	Brief Memory and Executive Test
CADASIL	Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy
DAS	Dimensional Apathy Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DTI	Diffusion Tensor Imaging
FWE	Family-wise error
GDS	Geriatric Depression Scale
GM	Grey matter
HADS	Hospital Anxiety and Depression Scale
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
ICL	Integrated Classification Likelihood
IQR	Interquartile range
LCA	Latent Class Analysis
MCI	Mild Cognitive Impairment
MoCA	Montreal Cognitive Assessment
mRS	Modified Rankin Scale

MS	Multiple Sclerosis
NIHSS	National Institutes of Health Stroke Scale
NPI	Neuropsychiatric Inventory
PD	Parkinson's Disease
QOL	Quality of Life
ROI	Region of interest
rTMS	Repetitive Transcranial Magnetic Stimulation
SF-36	36-Item Short Form Health Survey
SVD	Small Vessel Disease
TOAST	Trial of ORG 10172 in Acute Stroke Treatment Classification
VBM	Voxel-based morphometry
VLSM	Voxel-based lesion symptom mapping
WM	White matter
WMH	White-matter hyperintensities
ZBI	Zarit Burden Interview

Chapter 1: Introduction to apathy

Definition and diagnosis of apathy

Apathy is a common and debilitating behavioural syndrome that affects patients in many conditions. The presence of this disabling condition has been extensively reported in Alzheimer's Disease (AD), Multiple Sclerosis (MS), Parkinson's Disease (PD), and specifically following stroke (Jorge *et al., 2010;* Nobis *et al., 2018;* Pagonabarraga *et al.,* 2015; Raimo *et al.,* 2020). Apathy has been described as a loss in motivation or impairment in goal-directed behaviour (Van Dalen *et al.,* 2013). It usually presents as loss of interest and initiative concerning everyday activity, reduced social interactions, and emotional responsivity (Van Dalen *et al.,* 2013). Apathy is a strong predictor of poor clinical and functional recovery, diminished quality of life, with preliminary research suggesting increased carer burden (Douven *et al.,* 2017; Van Dalen *et al.,* 2013).

Recently an International Consensus Group put in writing clinical criteria for diagnosing apathy in brain disorders. The group produced a document suggesting the Diagnostic Criteria of apathy (Robert *et al.,* 2018). Four criteria to diagnose apathy were indicated, which can be summarised as follows:

1. Criterion A implies a decrease in goal-directed behaviour, in behavioural, cognitive, emotional or social dimensions, as compared to a previous level of functioning. Such reduction can be reported either by the patients themselves or by others.
2. Criterion B implies the presence of impairment in at least 2 out of 3 dimensions, for a period of at least four weeks and for most of the time. The 3 dimensions are:

   - B1. Behaviour and Cognition: the patient shows a reduced level of activity at home or work or makes less effort in initiating or continuing tasks. The patient may also have more difficulties in making choices and have less interest in her/his own health and personal image, or in external events.

   - B2. Emotion: the patient may show less spontaneous emotions or verbal or physical reactions displaying emotion. Similarly, less empathy may be exhibited towards others.

- B3. Social interaction: the patient shows a decrease in social interactions, prefers to stay at home and engages less frequently in conversations and social activities.

3. Criterion C specifies that the symptoms just described cause significant impairment in different aspects of life, such as at the personal, social, and/or occupational level.
4. Criterion D: apathy must be distinguished by transient states related to other causes (e.g. drug, medication) and cannot be exclusively attributable to physical or motor disabilities or to a diminished level of consciousness.

The International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) offers a formal classification of apathy, reporting it under the code 45.3, together with demoralisation (World Health Organization, 2016).

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), on the other hand, does not consider apathy as a distinct clinical manifestation or syndrome, thus no diagnostic criteria are reported to identify this syndrome (American Psychiatric Association, 2013). In this framework apathy is presented as a behavioural disturbance that can occur in mild and major neurocognitive disorders or as a symptom of frontotemporal neurocognitive disorder or as a personality change in other medical-related conditions (American Psychiatric Association, 2013). According to the DSM-5, apathy is defined as a reduction in motivation, goal-directed behaviour and emotional responses.

In addition to diagnostic criteria, various tests and questionnaires have been developed to gather quantitative information on the severity and prevalence of apathetic symptoms. These tools were created in order to facilitate clinical assessment of patients and obtain an objective and comparable measure of apathy.

One of the first instruments to be developed specifically to measure apathy is the Apathy Evaluation Scale (AES) (Marin *et al.,* 1991). The AES aims at measuring behavioural, cognitive, and emotional aspects of apathy, without making a distinction between these dimensions (Marin *et al.,* 1991). The scale is comprised of three forms, one for each rater source (clinician, informant, and self-rated). Each form contains 18 items that should be rated on a 4-point Likert-

type scale, from 1 (*Not at all*) to 4 (*A lot*). The rating should be based on the previous 4 weeks and higher scores indicate greater apathy.

Items were developed through consultation with expert clinicians and through the authors' observations and conceptualizations of apathetic patients. In particular, the scale was developed based on a definition of apathy formulated from literature review and clinical experience. The test was validated on a cohort of 123 subjects, aged 53-85: the sample included participants with a diagnosis of probable Alzheimer's disease or major depression or healthy elderly controls (Marin *et al.,* 1991). Internal consistency reliability, measured as coefficient α, was 0.86-0.94 for the different raters. Test-retest reliability (mean test-retest interval: 25.4 days) varied from 0.76 to 0.94. lntraclass correlation coefficient (ICC) for interrater reliability was 0.94 (Marin *et al.,* 1991).

The AES proved to have good psychometric properties, also when employed in different clinical populations (Gallais *et al.,* 2018; Marin *et al.,* 1991; Umucu *et al.,* 2019). Despite a formal validation of the test in stroke population has not been carried out to date, a study found that the AES was able to discriminate apathy and depression in a sample of patients with diagnoses of stroke, probable Alzheimer's disease, major depression or healthy elderly controls (Marin *et al.,* 1993).

Many studies focussed on the comparison between self-rated and informant-rated versions of the test. Njomboro and Deb, for instance, reported that brain damaged patients evaluated their apathy symptoms significantly lower than their informants (Njomboro and Deb, 2012). Similarly, other groups assessed this phenomenon by measuring interrater agreement between patients and their close others, finding that this was heavily affected by the cognitive status of the patient (Chatterjee *et al.,* 2005). Such findings may reflect the issue of awareness of apathy: indeed, patients may not be fully aware of the behavioural and emotional changes related to apathy that instead appear more clearly to others, therefore rating their apathetic symptoms significantly lower than their informants (Mehren *et al.,* 2018). These findings in literature seem to further emphasize the importance of consulting different sources of information when diagnosing and measuring apathy in patients. Similar analyses and studies appear to be missing from the stroke literature.

In 2014 Radakovic and Abrahams developed a new tool to assess apathy, the Dimensional Apathy Scale (DAS) (Radakovic and Abrahams, 2014). Reprising Levy and Dubois' theory of a multidimensional approach to apathy, they developed an instrument measuring different dimensions of apathy (Levy and Dubois, 2006). In particular, the DAS is composed of 24 items, with 8 items assessing each subscale (Executive, Emotional, and Behavioural/Initiation). The questionnaire was built so as to control for physical impairment, with items specifically avoiding direct reference to motor actions: therefore, the scale appears particularly suitable for patients with motor disabilities (Radakovic and Abrahams, 2014).

Items can be answered on a 4-point Likert scale (*Hardly Ever (1), Occasionally (2), Often (3), Almost Always (4)*), based on the frequency of occurrence in the last month. Similarly to AES, an informant/carer version of DAS was created, using the same items of the self-rated version. The DAS items were derived by an initial review of published English apathy scales based on Levy and Dubois' apathy subtypes (Levy and Dubois, 2006). Following the review, new items were designed following a structured procedure. The scale was then validated on 311 volunteers (217 females and 94 males), recruited from various volunteer panels, including University groups. Internal consistency reliability for the 24-item scale was established using Cronbach's standardized α. Between items α value was 0.798. The item-subscale total correlations were found to be moderate for each subscale (Radakovic and Abrahams, 2014).

The DAS proved to be a reliable and valid apathy measurement, in a diverse cohort of clinical populations, including those with motor impairment as their predominant condition. A study from 2020 found that DAS showed high consistency and good validity in a cohort of MS patients (Raimo *et al.*, 2020). A factor analysis further confirmed the three-factor structure of this test (Raimo *et al.*, 2020). Similar results were found in PD and Amyotrophic Lateral Sclerosis patients, with authors trying to outline what apathy dimensions are specifically affected in these groups (Radakovic *et al.,* 2018; Santangelo *et al.*, 2017). Radakovic and colleagues also assessed and verified reliability and validity of the test in AD patients (Radakovic *et al.,* 2017) and it was also found to have good consistency and validity in stroke patients (Myhre *et al.*, 2022). In particular, a group of 53 stroke patients and 71 healthy controls completed online measures of apathy (DAS and AES), depression, and anxiety. The DAS showed high internal consistency (α

= 0.84) and convergent validity with AES, considered the current gold standard unidimensional assessment for apathy (Myhre *et al.,* 2022).

Another measure of apathy which has been used by various authors is contained in the Geriatric Depression Scale (GDS), namely the Apathy subscale (Adams *et al.,* 2004). The GDS is a widely used clinical tool to assess depressive symptoms in elderly patients (Yesavage *et al.*, 1982). However, the 6-item subscale identified by Adams and colleagues through means of a confirmatory factor analysis allows the identification of apathetic symptoms (Adams *et al.,* 2004). In particular items contributing to the subscale are: 'prefer to stay at home', 'avoid social gatherings', 'dropped activities and interests', 'find life very exciting', 'hard to start new projects' and 'full of energy'. The structure of this subscale has been confirmed by further analysis and studies of small vessel disease (Hollocks *et al.,* 2015).

Diagnosing apathy might be complicated by the presence of other neuropsychiatric symptoms, especially depression. The shared symptoms and similar behavioural presentation with depression may lead to a misdiagnosis or delayed diagnosis and delayed treatment of apathy symptoms (Hama *et al.,* 2011). Correctly identifying and distinguishing apathetic and depressive symptoms is crucial for a timely and accurate diagnosis. Apathy and depression, in fact, share some characteristic aspects, including diminished interest in activities, fatigue, loss of energy and pleasure, physical/mental slowing (Tay *et al.,* 2021). Despite these commonalities, however, patients with only apathy usually present with a lack of emotional distress and general 'neutral' emotional expression while depression is characterised mainly by negative emotionality (including low mood, sadness, feeling of guilt and worthlessness) (Marin, 1990). Moreover, while depressed patients may actively avoid socializing and engaging in treatment interventions, apathetic patients appear passive and indifferent to these attempts (Marin, 1990). Lastly, when compared to depression, *post*-stroke apathy appears to have distinct prevalence rates, trajectories, and effects on functional outcomes (Caeiro *et al.,* 2013; Hama *et al.,* 2007; Matsuzaki *et al.,* 2015; Withall *et al.,* 2011).

Apathy in stroke

Apathy is one of the most frequent neuropsychiatric symptoms after stroke, with prevalence rates estimated between 20% and 40% in the first months after stroke (Hackett *et al.,* 2014; Jorge *et al.,* 2010; Van Dalen *et al.,* 2013). Apathy after stroke usually presents as a syndrome of decreased goal-directed behaviour and emotional response (Van Dalen *et al.,* 2013). Patients usually show loss of motivation and interest, and a reduction in interactions with the environment and social life (Van Dalen *et al.,* 2013).

Post-stroke apathy appears to be associated to worse functional recovery, general health and quality of life (Jorge *et al.,* 2010). In particular, apathy may result in a decreased engagement in rehabilitation programs: this, in turn, may negatively affect the course of physical and psychological rehabilitation, by nullifying or delaying their effect (Hama *et al.,* 2011). Understanding stroke related apathy is aided by previous research in which the neurobiological bases of apathy have been investigated in various conditions and attempts have been made to link symptoms to specific lesions or deficits. Levy and Dubois, for instance, proposed that apathy is comprised of three symptoms categories ('emotional affective', 'cognitive' and 'auto-activation'), each attributable to a specific and distinct focal damage to brain regions in the prefrontal cortex and basal ganglia (Levy and Dubois, 2006). Such areas, in fact, are traditionally believed to be core components of the goal-directed behaviour system (Levy and Dubois, 2006).

Some findings questioned the assumptions made by this framework, also related to stroke. For instance, reports of the trajectory of apathy symptoms show contrasting patterns, with some showing patients who are asymptomatic in the acute phase but develop apathy one year after stroke, and patients who have symptoms in the acute phase but later recover (Caeiro *et al.*, 2013; Withall *et al.*, 2011). Such findings cannot be only accounted for by a direct link between lesion location and symptoms.

A new approach to the neurobiological causes of apathy uses graph theory and the hypothesis that lesions to brain networks supporting goal-directed behaviour may actually be responsible for apathy development. According to this approach, damage to specific brain networks would produce a cascade of events that would eventually lead to apathy symptoms (Tay *et al.,* 2020a). Using graph theory and applying it to brain pathology, when considering apathy in

cerebrovascular disease, Tay and colleagues hypothesised that apathy following stroke might be the result of two different events. Apathy may develop following a lesion occurring focally to a goal-directed behaviour related central node, that is a node with a high number of connections to other nodes. These central nodes would correspond to brain areas previously found to be associated with apathy in literature (such as the anterior cingulate cortex, medial orbito-frontal cortex, ventral striatum, medial thalamus and ventral tegmental area). Damage to these central areas through focal ischaemic or haemorrhagic stroke would produce apathy, following along the lines of the traditional lesion-deficit models (Tay *et al.,* 2020a). Alternatively, a lesion to a peripheral node may result in functional changes and secondary events, such as diaschisis or transneuronal degeneration (Tay *et al.,* 2020a). Diaschisis refers to a functional deficit in a region that is connected to a focally damaged area, which in turn causes a reduction or interruption in the connectivity pattern (Carrera and Tononi, 2014). Transneuronal degeneration, on the other hand, is a process by which damage to distant nodes propagates through structural or functional connections creating secondary morphological damage. Both instances may eventually result in apathy (Tay *et al.,* 2020a).

Apathy appears to be a common symptom not only following ischaemic or haemorrhagic stroke, but also in small vessel disease (SVD) (Tay *et al.,* 2019). Cerebral SVD refers to various forms of pathologies affecting the small vessels of the brain, such as small arteries, arterioles and venules (Pantoni, 2010). SVD includes a group of heterogenous pathological processes that usually manifest radiologically as lacunes, white-matter hyperintensities (WMH), or microbleeds and that may result in cognitive impairment of varying degree (Markus and de Leeuw, 2023). Most SVD is related to ageing processes and vascular risk factors such as hypertension, however a small percentage of cases are caused by inherited disorders such as Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) (Markus and de Leeuw, 2023).

According to some accounts, apathy in SVD may be brought about by white matter damage. Some studies, in fact, found that apathy is associated to widespread reduction in white matter integrity, especially in limbic association tracts such as the anterior cingulum and corpus callosum (Hollocks *et al.,* 2015). Similarly, Tay and colleagues found that apathy is associated with white matter tract disconnection in SVD and that global white matter network efficiency has

a mediating role in the relationship between WMH volumes and apathy (Tay *et al.,* 2019). Taken together these results seem to suggest that WMH, disruption of neural networks and apathy may be linked together. Apathy in SVD may therefore be the consequence of a cascade of events, including chronic ischaemia due to SVD, progressive neurodegeneration, cortical thinning, and acute infarcts (Tay *et al.,* 2020a).

Taking into consideration these findings, it would appear that certain types of stroke might be specifically associated to apathy symptoms through a variety of different mechanisms. However, questions regarding specific brain networks and regions involved in the apathy syndrome still remain unanswered and the novel models regarding apathy networks need to be further validated.

Interventions for Apathy

Although apathy has been extensively described in different disease pathologies, the best approach to treatment or rehabilitation remains unclear and no gold standard has been established yet (Manera *et al.,* 2020). Several possible treatments have been considered, including pharmacological treatments, magnetic stimulation, and behavioural interventions.

There have been various approaches with different pharmacological treatments. For instance, two studies reported on clinical trials using nefiracetam, a nootropic agent which has been used in animal studies to enhance aminergic, glutaminergic, and cholinergic neurotransmission (Robinson *et al.,* 2009). However, while the first study found an improvement in apathy scores as compared to placebo, the second study showed no significant differences between the treatment and the control group (Robinson *et al.,* 2009; Starkstein *et al.,* 2016).

Other studies attempted to use acetylcholinesterase inhibitors to target the cholinergic system, since it has been observed that apathy might result from a decrease in cholinergic innervation (Cummings *et al.,* 1996). Acetylcholinesterase inhibitors have been previously reported to reduce apathy levels in dementia patients (Kaufer *et al.,* 1999). Whyte and colleagues, for instance, conducted a trial on cognitively impaired stroke patients with galantamine and donepezil, both acetylcholinesterase inhibitors, but found no significant improvement in apathy levels (Whyte *et al.,* 2008).

Another attempt at reducing apathy symptoms has been made using anti-depressants, in particular selective serotonin reuptake inhibitors. Mikami and colleagues found that stroke patients were less likely to develop apathy symptoms if given Escitalopram, as compared to placebo (Mikami *et al.,* 2013). According to the authors, antidepressants would be related to neurogenesis in several brain regions and this might contribute to preserving motivation, a key aspect in the apathy syndrome (Mikami *et al.,* 2013). A recent study however found that fluoxetine improves depression but not apathy after stroke and that it would be ineffective in preventing *post*-stroke apathy (Tay *et al.,* 2023).

Pharmacological therapies, despite targeting different neurotransmitter systems, appear to have limited efficacy in the management of apathetic symptoms and results from various studies have yet to yield consistent results and this area of research needs further development. A different approach to apathy treatment is represented by the employment of repetitive transcranial magnetic stimulation (rTMS). rTMS is a non-invasive method whereby neuronal activity changes are induced by applying a wire coil to the scalp and generating a magnetic field. These excitability changes can last beyond the stimulation period and are used as a treatment for several neuropsychiatric conditions, including apathy and depression (Klomjai *et al.,* 2015; Padala *et al.,* 2020). Mitaki and colleagues, for instance, report the case of a stroke patient whose apathy symptoms improved after 2 weeks of rTMS training, thanks to an amelioration of interhemispheric connections (Mitaki *et al.,* 2016). Another study with a larger sample size also showed a significant improvement in Apathy Scale scores as compared to the sham stimulation group (Sasaki *et al.,* 2017). This approach seems to yield promising results, although the small sample sizes in literature prevents drawing definitive conclusions about the efficacy of this intervention.

Psychosocial interventions may hold promise as an effective intervention to reduce apathy levels in various patients populations. For instance, Butterfield and colleagues developed a specific protocol to target apathy in Parkinson's Disease patients consisting of six weekly sessions delivered by telephone where participants were invited to select and work on the completion of several goals (Butterfield *et al.,* 2017). Similarly, cognitive rehabilitation approaches in stroke patients mainly focused on strategy training or problem-solving therapy (Mikami *et al.,* 2013; Skidmore *et al.,* 2015). Both interventions proved effective in reducing apathy levels and

preventing the onset of new symptoms. It should be noted that the variety of techniques and apathy measurements used, as well as the small sample sizes may reduce the generalizability of results reported in these studies (Manera *et al.,* 2020).

A novel approach to apathy rehabilitation may be represented by technological devices employed to stimulate cognitive functions and ultimately improve levels of apathy. This approach appears to be of interest especially because of ecological validity and the possibility to create tailored interventions (Manera *et al.,* 2020). Manera and colleagues, for instance, tried to implement a cooking themed video game with Dementia and Mild Cognitive Impairment patients, including a subgroup of patients diagnosed with apathy (Manera *et al.,* 2015). In particular the game, installed on a tablet, required participants to plan and complete certain tasks in four different possible scenarios. The goal of the game was to specifically target executive functions, besides attention and object recognition. The apathetic group of patients reported interest and motivation in completing the training, although no results on the efficacy of the game on apathy rehabilitation were available in this study. New and specific randomized controlled trials should be implemented to test the effectiveness of technology-based apathy interventions and the duration of results.

When thinking about apathy rehabilitation it is worth noting that this syndrome may actually have a similar impact on the psychological wellbeing of carers and patients, as shown by research in other diseases (de Vugt *et al.,* 2006; Feast *et al.,* 2016). Several studies involving patients with dementia found that carers report high distress scores for apathy and that apathy was especially associated with worsening of the relationship between patient and carer (de Vugt *et al.,* 2006; de Vugt *et al.,* 2003). Similarly, studies conducted with Parkinson's disease patients and their carers showed that carer distress is higher for those neuropsychiatric symptoms that are reported to happen more frequently, such as apathy (Aarsland *et al.,* 2007). It is also well known that an increased carer burden leads to poorer Quality of Life (QOL) for the carer, which eventually results in a reduced ability to provide optimal care and in a negative outcome for both parties (Hiseman *et al.,* 2017). Research in cerebrovascular diseases is still lacking in this regard and the relationship between *post*-stroke apathy, carer strain and QOL has yet to be understood. A greater understanding of the impact of apathy on carers wellbeing and QOL may also help the development of appropriate patients rehabilitation programs or carer interventions.

Purposes of thesis

Apathy is a common and debilitating syndrome affecting stroke survivors and symptoms may affect various aspects of patients' life, including functional recovery and quality of life. Despite apathy being so frequent after stroke, some aspects of the syndrome remain unclear and a better understanding and characterisation of apathy presentation is needed to provide finer interventions and support.

In this thesis, I assess these questions:

1) What is the prevalence of *post*-stroke apathy and how do symptoms evolve over one year?
2) Are specific dimensions of apathy affected in stroke patients?
3) How is apathy associated with quality of life and disability following stroke?
4) What is the relationship between apathy, depression, and cognition in stroke?
5) Can lesion location and burden explain apathy symptoms?
6) Does damage to goal-directed behaviour networks cause apathy?
7) Does apathy impact carer burden and quality of life in people with small vessel disease and their carers?

This work primarily focuses on answering these questions in the context of the Apathy and Outcome after Stroke Study. The framework of this study will be described first in Chapter 2.

In Chapter 3, the prevalence of apathy over one year after stroke will be investigated, as well as a finer analysis of longitudinal trajectories of symptoms.

Chapter 4 focuses on the dimensions of apathy affected in stroke and the different presentation of symptoms in a cohort of stroke survivors.

The relationship of apathy with cognition, quality of life and disability will be explored in Chapter 5. Here, the role of depression in the context of apathy will be also taken into consideration.

In Chapter 6, the association of apathy with acute infarct and damage to white matter networks will be investigated by means of neuroimaging analysis. An extensive investigation will be conducted to clarify the role of lesion burden and location.
Chapter 7 briefly touches on symptoms awareness in apathy patients. Here, apathy scores rated by patients and their informants are compared to obtain an estimate of symptoms awareness.

The extent of apathy effect on carers will be explored in Chapter 8. Here, a new study focussing on small vessel disease patients will be described and association of apathy with carer burden and quality of life investigated.

Finally, a summary and interpretation of findings will be provided in Chapter 9. Further questions that have not been answered and future directions will be discussed here.

Chapter 2: Apathy and Outcome after Stroke Study

In the previous chapter, certain unanswered questions were highlighted, such as the longitudinal trajectory of apathy following stroke and the association of this with stroke outcome. In order to try and address these questions, a study was set up that focussed on apathy symptoms, longitudinal changes, effects on functional outcome, and brain imaging features.
In this chapter, the Apathy and Outcome after Stroke Study is described: the study constituted the basis of the main analysis described in the following chapters.

2.1 Study design

The Apathy and Outcome after Stroke Study (full title "Apathy and outcome of the stroke and its relationship to cerebral small vessel disease") is a prospective longitudinal study conducted in three acute stroke services in the East of England, UK.

Two hundred ischaemic stroke patients were recruited if they met the following inclusion criteria: mild to moderate radiologically confirmed ischaemic stroke (1-4 modified Rankin Scale, mRS); age ≥ 18 years; time window since stroke onset < 2 weeks; able to give informed consent; sufficiently fluent in English to allow cognitive testing. Participants were excluded in case of: aphasia of a severity that precluded consent or administration of cognitive tests; pre-existing clinical diagnosis of dementia; comorbidity likely to limit life expectancy to < 1 year; other major central nervous system or psychiatric disorder (past history of depression or anxiety permitted); MRI contraindication; pre-stroke Rankin score ≥ 3; previous non-lacunar stroke (previous lacunar infarcts ≤ 1.5 cm diameter allowed). Medical history was reviewed to exclude participants with pre-existing diagnosis of dementia. Participants with a pre-stroke Rankin score of 3 or greater were excluded as patients with less severe stroke could guarantee better adherence to the study multi-assessment longitudinal procedure.

Patients were identified from those admitted as inpatients with acute strokes and screened. In cases where a carer/partner was available, and with the patient's consent, the carer's consent was also sought to take part in the study.

Participants underwent an assessment at four time-points: baseline, 30 days, 6 months, and 12 months after stroke. Recruitment started in February 2017 and ended in November 2020, with the latest 12-month follow-up performed in November 2021. Recruitment and follow-ups were partly performed during the COVID-19 pandemic and related lockdowns.

The Study was approved by the East of England – Cambridge Central Research Ethics Committee (REC reference: 16/EE/0333) and written informed consent was obtained from all patients and informants. Copies of approval letters from the Research Ethics Committee and HRA can be found in an Appendix at the end of this thesis. The Appendix also contains copies of the Participant Information Sheet and Informed Consent Form: these were approved for this study by the Research Ethics Committee.

2.2 Measures

Table 1 summarises the measures and data collected at each time point. At baseline, information regarding demographics, risk factors, medical history, current medication, and details of the presenting stroke were assessed. Stroke severity was measured with the National Institutes of Health Stroke Scale (NIHSS) (Lyden *et al.*, 1994) and stroke subtype was identified based on the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification system (Adams *et al.,* 1993). This classification identifies five major subtypes: large artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology (Adams *et al.,* 1993). All stroke subtyping was performed by a neurologist with review of original imaging. Changes in medication and medical history were updated at each subsequent assessment.

2.2.1 Cognitive tests

Cognition was assessed with the Montreal Cognitive Assessment (MoCA) (Nasreddine *et al.*, 2005) and the Brief Memory and Executive Test (BMET) (Brookes *et al.*, 2012). The MoCA is a test of global cognition and appears to be more sensitive in assessing cognitive impairment in stroke patients than a main alternative, namely the Mini Mental State Examination (Dong *et al.*, 2010). The total possible score on this test is 30. The BMET is a screening test specifically developed to assess cognitive impairment in small vessel disease and includes tests of memory

(immediate and delayed recall), space and time orientation, executive functions and processing speed. The eight subtests provide raw scores that can be used to determine the overall degree of cognitive impairment by converting these into age-normed scaled scores. A total score (0-16) can then be obtained.

Table 1. Measures collected at each time point

	Baseline	30 days	6 months	12 months
Demographics, medical history, stroke details	X			
Montreal Cognitive Assessment Test	X			X
Brief Memory and Executive Test	X			X
Apathy Evaluation Scale	X	X	X	X
Dimensional Apathy Scale	X	X	X	X
Geriatric Depression Scale	X	X	X	X
Modified Rankin Scale	X	X	X	X
36-Short Form Survey Instrument				X
Clinical MRI scan	X			

2.2.2 Apathy and mood measures

Apathy was measured at each time point with the Apathy Evaluation Scale (AES) (Marin *et al.*, 1991) and the Dimensional Apathy Scale (DAS) (Radakovic and Abrahams, 2014). The choice of using these questionnaires to assess apathy, instead of the diagnostic criteria previously described, was guided by the fact that they are routinely employed tools in the field: hence, results from this study might be more easily compared with others. Moreover, both AES and DAS scales allowed the use of validated cut-offs to distinguish apathetic from non-apathetic patients; this will allow future studies to compare apathy prevalence among studies employing the same tests.

The AES is a measure of behavioural, cognitive, and emotional aspects of apathy. It contains 18 items that are rated on a 4-point Likert-type scale, based on the previous 4 weeks. Identical versions of this test exist for patient (self-rated version) and informant (informant-rated version).

Scores range from 18 to 72. A cut-off of 38 and 40 are used to identify apathetic patients respectively for self-rated and informant-rated versions of the test (Marin *et al.*, 1991). While the AES is a widely used test and allows comparisons of our results with other data in the field, it measures apathy as a single construct. On the other hand, the DAS assesses different dimensions of apathy and was included in this study to account for different presentations of apathy.

The DAS is an instrument measuring different dimensions of apathy: it is composed of 24 items, with 8 items assessing each identified dimension (Executive, Emotional, and Behavioural/Initiation). The questionnaire was built so as to control for physical impairment, with items specifically avoiding direct reference to motor actions, therefore being particularly suitable for patients with motor disabilities (Radakovic and Abrahams, 2014). Items are answered on a 4-point Likert scale, based on the frequency of occurrence in the last month. The score range is 0-72. Higher scores on the test indicate greater apathy and a cut-off of 39 is used to identify apathy in stroke (Myhre *et al.*, 2022). Specific cut-offs for apathy in stroke patients were introduced by Myhre and colleagues (2022). In particular, a cut-off of 39 is used for the total score, 14 for the Executive dimension, 15 for the Emotional dimension, and 16 for the Behavioural/Initiation dimension. An informant version of DAS exists, with items identical to the self-rated version, but with questions adapted for the informant evaluating the patient.

Depression was measured at each time point with the Geriatric Depression Scale (GDS) (Yesavage *et al.*, 1982), a 30-item self-rated scale assessing depression in elderly individuals. Scores range from 0 to 30, with higher scores indicating increasing levels of depression; specifically, scores of 0-9 are considered normal, 10-19 indicate mild depression, and 20-30 indicate severe depression (Yesavage *et al.*, 1982). Studies identified two subscales respectively identifying depression and apathy and composed of 24 and 6 items each (Adams *et al.*, 2004). The subscales have been shown to differentiate depression and apathy in SVD, hence validating the scale in this population (Hollocks *et al.,* 2015). In the current study, the 24-item depression subscale (from here onwards described as GDS-24) was used to quantify depression symptoms.

2.2.3 Outcome measures

Measures of outcome included the Modified Rankin Scale (mRS) and the 36-Item Short Form Health Survey (SF-36). The Modified Rankin Scale is an instrument commonly employed in stroke survivors to measure the degree of disability or dependence in the daily activities (Farrell *et al.*, 1991). The scale score ranges from 0 to 6 where 0 indicates no disability or symptoms and 6 means the individual is dead. At baseline pre-stroke disability was assessed and scored.
The SF-36 is a self-report measure of health and quality of life, investigating physical health, social functioning, and mental health (Ware and Sherbourne, 1992). Each section of the test results in a score ranging from 0 – more disability, to 100 – excellent health. Mental Component Summary (MCS) and Physical Component Summary (PCS) are aggregating scores of the eight subscales of the test. MCS and PCS are calculated by first obtaining z-scores from the subscales, multiplying these by the factor score of each summary score, and finally calculating T-scores (Taft *et al.*, 2001). The test has been validated for stroke patients and proved to be a valid and comprehensive measure of quality of life (Anderson *et al.*, 1996).

2.2.4 Brain MRI

An MRI scan of the brain was performed at baseline (2.1±2.9 days after stroke) as part of the clinical standard routine. T1, T2, T2*, T2-FLAIR, and DWI sequences were obtained. Scans were performed on a variety of scanners with different sequences. Resolution ranged from 0.94x0.94x4.40mm to 1.20x1.20x6.50mm for DWI images and from 0.47x0.47x5.20mm to 0.75x0.75x5.20mm for T2-FLAIR images. Raw images were converted to NIfTI format.

T1, DWI, and T2-FLAIR images were stripped of skull. Infarct volume and white matter hyperintensity (WMH) volume were calculated with a semi-automatic drawing of lesions respectively on DWI images and T2-FLAIR images. Volumes were then transformed to z-scores to avoid scaling issues. Brain tissue volume, normalised for subject head size, was estimated with SIENAX (Smith *et al.*, 2002), part of FSL (Smith *et al.*, 2004), from T1 images. Tissue-type segmentation with partial volume estimation was carried out in order to calculate total volume of brain tissue (including separate estimates of volumes of grey matter, white matter, and ventricular CSF). Segmentations were visually checked and manually corrected where needed.

2.3 Statistical analysis

Only participants who completed apathy measures were included in each analysis.

Missing data due to single assessment refusal were imputed via multiple-imputation using chained equations, unless otherwise specified (van Buuren *et al.*, 2011). The number of datasets was generated and analysed in combination using Rubin's rules (Rubin, 1987). Analyses were considered significant when $p \leq 0.05$. All analysis was performed using R 4.2.3 (R Core Team, 2023).

2.4 Study sample

The sample size for this study was calculated based on the data from a study of 76 stroke patients comparing outcome in patients with and without apathy (Caeiro *et al.*, 2013). The study was not large enough to show a significant difference in outcome based on mRS. Based on these results, and using the same statistical approach (chi-squared), achieving a power of 0.9 required a total sample size of 122. To provide additional power for analyses taking into account covariates, the proposed sample size of the study was 200 patients.

Figure 1 shows the total number of participants and that of participants assessed at each time point. 200 participants were recruited at baseline: of these, 12 withdrew from the study and 7 passed away. Some participants did not complete every assessment, either because they were lost to follow-up or because they refused the assessment. Unless participants decided to withdraw from the study, they were contacted again at the next assessment, at which point they could complete the assessment, refuse it, or withdraw.

Where possible informants were included in the study and assessed at the same time points. In total 117 informants were recruited. Of these 112 completed the assessment at baseline, 92 at 30 days, 95 at 6 months, and 89 at 12 months.

Baseline characteristics of the study sample were analysed and are reported in Table 2. Table 3 specifies the cohort characteristics based on the stroke subtype.

Participants who withdrew from the study for causes other than death (n=12) showed no differences in apathy scores at baseline (p=0.756), depression (p=0.990), cognition (p=0.066), disability (p=0.525), NIHSS (p=0.088), acute infarct volume (p=0.283), but had higher WMH burden (p=0.013). A binomial logistic regression showed baseline characteristics did not predict drop-out (p=0.671).

Figure 1. Participants recruitment

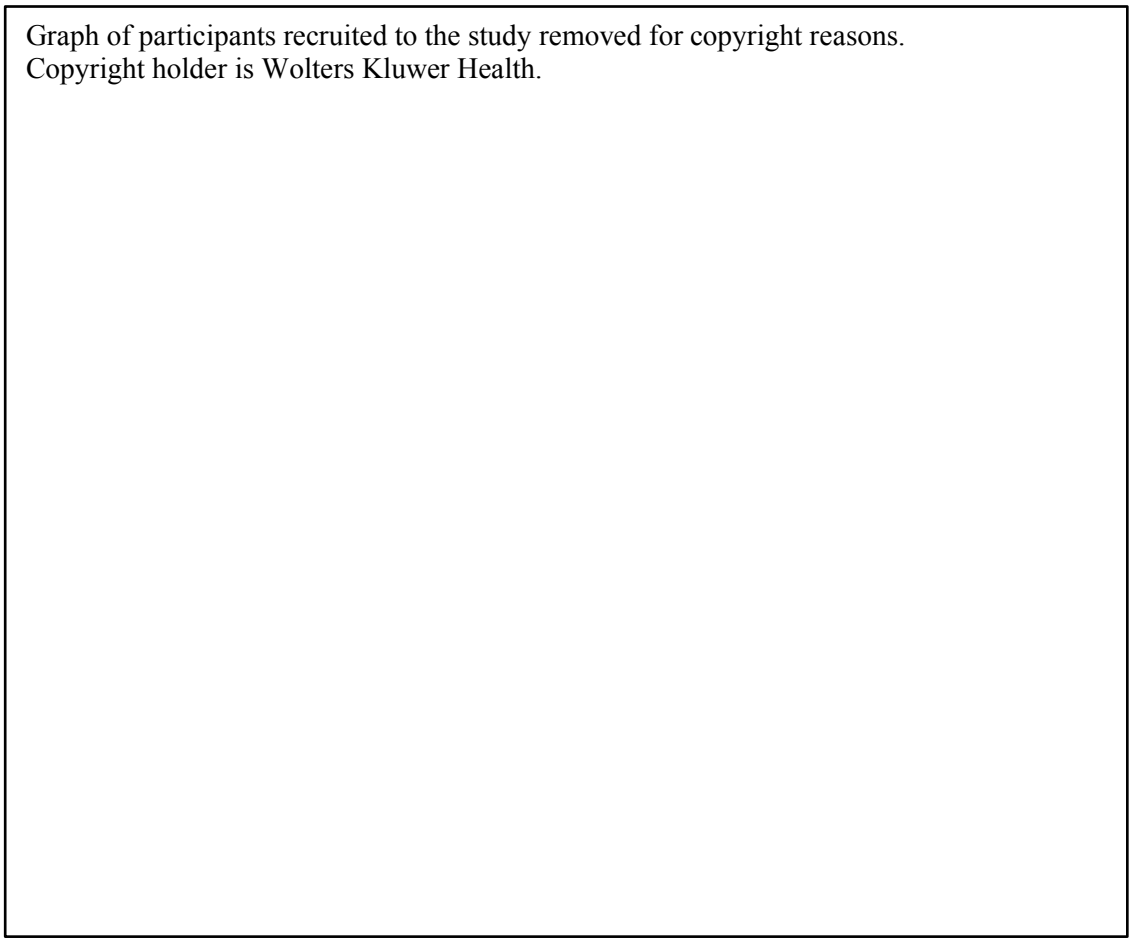

Table 2. Study sample demographics

	Baseline (n = 199)	30 days (n = 176)	6 months (n = 171)	12 months (n = 167)
Age *M SD*	65.9 ± 13.7	66.5 ± 13.2	66.2 ± 13.9	66.2 ± 13.8
Sex – female *n (%)*	77 (38.9%)	65 (38.2%)	61 (36.8%)	60 (36.4%)
Years of education *Mdn (IQR)*	13.5 (12-16)	13.5 (12-16)	13.5 (12-16)	13.5 (12-17)
Ethnicity *n (%)*				
Asian	2 (1.0%)			
Mixed	1 (0.5%)			
White	188 (95.0%)			
Not stated	7 (3.5%)			
NIHSS *M SD*	3.2 ± 3.4			
TOAST				
Cardioembolism	49 (24.7%)			
Large artery	21 (10.6%)			
SVD	69 (35.2%)			
Other	9 (4.8%)			
Undetermined	49 (24.7%)			
MoCA total score *M SD*	24.7 ± 3.8			25.5 ± 3.8
BMET total score *M SD*	12.4 ± 3.5			12.7 ± 4.2
AES *M SD*	29.4 ± 7.5	29.9 ± 8.3	30.4 ± 8.5	31.3 ± 9.4
Self-rated				
Informant-rated	30.3 ± 9.4	30.4 ± 9.3	29.5 ± 8.4	29.8 ± 8.9
DAS *M SD*				
Self-rated	24.7 ± 8.9	25.6 ± 9.2	26.0 ± 9.6	26.7 ± 10.7
Informant-rated	23.4 ± 10.6	28.6 ± 10.1	23.1 ± 10.8	24.7 ± 11.3
GDS-30*M SD*	7.6 ± 5.8	6.9 ± 5.7	7.4 ± 6.9	7.9 ± 7.6
GDS-24 *M SD*	5.1 ± 4.7	4.3 ± 4.4	4.9 ± 5.6	5.3 ± 5.9
mRS *Mdn (IQR)*	0 (0-0)	1 (0.5-2)	1 (0-2)	1 (0-2)
SF36 – MCS *M SD*				50.4 ± 11.9
SF36 – PCS *M SD*				42.1 ± 12.2
Acute lesion volume *M SD*	5487.5 ± 12954.6			
WMH volume *M SD*	18522.7 ± 23701.9			

Years of education were calculated as the sum of compulsory and higher education (including full-time and part-time).

Acute lesion volume and WMH volume are expressed in cubic millimetres.

Key: M, mean; SD, standard deviation; Mdn, median; IQR, interquartile range; SVD, Small Vessel Disease; NIHSS, National Institutes of Health Stroke Scale; WMH, white-matter hyperintensity; AES, Apathy Evaluation Scale; DAS, Dimensional Apathy Scale; GDS, Geriatric Depression Scale; mRS, Modified Rankin Scale; SF-36 MCS, 36-Item Short Form Health Survey Mental Component Summary; SF-36 PCS, 36-Item Short Form Health Survey Physical Component Summary; MoCA, Montreal Cognitive Assessment.

Table 3. Characteristics of the study sample at baseline based on stroke subtype

	Large artery (*n* = 21)	Cardioembolism (*n* = 49)	SVD (*n* = 69)	Other (*n* = 9)	Undetermined (*n* = 49)
Age *M SD*	70.9 ± 9.19	66.2 ± 15.5	68.2 ± 10.9	53.3 ± 19.2	62.9 ± 14.3
Sex – female *n (%)*	3 (14.3%)	23 (46.9%)	28 (40.6%)	5 (55.6%)	18 (36.7%)
Years of education *Mdn (IQR)*	12.0 (11-14)	12.0 (12-17)	13.0 (12-16)	14.5 (13-19)	13.5 (12-16)
Ethnicity *n (%)*					
Asian	0 (0%)	1 (2.0%)	0 (0%)	0 (0%)	1 (2.0%)
Mixed	0 (0%)	0 (0%)	1 (1.5%)	0 (0%)	0 (0%)
White	21 (100%)	47 (96.0%)	65 (94.2%)	9 (100%)	45 (91.8%)
Not stated	0 (0%)	1 (2.0%)	3 (4.3%)	0 (0%)	3 (6.2%)
NIHSS *M SD*	3.3 ± 2.8	4.2 ± 4.6	2.7 ± 2.6	2.9 ± 2.4	2.8 ± 3.5
Acute lesion volume *M SD*	7482.0 ± 10206.7	9066.5 ± 21615.1	1732.3 ± 5618.6	7594.9 ± 8346.9	6017.9 ± 9241.3
WMH volume *M SD*	23530.1 ± 18778.7	15115.4 ± 23043.6	25713.1 ± 28126.4	4837.5 ± 4000.9	10506.6 ± 13752.1
AES *M SD*					
Self-rated	29.0 ± 8.3	30.0 ± 6.5	29.9 ± 8.4	29.7 ± 5.1	28.4 ± 7.3
Informant-rated	29.9 ± 8.5	29.9 ± 8.7	29.3 ± 9.9	37.3 ± 6.2	30.3 ± 10.2
DAS *M SD*					
Self-rated	23.7 ± 10.8	25.8 ± 9.5	25.0 ± 9.0	25.6 ± 3.57	23.0 ± 8.5
Informant-rated	23.2 ± 9.2	22.4 ± 9.1	23.5 ± 10.6	33.9 ± 15.2	21.5 ± 10.3
GDS-24 *M SD*	4.5 ± 4.1	5.7 ± 5.3	4.6 ± 3.8	6.6 ± 5.4	5.3 ± 5.1
mRS *Mdn (IQR)*	0 (0-0)	0 (0-1)	0 (0-0)	0 (0-0)	0 (0-0)
MoCA total score *M SD*	23.7 ± 3.7	24.7 ± 4.4	25.4 ± 3.3	23.6 ± 4.3	24.4 ± 3.8

Acute lesion volume and WMH volume are expressed in cubic millimetres.
Key: SVD, Small Vessel Disease; M, mean; SD standard deviation; Mdn, median; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; WMH, white-matter hyperintensity; AES, Apathy Evaluation Scale; DAS, Dimensional Apathy Scale; GDS-24, Geriatric Depression Scale – depression subscore; mRS, pre-stroke Modified Rankin Scale; MoCA, Montreal Cognitive Assessment.

Chapter 3: Prevalence and symptom trajectory of apathy after stroke

Apathy is one of the most common symptoms after stroke and it is reported that between 20% and 40% of stroke survivors are affected (Hackett *et al.*, 2014; Jorge *et al.*, 2010). Despite apathy being so prevalent in this population, the trajectory of symptoms following stroke is still poorly understood; while some studies report that apathy develops soon after stroke, others report symptoms develop later (Caeiro *et al.*, 2013; Withall *et al.*, 2011). Caeiro and colleagues, for instance, report that at one year after stroke 41% of apathetic patients were still apathetic (Caeiro *et al.*, 2013). Interestingly, more than 60% of new apathetic patients were detected at the same time point. Another longitudinal study, instead, found that around 12 months after stroke the number of patients with apathy decreased. The rate of patients presenting both apathy and depression at one year, however, was reported to have increased (Withall *et al.*, 2011). Other longitudinal studies report that 12 months after stroke most stroke survivors have a constant or low level of apathy, whereas only about 7% shows an improvement or worsening of symptoms (Mayo *et al.,* 2009). When looking at a five-year follow-up, the prevalence of apathy seems to increase by around 10% (Brodaty *et al.,* 2013). The estimates reported so far, however, might underrepresent the actual prevalence of apathetic patients due to a higher likelihood of dropping out of studies (Mayo *et al.,* 2009).

The extent to which apathy symptoms change over time is therefore unclear and further longitudinal studies are required to clarify the prevalence of apathy symptoms and how these change over time.

To clarify the time course of apathy after stroke, the prevalence of apathy symptoms in a cohort of ischaemic stroke patients was first determined by calculating the proportion of apathetic patients at each time point based on the validated cut-offs of the Dimensional Apathy Scale and the Apathy Evaluation Scale.
The longitudinal trajectory of apathy symptoms over the initial year after stroke was then investigated using linear mixed models.

Once a trajectory was identified, further analyses were conducted to identify longitudinal clusters of apathy scores and how these changed over one year after stroke: latent class mixed models were fit to longitudinal apathy data to estimate each latent class specific trajectory.

3.1 Methods

Study sample

The data analysed in this chapter was obtained from the Apathy and Outcome after Stroke Study: the study framework was described in detail in Chapter 2.

Prevalence of apathy after stroke

At each time point the number of participants with apathy was identified using previously defined cut-offs; above 38 and 40 on the self-rated and informant-rated versions of AES and above 39 on the DAS total score (Marin *et al.*, 1991; Myhre *et al.*, 2022). Prevalence of apathy was compared with a Chi-square test.

Trajectory of apathy symptoms after stroke

Individual changes in apathy scores were analysed with a linear mixed model using the lme4 package (Bates *et al.*, 2015). This type of modelling incorporates both fixed- and random-effects terms in a linear predictor model. For the current analysis, longitudinal changes in AES self-rated total scores, DAS self-rated total scores, and DAS self-rated scores on the three dimensions were modelled using months from stroke as the underlying timescale. The model included a random intercept only. Participants who did not complete the 12 month assessment were excluded from analysis. Analyses were adjusted for age, sex, years of education, MoCA total score at baseline, pre-stroke mRS, NIHSS, acute infarct volume, and TOAST classification. A total of 165 participants were included in this analysis.

Longitudinal clusters of apathy scores

Analyses were conducted to identify patterns of change in total apathy scores with the lcmm function of the lcmm package (version 2.0.2, Proust-Lima *et al.,* 2023) in R (R Core Team, 2023). A random intercept and random slope were considered in the modelling of self-rated AES

and DAS total scores. A linear term for months after stroke was used to specify the random effects of the model, *i.e.* the individual changes around the average change over time. To select the best model, a series of linear and non-linear models, including linear, quadratic, and cubic terms for the time (months) with a class number ranging from 1 to 3, were assessed. The best fit model with the optimal number of latent classes was selected by the following criteria: the least Bayesian information criterion (BIC); a reduction of BIC of at least ten points; a posterior probability above 0.7 for all latent classes; no less than 5% of the participants in any single class. Groups were subsequently defined based on their probability (Nagin *et al.*, 2018). Clinical and demographic variables were then used in logistic regression to identify which factors determined apathy scores and could predict the latent class membership: sex, age at baseline, MoCA total score at baseline, mRS, NIHSS score, and stroke volume were considered in these analyses.

3.2 Results

Prevalence of apathy after stroke

Table 4 reports the percentage of apathetic and non-apathetic participants at each time point, as measured on AES and DAS, both on self-report and on the informant-rated version of the tests. The prevalence of participants with self-rated apathy significantly increased from baseline to 12 months after stroke; from 10.8% at baseline to 22.4% at 12 months for the AES (X^2 (3) = 9.86, p = 0.019), and from 3.6% to 11.0% when measured with DAS (X^2 (3) = 8.49, p = 0.037). In contrast, informant-rated apathy did not show any significant change, with prevalence of apathy at baseline and 12 months being 15.6% and 11.5% for the AES and 7.3% and 12.6% for the DAS (AES X^2 (3) = 0.75, p = 0.862; DAS X^2 (3) = 2.45, p = 0.484).

Table 4. Prevalence of apathetic and non-apathetic patients at each time point

	Baseline	30 days	6 months	12 months
AES self-rated				
Apathetic n (%)	21 (10.8%)	25 (14.7%)	31 (18.7%)	37 (22.5%)
Non-apathetic n (%)	174 (89.2%)	145 (85.3%)	135 (81.3%)	128 (77.5%)
DAS self-rated				
Apathetic n (%)	7 (3.6%)	10 (5.9%)	15 (9.0%)	18 (10.9%)
Non-apathetic n (%)	188 (96.4%)	160 (94.1%)	151 (91.0%)	147 (89.1%)
AES informant-rated				
Apathetic n (%)	17 (15.6%)	13 (14.8%)	12 (13.5%)	10 (11.5%)
Non-apathetic n (%)	92 (84.4%)	75 (85.2%)	77 (86.5%)	77 (88.5%)
DAS informant-rated				
Apathetic n (%)	8 (7.3%)	8 (9.0%)	6 (6.6%)	11 (12.6%)
Non-apathetic n (%)	101 (92.7%)	81 (91.0%)	85 (93.4%)	76 (87.4%)

Trajectory of apathy symptoms after stroke

The linear mixed model demonstrated a significant increase in self-rated apathy scores with time from stroke. For AES the model's total explanatory power was substantial (conditional R^2 = 0.61). The effect of months from stroke was statistically significant and positive (β = 0.13, 95% CI [0.05, 0.21], p = 0.002). Figure 2 shows the predicted mean value of AES assessed using the self-report questionnaire over time. The effect of months from stroke was significant after introducing co-variates in the model (age, sex, years of education, MoCA total score at baseline, pre-stroke mRS, NIHSS, acute infarct volume, and TOAST classification) (β = 0.13, 95% CI [0.05, 0.21], p = 0.002).

The DAS model's total explanatory power was substantial (conditional R^2 = 0.65). The effect of months from stroke was statistically significant and positive (β = 0.12, 95% CI [0.04, 0.21], p = 0.005). Figure 2 shows the predicted values of self-report derived DAS. The effect was still significant when introducing co-variates (age, sex, years of education, MoCA total score at

baseline, pre-stroke mRS, NIHSS, acute infarct volume, and TOAST classification) ($\beta = 0.13$, 95% CI [0.04, 0.21], $p = 0.005$).

Since 10 assessments were performed up to 20 months after stroke for the 12 month assessment, sensitivity analyses were conducted and participants whose assessment was performed over 14 months after stroke were excluded. These analyses revealed no differences with the main results reported. Sensitivity analyses were also performed to account for study drop-out: no participants were excluded from analysis and missing data was imputed with multiple-imputation. No differences were observed in results.

The linear mixed model demonstrated a significant increase in self-rated DAS Executive apathy scores. The model's total explanatory power was substantial (conditional $R^2 = 0.64$). The effect of months from stroke was statistically significant and positive ($\beta = 0.08$, 95% CI [0.03, 0.12], $p < 0.001$). Figure 3 shows the predicted mean values of DAS Executive over time. The effect of months from stroke was significant after adjusting for the aforementioned covariates ($\beta = 0.08$, 95% CI [0.03, 0.12], $p < 0.001$).

There was no evidence of the effect of months after stroke on self-rated DAS Emotional apathy scores ($\beta = 0.01$, 95% CI [-0.03, 0.05], $p = 0.530$). Figure 3 shows the predicted mean of DAS Emotional over time.

The linear mixed model was not significant for the self-rated DAS Initiation apathy scores. The effect of months after stroke was not statistically significant ($\beta = 0.03$, 95% CI [-0.01, 0.08], $p = 0.134$). Figure 3 shows the predicted mean values of DAS Initiation over time.

Figure 2. Predicted values of AES and DAS self-report

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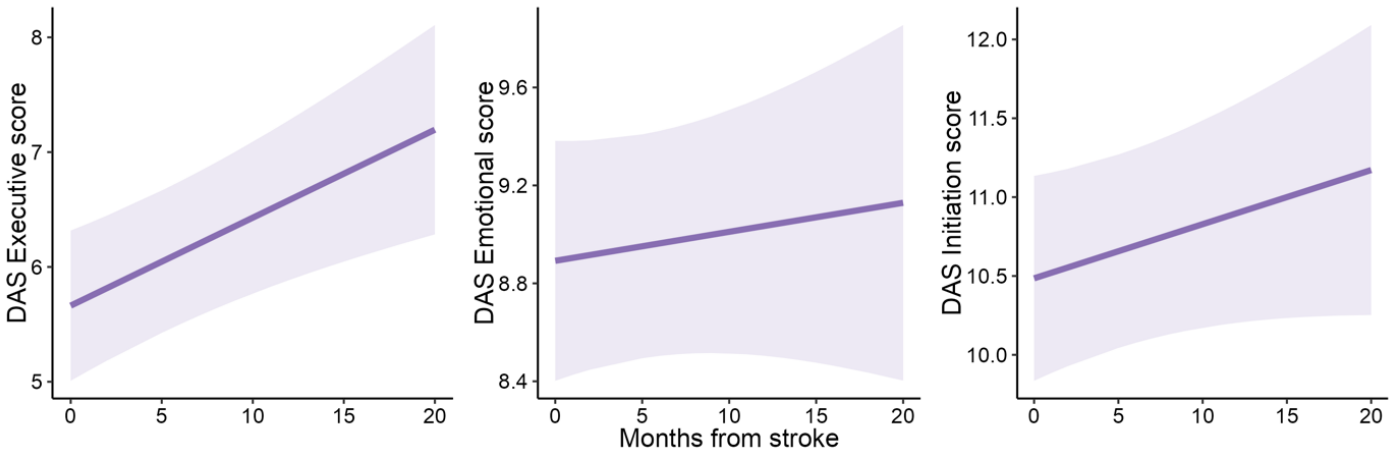
Figure 3. Predicted apathy scores of self-rated DAS Executive, Emotional, and Initiation



Predicted values of DAS Executive (left panel), DAS Emotional (central panel), and DAS Initiation (right panel) are shown in the plots with a solid purple line. Confidence intervals are presented in light purple.

Longitudinal clusters of apathy scores

Based on the criteria described above, the best fitting model for AES self-rated scores was a model of quadratic terms with two distinct patterns of score development over time. The average posterior probability of class membership was high for each class. Figure 4 shows the predicted mean of AES self-rated scores for two identified trajectories, which are labelled as class 1, representing the majority of patients (63.6%, n = 105), and class 2 (36.4%, n = 60). Logistic regression showed that apathy scores (β = 0.34, 95% CI [0.29, 0.39], p < 0.001), age (β = 0.02, 95% CI [0.00, 0.05], p = 0.028), greater NIHSS score (β = 0.13, 95% CI [0.04, 0.21], p = 0.003), and lower acute infarct volume (β = -1.39, 95% CI [-2.21, -0.66], p < 0.001) increased the probability of belonging to class 2.

The best fitting model for DAS self-rated total scores was a linear model, which identified two classes. The average posterior probability of class membership was high for each class. Figure 5 depicts the two identified trajectories, with class 1 representing the larger group (64.2%, n = 106), and class 2 the smallest group in the cohort (35.8%, n = 59). The probability of belonging to class 2 increased with apathy scores (β = 0.35, 95% CI [0.30, 0.41], p < 0.001), age (β = 0.13, 95% CI [0.10, 0.15], p < 0.001), and MoCA score at baseline (β = 0.17, 95% CI [0.09, 0.25], p < 0.001).

A *post-hoc* analysis was conducted to identify patterns of change in Executive apathy scores with the lcmm function using the same parameters described above. A model of linear terms with two distinct trajectories of DAS Executive was chosen. The average posterior probability of class membership was high for each class. Figure 6 shows the trajectories of Executive scores for the two identified classes. One trajectory, representing the largest group (81.8%, n = 135), is depicted in Figure 6 as class 1, whereas class 2 represented the minority of the cohort (18.2%, n = 30). Apathy scores (β = 0.39, 95% CI [0.32, 0.46], p < 0.001) and being female (β = 0.60, 95% CI [0.05, 1.16], p = 0.033) increased the probability of belonging to class 2.

Figure 4. Trajectories of AES total score after stroke

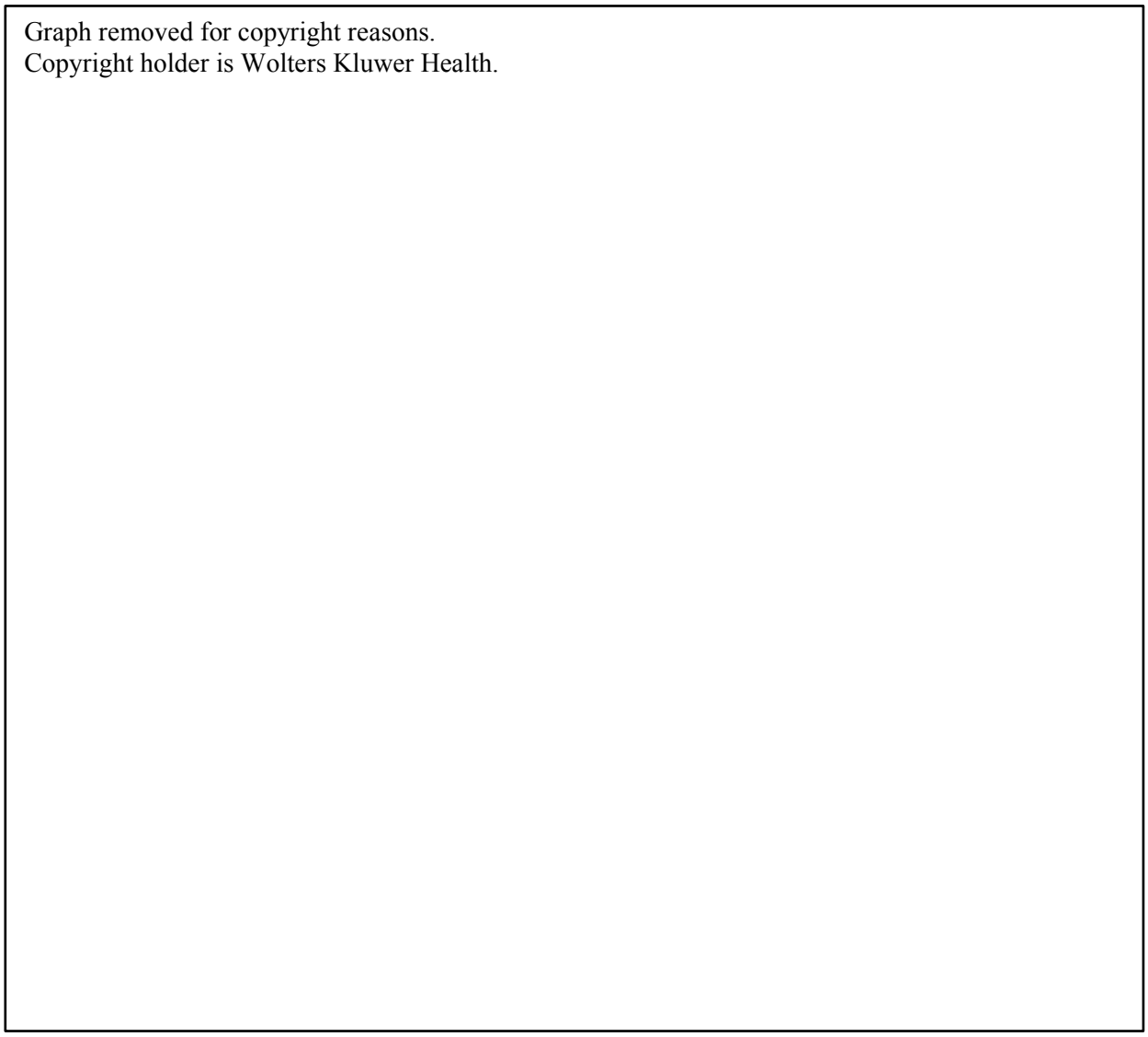


Figure 5. Trajectories of DAS total score after stroke

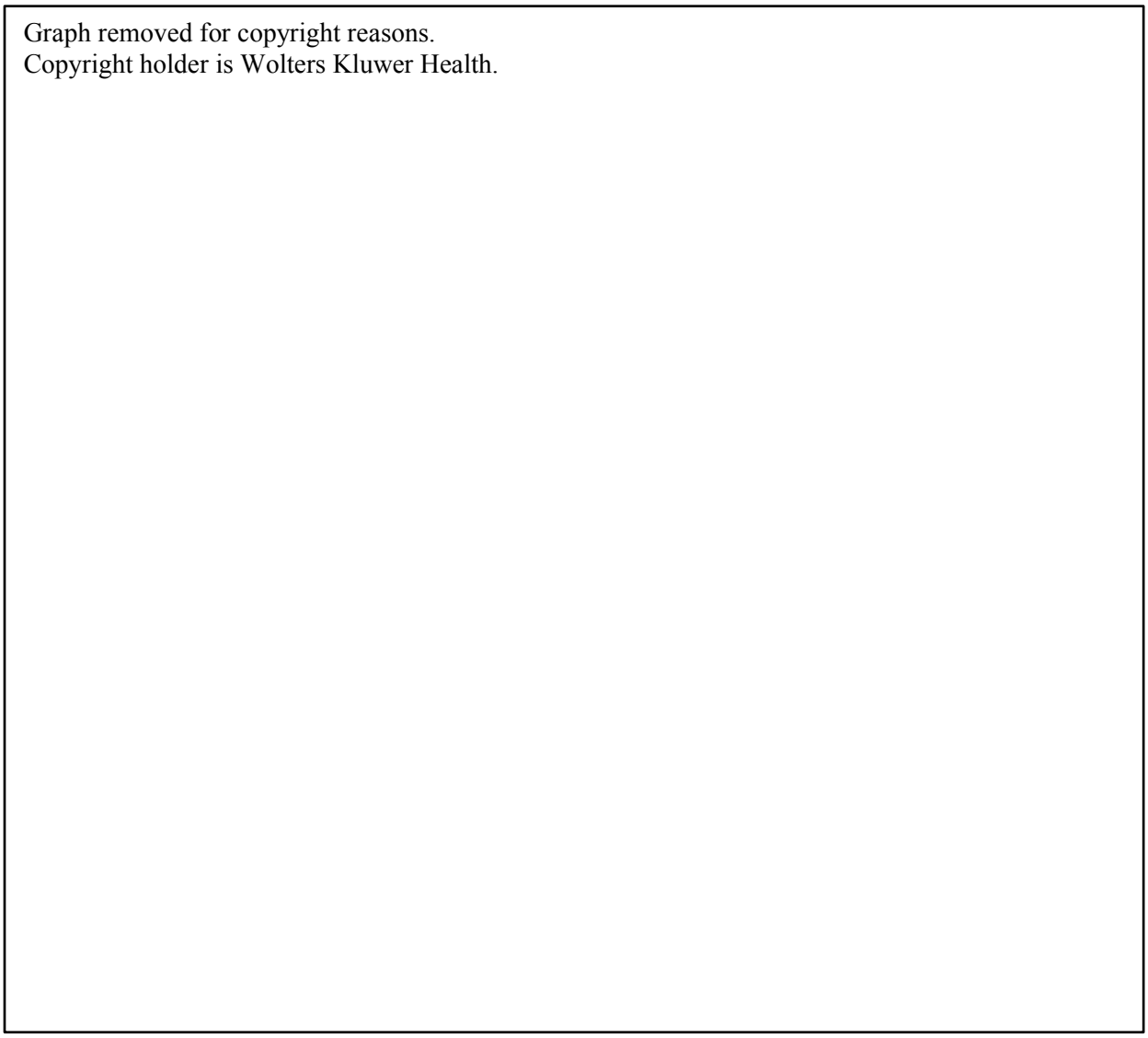
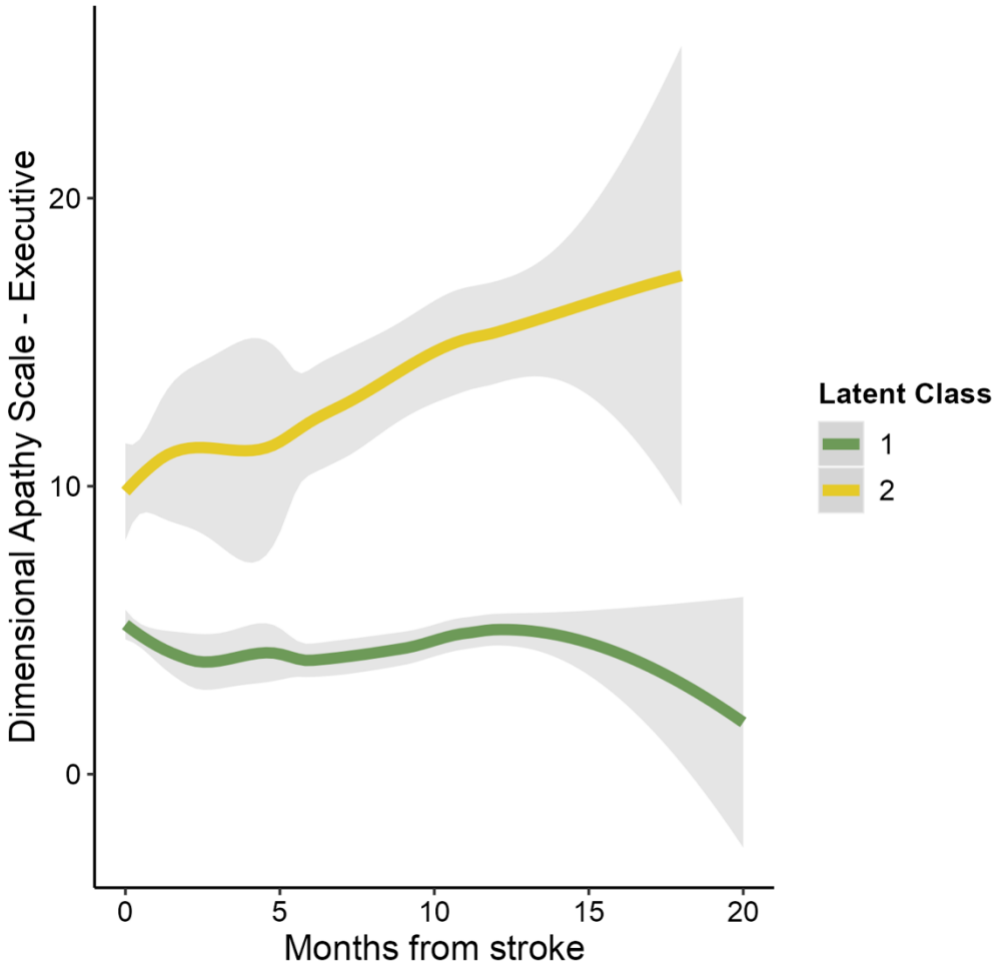


Figure 6. Trajectories of DAS Executive scores after stroke



Longitudinal trajectories of DAS Executive scores were obtained. Predicted DAS Executive values of Class 1 (green) and Class 2 (yellow) are shown in the plots with a solid line. Confidence intervals are presented in grey.

3.3 Discussion

In this prospective longitudinal study, we found that apathy is a common problem after stroke, and that its prevalence progressively increases in the initial year after stroke.

Previous studies have reported a wide variety of estimates of the prevalence of apathy after stroke and our estimate is at the lower end of these. This may partly reflect the fact that the study population was predominantly mild and moderate stroke with a mean mRS of 1 when assessed 30 days after stroke. However, these findings also emphasize the influence of the measurement

tool and definition used to define apathy on prevalence estimates, as apathy was two-fold more common using the AES than the DAS.

The severity of neurological deficit and disability usually reduces in the first few months following stroke. In contrast, this study and previous reports indicate that the prevalence of apathy increases over time after stroke, although not all studies have confirmed this increase (Brodaty *et al.*, 2013; Caeiro *et al.*, 2013; Mayo *et al.*, 2009; Withall *et al.*, 2011). A number of factors could explain this, including an increasing awareness of the more psychological consequences of stroke as the physical deficit improves. However, neurobiological explanations have also been hypothesized including a recent theory that suggests that cerebrovascular disease-related pathology can lead to network changes outside of initially damaged territories, which may propagate to regions that share structural or functional connections (Tay *et al.*, 2020a).

It was striking that in contrast to patient self-report data, the informant-rated versions of both the AES and DAS showed no increase in apathy over time. The explanation for this is not immediately apparent. It could be that it reflects a lack of awareness of apathetic symptoms by patients in the early stages after stroke. Informants might be able to notice apathy early on and therefore would not change their ratings. Previous studies on apathy in neurological disease have also suggested that measures from self- and informant questionnaires reveal different phenotypic and neuroanatomical basis (Lansdall *et al.*, 2017). Another possibility is that apathy and a consequent decrease in activation would result in a positive feedback mechanism by which the cues that would usually activate behaviour are reduced, so that the less activation decreases the likelihood of encountering activating cues. The gradual loss of cues would trigger a downward spiral where the person lacks activation stimuli and this in turns would be worsened by apathy. It is also important to highlight that not all patients had informants, significantly decreasing the analysis sample size. It should also be noticed that patients who did not have informants had significantly higher self-rated apathy at 12 months (AES $W = 4124.50$, $p = 0.017$, 95% CI [0.04, 0.38]; DAS $W = 4229.50$, $p = 0.006$, 95% CI [0.07, 0.40]). Having fewer personal contacts and social interactions might explain higher level of apathy in patients; however, this association needs to be further explored.

The current results suggest that while a gradual increase in apathy symptoms after stroke is a real phenomenon, this seems to only affect a minority of stroke survivors and relate especially to executive symptoms as demonstrated on examination of the different apathy dimensions on the DAS. About 35% of the cohort presented higher apathy scores at baseline with a peak around 5 months after stroke. After 6 months, symptoms gradually increased when measured with DAS. AES models, instead, showed that apathy remained stable with a second peak around 10 months. Previous findings reported that apathy tends to be stable or decrease over time, with only a minority developing symptoms few months after stroke (Lammers *et al.,* 2023; Withall *et al.,* 2011). Other findings, however, found that apathy rates steadily increases and levels grew modestly over 5 years, suggesting that findings might also be influenced by the timescale investigated (Brodaty *et al.,* 2013). Further work is needed to identify biological and cognitive factors that may contribute to this and to clarify the impact of each factor on different symptom trajectories.

A possible limitation in these analyses is that self-rated scores were used in latent class modelling since the low sample sizes based on informant-rated scores would not allow a reliable classification of participants into latent classes. However, apathy awareness might be lower in stroke patients. Hence, these analyses should be replicated by increasing the sample size and compare the differences between informant- and patient-based clustering.

It should be noted that these analyses did not take into consideration the effects of acute stroke treatments and interventions, such as thrombolysis or thrombectomy. This was due to the fact that only 22 participants in this cohort had thrombolysis and 3 had thrombectomy, thus reducing the likelihood of observing any significant differences with the other participants. While there does not seem to be enough research specifically linking acute treatments to *post*-stroke apathy, future studies should take into consideration the effects of interventions in the acute phase of stroke on apathy symptoms and longitudinal changes.

Moreover, this study did not take into consideration whether participants switched in and out of category, that is whether apathetic patients at one point resulted non-apathetic at following assessments, or vice versa. As previously reported, studies show that patients who are

asymptomatic in the acute phase might develop apathy one year after stroke, whereas patients who have symptoms in the acute phase might later recover (Caeiro *et al.*, 2013; Withall *et al.*, 2011). Future studies might look into whether and how patients switch apathy category and whether prevalence data changes when taking into account this phenomenon.

Another limitation to these analyses is represented by the multiple comparisons problem: in this study, analyses were conducted by comparing multiple scales at different timepoints while accounting for multiple variables. This might increase the probability of finding false positive results. A possible solution to this issue would be to apply stricter controls on the significance level by using a controlling procedure (such as controlling the family-wise error rate or the false discovery rate), or to adopt a Bayesian approach (Lee and Lee, 2018; Sjölander and Vansteelandt, 2019).

When looking at individual apathy dimensions, executive symptoms seemed to predominantly drive the general increase in apathy symptoms. As defined by Radakovic and Abrahams, this scale would measure those behaviours falling under the umbrella term of executive functions: this includes all the aspects involved in organisation, attention, and planning (Radakovic and Abrahams, 2014). These results seem to suggest that apathy in stroke survivors mainly affects the ability to plan and organise, more than the emotional or cognitive domains.

Taken together, the results presented in this chapter might help clarify the clinical presentation of apathy, allowing clinicians to better identify predominant symptoms following stroke, as well as associate these to a precise time scale. However, further work is needed to identify biological and cognitive factors that may contribute to the development and course of apathy symptoms following stroke and to clarify the impact of each factor on different symptom trajectories.

Chapter 4: Apathy profiles in stroke

Most studies of apathy treat this symptom as a single construct; however, this might not be the case and some have described apathy as a multidimensional syndrome instead (Levy and Dubois, 2006). As previously mentioned, apathy appears to encompass elements of emotion, cognition, and behaviour, each originating from distinct brain regions and neural pathways (Radakovic and Abrahams, 2014). According to Radakovic and Abrahams, specifically, Executive apathy refers to attention, planning, and the organisation of thoughts and actions; this dimension fundamentally encompasses executive functions and is most comparable to Levy and Dubois' Cognitive apathy type (Radakovic and Abrahams, 2014). Emotional apathy pertains to the integration of emotional behaviours and includes a greater number of processes compared to the Emotional-affective subtype described by Levy and Dubois, who refer to this as the expression, processing, and recognition of emotions (Radakovic and Abrahams, 2014). Finally, Initiation/Cognitive apathy is concerned with the initiation of behaviours and thoughts and sustained response to tasks such as verbal fluency. This dimension is similar to the Auto-activation one described by Levy and Dubois, however it does not relate as much to motor responsiveness and motor functions (Radakovic and Abrahams, 2014).

Various patterns of symptom presentation have been observed in neurological diseases. Radakovic and colleagues, for instance, identified subgroups of people with Alzheimer's Disease showing Executive and Initiation apathy, Global apathy, and Minimal apathy (Radakovic *et al.,* 2017). Similar analyses have not yet been undertaken in a stroke cohort and a finer characterisation of apathy subtypes in people with stroke might allow a better understanding of apathy presentation. This, in turn, might provide with more accurate treatment solutions to tackle the specific impaired dimensions.

Here, an exploratory analysis was performed to identify different subtypes of apathy after stroke, and whether they manifested a different course and had different associations with clinical and cognitive features and outcome. The aim of this study was to analyse the presentation of apathy dimensions at multiple points after stroke. Moreover, the goal was to establish whether apathy presented following different patterns and whether these could be defined by specific clinical and

cognitive characteristics. This is the first study of apathy dimension presentation conducted with similar methods in a cohort of stroke patients. Data was collected from a cohort of ischaemic stroke patients at four time points (baseline, 30 days, 6 and 12 months after stroke) and Latent Class Analysis was performed considering scores on the three DAS dimensions. Such analysis allowed for classification of scores into distinct classes and a subsequent analysis of clinical and demographic characteristics of each class. A finer classification of apathy profiles in stroke might help identifying treatments and interventions better suited for the specific impaired dimension.

As previously discussed, close relationships between apathy and depression have been observed and these two symptoms can often co-occur in patients (Lopatkiewicz *et al.,* 2021; Withall *et al.,* 2011). However, the interaction with depression may differ by apathy subtype and predominant symptoms. Here, the aim was to get a better understanding of the association of apathy dimensions with depression. To do this, linear regression analyses were used to assess GDS-24 in relation to DAS dimensions at 30 days.

4.1 Methods

Study sample

The data analysed in this chapter was collected for the Apathy and Outcome after Stroke Study: details of the study are reported in Chapter 2. Two hundred ischaemic stroke patients were recruited: of these, 199 completed the assessment at baseline, 176 at 30 days, 171 at 6 months, and 167 at 12 months. Moreover, 112 informants completed the assessment at baseline, 92 at 30 days, 95 at 6 months, and 89 at 12 months. Only patients and informants who completed the DAS at each time point were included in the relevant analysis.

Apathy profiles in stroke

The number of participants impaired on DAS dimensions was calculated at baseline and 12 months based on cut-offs validated in stroke patients (Myhre and Radakovic, 2022).

Latent Class Analysis (LCA) was performed to identify clusters of stroke patients based on their scores on the three DAS subscales (Executive, Emotional, and Behavioural/Initiation) using Mclust package in R (Scrucca *et al.*, 2016). Mclust is a model-based clustering, classification and density estimation software that is based on finite Gaussian mixture modelling. The optimal LCA model and number of clusters was automatically selected according to Bayesian Information Criterion (BIC) (Schwarz, 1978). The Integrated Classification Likelihood (ICL) criterion was also used to support Mclust model selection (Biernacki *et al.,* 2000). A one-way MANOVA was used to confirm classes identified through LCA. Clusters were then identified, and clinical and demographics characteristics compared using two-sample t-test, Mann-Whitney U test, Chi squared test, and one-way ANOVAs where appropriate. Significant ANOVA results were followed by *post-hoc* Tukey's tests. Sex, age at baseline, years of education, AES self-rated total score, MoCA total score at baseline, GDS-24, mRS, and NIHSS score were considered in these analyses. Clustering of apathy scores was performed on self- and informant-rated scores at baseline, 30 days, 6 and 12 months.

Association of apathy and depression

The overlap between apathy and depression was assessed based on the AES self-rated and GDS-30 cut-offs. Odds ratios and 95% confidence intervals were calculated for the relative risk of depression disorders. In order to assess the trajectory of depression over one year after stroke, individual changes in depression scores were analysed with a linear mixed model using the lme4 package (Bates *et al.*, 2015). As described in Chapter 3, this type of modelling incorporates both fixed- and random-effects terms in a linear predictor model. For the current analysis longitudinal changes in GDS-24were modelled using months from stroke as the underlying timescale. The model included a random intercept only. Participants who did not complete the 12 month assessment were excluded from analysis. Analyses were adjusted for age, sex, years of education, MoCA total score at baseline, pre-stroke mRS, NIHSS, acute infarct volume, and TOAST classification. A total of 165 participants were included in this analysis.

Linear regression analyses were used to investigate the association of depression (GDS-24 at 30 days) with apathy dimensions (DAS Executive, Emotional, and Initiation at 30 days). Scores at 30 days were considered in the current analysis instead of baseline scores since the latter were

deemed too close to the acute stage of stroke to accurately represent participants mood. Analyses were controlled for age, sex, years of education, baseline MoCA, NIHSS, mRS at 30 days.

4.2 Results

4.2.1 Apathy profiles in stroke

Apathy profiles at baseline

At baseline, 36 (16.9%) participants were impaired on at least 1 dimension: of these, 10 (5.1%) were affected on DAS Emotional, 20 (10.1%) on Initiation, and 13 (6.6%) on Executive. At 12 months, 13 (6.6%) were impaired on Emotional, 28 (14.1%) on Initiation, and 24 (12.1%) on Executive.

The LCA of self-rated scores at baseline identified an ellipsoidal multivariate normal model, supporting a 1-class solution, with a BIC value of -1650.6.
The comparison of different models based on informant-rated scores showed that a model "EII" (spherical, equal volume) supporting a 3-class solution yielded a best fitting model with a BIC value of -889.3. The second best model was "EEI" (diagonal, equal volume and shape) with 3-classes, presenting with a BIC value of -889.8. This was a 0.5 point difference from the first model. The ICL criterion supported 3-class solution "EII" model with a ICL value of -912.3. A one-way MANOVA showed a significant difference between the DAS subscales, supporting 3-class solution ($F(6, 120) = 59.3$, $p < 0.001$; Wilk's $\Lambda = 0$, partial $\eta 2 = 0.6$). Figure 7 shows the profiles of the three DAS groups. Cluster 2 was the largest (n = 63) and was characterised by generally lower apathy. Using dimension cut-offs (Radakovic *et al.,* 2022), no patients were impaired on apathy subscales. Cluster 1 (n = 26) displayed higher scores on the Emotional and Initiation dimensions, with 15% impaired on the first dimension and 23% on the second. Cluster 3 (n = 20) showed distinctly higher apathy scores in all dimensions, with up to 70% impaired on the Initiation dimension. The clusters also were significantly different on AES informant-rated and depression (GDS-24). Tukey's tests showed that Cluster 3 was more depressed compared to Cluster 1 ($p = 0.001$) and 2 ($p = 0.007$), and had significantly higher AES compared to the other clusters ($p < 0.001$). No significant differences were found on other variables. Table 5 shows the clinical and demographic characteristics of each identified class.

Figure 7. Baseline informant-rated clusters based on LCA of DAS subscale scores

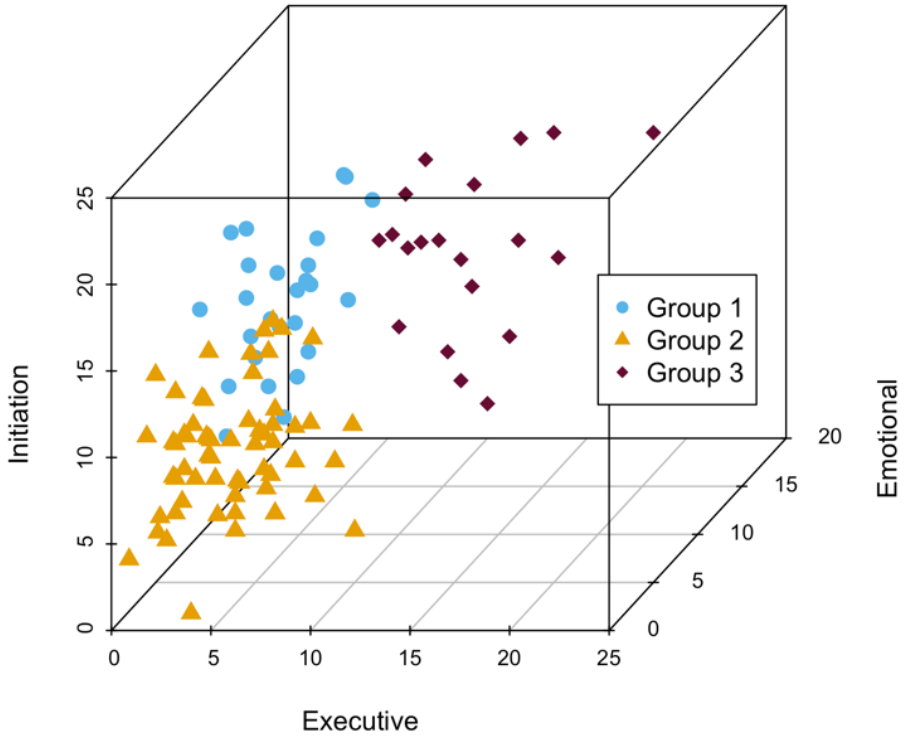


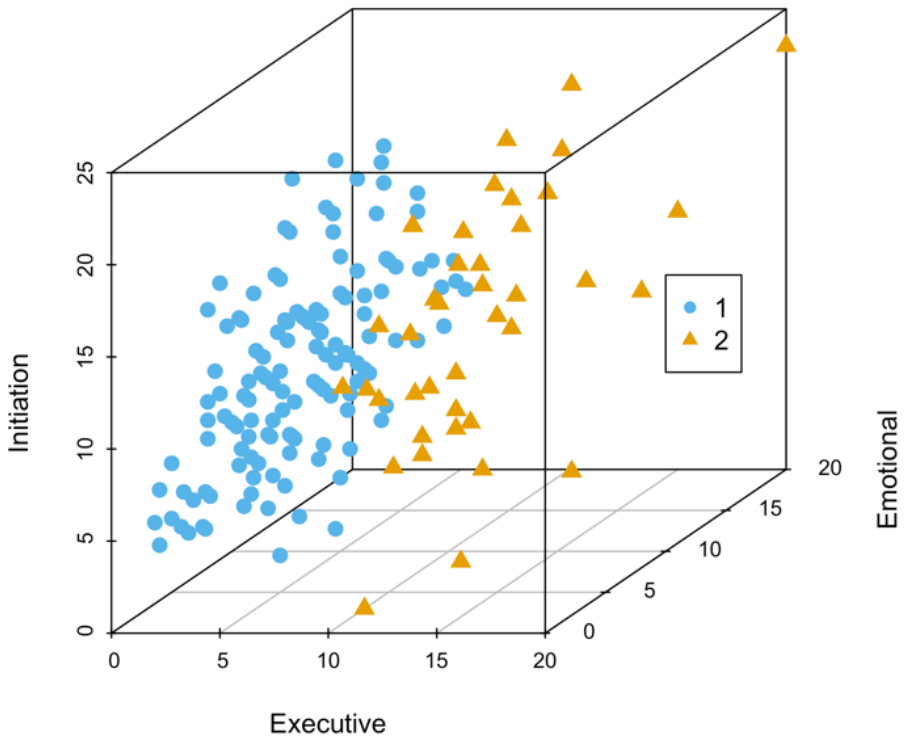
Table 5. Cluster comparison on DAS subscales, descriptive and clinical characteristics

	Cluster 1 (n = 26)	Cluster 2 (n = 63)	Cluster 3 (n = 20)	*p*-value
DAS subscale (mean, SD)				
Executive	**3.2 (2.1)**	**3.5 (2.6)**	**13.2 (3.2)**	**<0.001**
Emotional	**12.2 (2.2)**	**5.8 (2.5)**	**10.8 (3.5)**	**<0.001**
Behavioural	**12.2 (4.1)**	**7.2 (3.3)**	**16.1 (3.8)**	**<0.001**
AES informant-rated (mean, SD)	**33.0 (7.7)**	**25.5 (6.8)**	**42.4 (5.9)**	**<0.001**
GDS-24 (mean, SD)	**3.1 (3.1)**	**4.3 (3.9)**	**5.2 (7.5)**	**0.001**
Sex female *n* (%)	6 (23.1%)	28 (44.4%)	8 (40.0%)	0.167
Age (mean, SD)	68.5 (8.2)	64.2 (14.8)	65.7 (15.4)	0.400
Years of education (mean, SD)	14.7 (3.6)	14.5 (2.9)	14.9 (4.1)	0.861
NIHSS (mean, SD)	2.4 (3.4)	3.3 (3.5)	3.4 (3.7)	0.522
MoCA total score (mean, SD)	24.9 (3.5)	25.1 (4.2)	23.9 (4.4)	0.573

Apathy profiles at 30 days

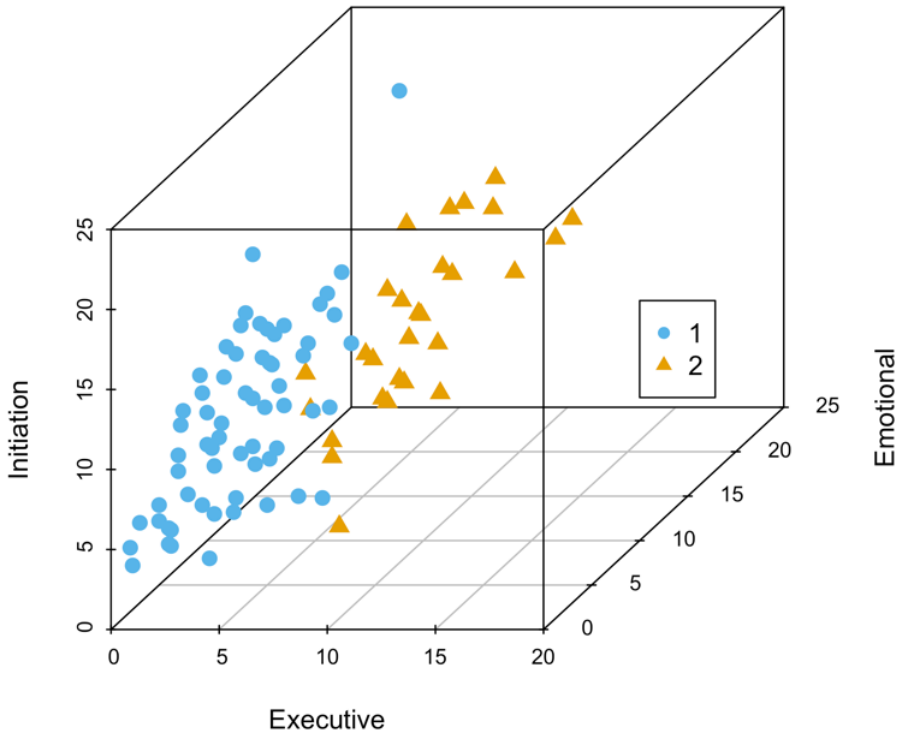
At 30 days, the comparison of different models based on self-rated scores showed that a model "VEE" (ellipsoidal, equal shape and orientation) supporting a 2-class solution yielded a best fitting model with a BIC value of -1454.6. The second best model was "EEE" (ellipsoidal, equal volume, shape and orientation) with 2-classes, presenting with a BIC value of -1457.8. This was a 3.2 point difference from the first model. The ICL criterion supported 3-class solution "VEE" model with a ICL value of -1489.4. A one-way MANOVA showed a significant difference between the DAS subscales, supporting 2-class solution ($F(3, 170) = 104.7$, $p < 0.001$; Wilk's $\Lambda = 0$, partial $\eta 2 = 0.7$). Figure 8 shows the profiles of the two DAS groups. Cluster 1 was the largest (n = 134) and was characterised by generally lower apathy. Using dimension cut-offs (Radakovic *et al.,* 2022), around 11.2% of participants were impaired on the Emotional and Initiation dimensions. Cluster 2 (n = 40) displayed higher scores on every dimension, with 25% impaired on Executive and 35% on Initiation. *Post-hoc* tests showed that Cluster 2 was more depressed compared to Cluster 1 ($p < 0.001$) and had significantly higher AES compared to the other cluster ($p < 0.001$). No significant differences were found on other variables.

Figure 8. 30 days self-rated clusters based on LCA of DAS subscale scores



At 30 days, the comparison of different models based on informant-rated scores showed that a model "VEE" (ellipsoidal, equal shape and orientation) supporting a 2-class solution yielded a best fitting model with a BIC value of -746.7. The second best model was "EEV" (ellipsoidal, equal volume and shape) with 2-classes, presenting with a BIC value of -752.5. This was a 5.8 point difference from the first model. The ICL criterion supported 2-class solution "EEV" model with a ICL value of -750.8. A one-way MANOVA showed a significant difference between the DAS subscales, supporting 2-class solution ($F(3, 87) = 84.2$, $p < 0.001$; Wilk's $\Lambda = 0$, partial $\eta 2 = 0.7$). Figure 9 shows the profiles of the two DAS groups. Cluster 1 was the largest (n = 134) and was characterised by generally lower apathy. Using dimension cut-offs (Radakovic *et al.,* 2022), around 7.9% of participants were impaired on the Initiation dimension. Cluster 2 (n = 28) displayed higher scores on every dimension, with up to 32% impaired on the Initiation dimension. *Post-hoc* tests showed that Cluster 2 was more depressed compared to Cluster 1 ($p = 0.003$), had significantly higher AES compared to the other cluster ($p < 0.001$), and had greater disability as measured with the mRS ($p = 0.001$). No significant differences were found on other variables.

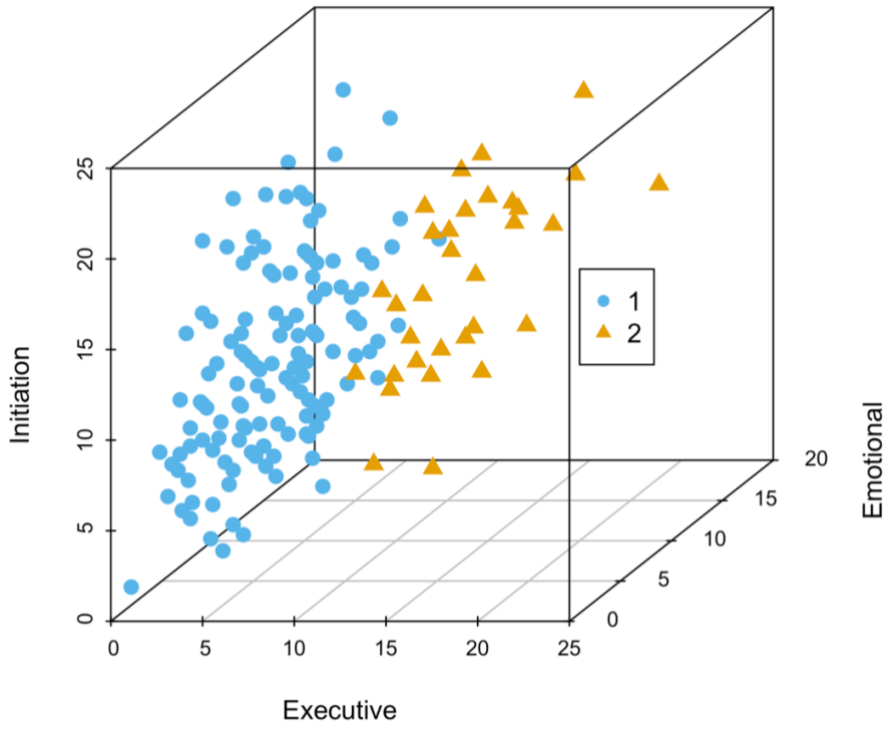
Figure 9. 30 days informant-rated clusters based on LCA of DAS subscale scores



Apathy profiles at 6 months

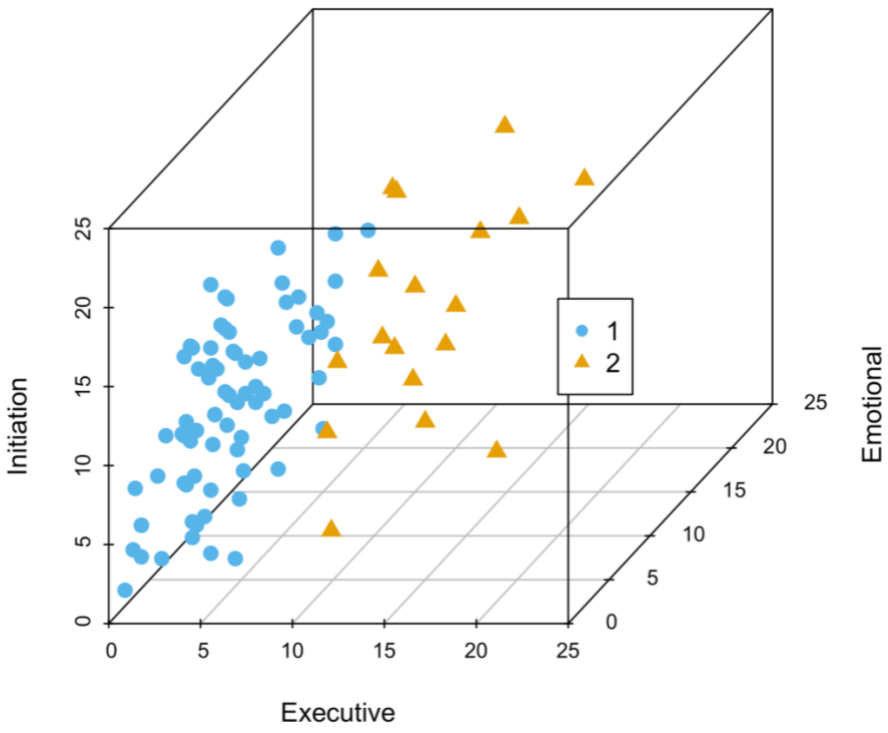
At 6 months, the comparison of different models based on self-rated scores showed that a model "VEE" (ellipsoidal, equal shape and orientation) supporting a 2-class solution yielded a best fitting model with a BIC value of -1385.7. The second best model was "VEV" (ellipsoidal, varying volume, equal shape, varying orientation) with 2-classes, presenting with a BIC value of -1386.5. This was a 0.8 point difference from the first model. The ICL criterion supported 2-class solution "VEE" model with a ICL value of -1400.5. A one-way MANOVA showed a significant difference between the DAS subscales, supporting 2-class solution ($F(3, 163) = 121.3$, $p < 0.001$; Wilk's $\Lambda = 0$, partial $\eta 2 = 0.7$). Figure 10 shows the profiles of the two DAS groups. Cluster 1 was the largest (n = 135) and was characterised by generally lower apathy. Using dimension cut-offs (Radakovic *et al.,* 2022), around 13% of participants were impaired on the Initiation dimension. Cluster 2 (n = 32) displayed higher scores on Executive and Initiation dimensions, with up to 50% of patients impaired on these apathy subtypes. *Post-hoc* tests showed that Cluster 2 had significantly higher AES compared to Cluster 1 ($p < 0.001$), was more depressed on the GDS-30 ($p = 0.003$), and had greater disability as measured with the mRS ($p = 0.003$). No significant differences were found on other variables.

Figure 10. 6 months self-rated clusters based on LCA of DAS subscale scores



At 6 months, the comparison of different models based on informant-rated scores showed that a model "EEV" (ellipsoidal, equal volume and shape) supporting a 2-class solution yielded a best fitting model with a BIC value of -772.6. The second best model was "VEV" (ellipsoidal, varying volume, equal shape, varying orientation) with 2-classes, presenting with a BIC value of -773.0. This was a 0.4 point difference from the first model. The ICL criterion supported 2-class solution "EEV" model with a ICL value of -782.4. A one-way MANOVA showed a significant difference between the DAS subscales, supporting 2-class solution ($F(3, 89) = 63.10$, $p < 0.001$; Wilk's $\Lambda = 0$, partial $\eta 2 = 0.7$). Figure 11 shows the profiles of the two DAS groups. Cluster 2 was the largest (n = 75) and was characterised by generally lower apathy. Using dimension cut-offs (Radakovic *et al.,* 2022), less than 10% of participants were impaired on Emotional and Initiation dimensions. Cluster 1 (n = 18) displayed higher scores on every dimension, with up to 39% impaired on the Executive dimension. *Post-hoc* tests showed that Cluster 1 had significantly higher AES and GDS-30 compared to the other cluster ($p < 0.001$; $p = 0.047$).

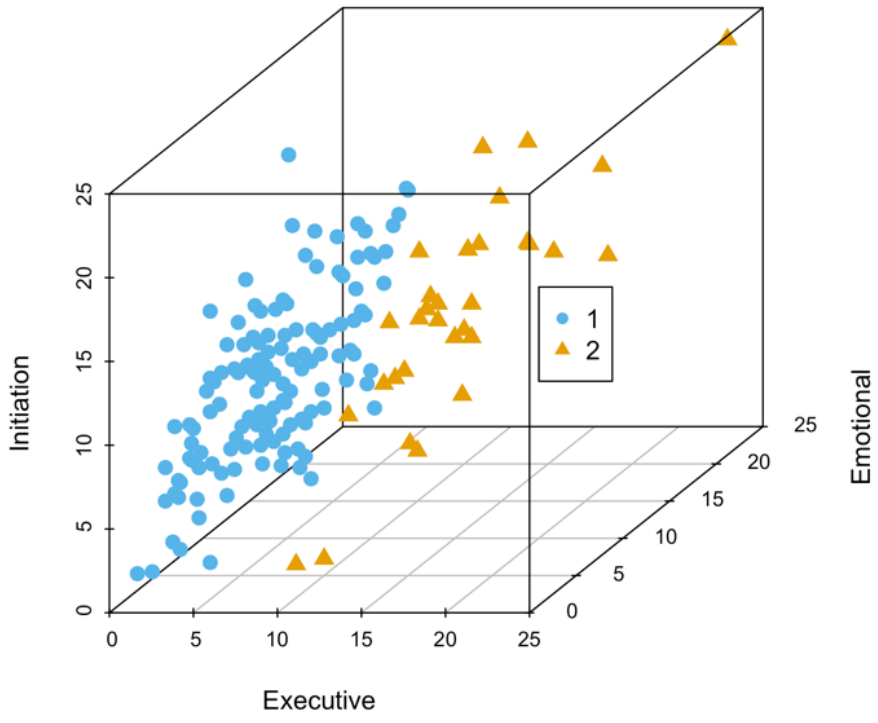
Figure 11. 6 months informant-rated clusters based on LCA of DAS subscale scores



Apathy profiles at 12 months

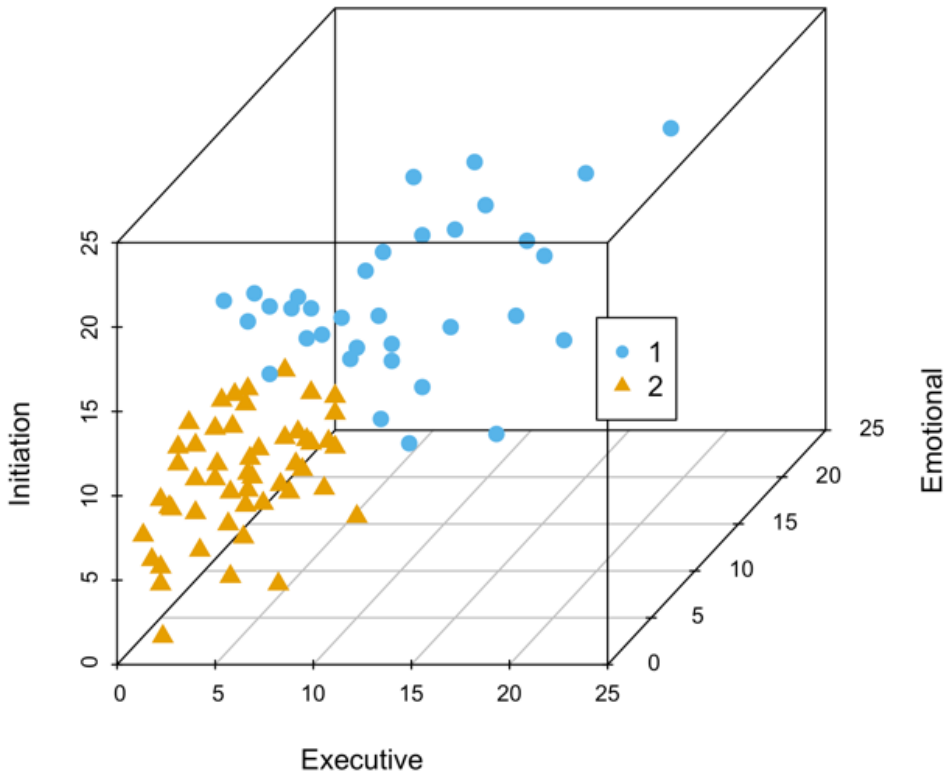
At 12 months, the comparison of different models based on self-rated scores showed that a model "EEE" (ellipsoidal, equal volume, shape and orientation) supporting a 2-class solution yielded a best fitting model with a BIC value of -1340.3. The second best model was "VEE" (ellipsoidal, equal shape and orientation) with 2-classes, presenting with a BIC value of -1343.1. This was a 2.8 point difference from the first model. The ICL criterion supported 2-class solution "EEE" model with a ICL value of -1352.4. A one-way MANOVA showed a significant difference between the DAS subscales, supporting 2-class solution ($F(3, 161) = 111.6$, $p < 0.001$; Wilk's $\Lambda = 0$, partial $\eta 2 = 0.7$). Figure 12 shows the profiles of the two DAS groups. Cluster 1 was the largest (n = 133) and was characterised by generally lower apathy. Using dimension cut-offs (Radakovic *et al.,* 2022), around 11% of participants were impaired on the Initiation dimension. Cluster 2 (n = 32) displayed higher scores on every dimension, with up to 75% impaired on the Executive dimension. *Post-hoc* tests showed that Cluster 2 was more depressed compared to Cluster 1 ($p < 0.001$), had significantly higher AES compared to the other cluster ($p < 0.001$), and had greater disability as measured with the mRS ($p < 0.001$). No significant differences were found on other variables.

Figure 12. 12 months self-rated clusters based on LCA of DAS subscale scores



At 12 months, the comparison of different models based on informant-rated scores showed that a model "VII" (spherical, varying volume) supporting a 2-class solution yielded a best fitting model with a BIC value of -721.8. The second best model was "VEI" (diagonal, varying volume, equal shape) with 2-classes, presenting with a BIC value of -724.3. This was a 2.5 point difference from the first model. The ICL criterion supported 2-class solution "EEE" model with a ICL value of -740.5. A one-way MANOVA showed a significant difference between the DAS subscales, supporting 2-class solution ($F(3, 84) = 56.78$, $p < 0.001$; Wilk's $\Lambda = 0$, partial $\eta 2 = 0.7$). Figure 13 shows the profiles of the two DAS groups. Cluster 2 was the largest (n = 54) and was characterised by generally lower apathy. Using dimension cut-offs (Radakovic *et al.,* 2022), no participants were impaired on the three dimensions. Cluster 1 (n = 34) displayed higher scores on every dimension, with up to 44% impaired on the Initiation dimension. *Post-hoc* tests showed that Cluster 1 had significantly higher AES compared to the other cluster ($p < 0.001$).

Figure 13. 12 months informant-rated clusters based on LCA of DAS subscale scores



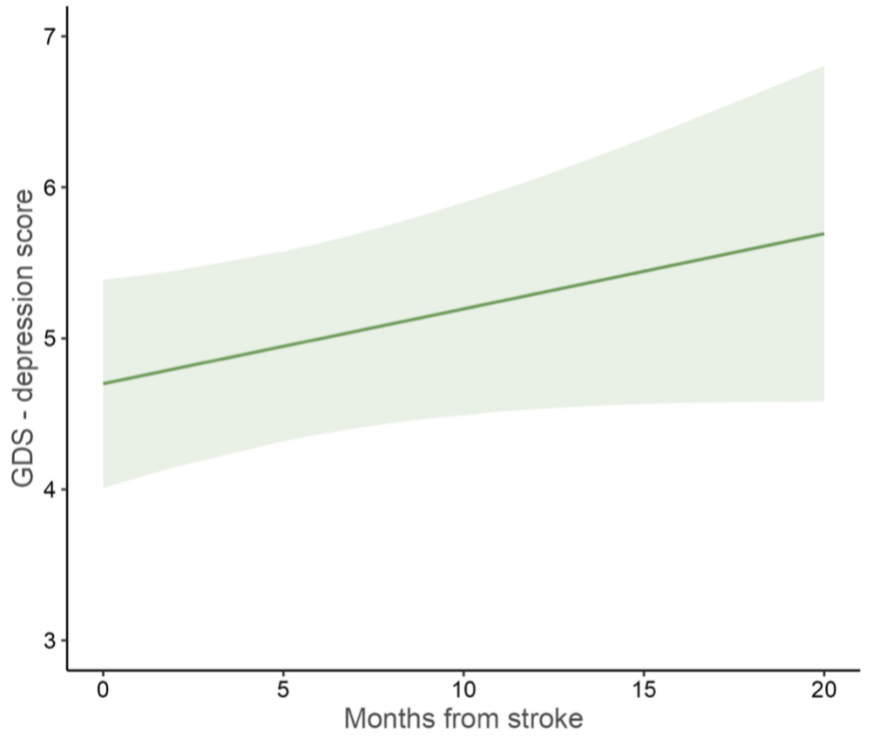
4.2.2 Association of apathy and depression

At baseline, 29.3% participants had depression (based on GDS-30) and 66.7% of apathetic patients displayed co-occurring depression. The overlap between apathy and depression was significant at baseline (OR = 5.56, 95% CI 2.15, 15.76). At 12 months, 23.7% scored above the GDS-30 cut-off and 70.3% of apathetic individuals had co-occurring depression. The overlap between apathy and depression was significant (OR = 12.04, 95% CI 5.25, 29.48).

When looking at longitudinal changes of depression scores, there was no evidence of the effect of months after stroke on GDS-24 scores ($\beta = 0.05$, 95% CI [-0.00, 0.1], $p = 0.101$). Figure 14 shows the predicted mean of GDS-24 over time.

GDS-24ubscore was positively associated with both self- and informant-rated DAS Executive ($t(171) = 12.55$, $p < 0.001$; $t(89) = 4.38$, $p < 0.001$) and Initiation ($t(171) = 4.95$, $p < 0.001$; $t(89) = 3.73$, $p < 0.001$). All the associations remained significant after including co-variates. Neither the self- nor the informant-rated version of the DAS Emotional were significant ($t(171) = 0.19$, $p = 0.848$; $t(89) = 1.12$, $p = 0.266$).

Figure 14. Trajectories of GDS-24 after stroke



Predicted values of GDS-24 (Geriatric Depression Scale – depression subscore) are shown in the plot with a solid green line. Confidence intervals are presented in light green.

4.3 Discussion

A better characterisation of apathy symptom presentation in stroke was obtained through latent class analysis in this prospective longitudinal study. This allowed the identification of different groups of stroke patients based on their scores on the three DAS dimensions. Depending on the time point after apathy and on the rater, latent class analysis identified different clusters.

In particular, at baseline no clusters were identified when considering self-rated scores. Informant-rated scores however identified three groups with increasingly higher level of apathy, from completely non-apathetic to severely apathetic in every dimension. In particular, the largest cluster was characterised by low apathy scores, with no participants impaired on any of the three dimensions. A second group showed impairment on the Emotional and Initiation dimensions, whereas the smallest group showed distinctly higher apathy scores in all dimensions, with up to 70% impaired on the Initiation dimension. The apathetic group was also significantly more depressed.

At 30 days, the optimal model was represented by two clusters: the largest one had lower apathy scores and the smaller one was more apathetic on every DAS dimension, regardless of whether the scores were self- or informant-rated. Using DAS dimension cut-offs, analyses on self-rated scores showed that some patients in the largest cluster were impaired on the Emotional and Initiation dimensions, despite having lower apathy scores. On the other hand, almost a third of patients in the smaller group were impaired on Executive and Initiation. Clusters obtained from informant-rated scores revealed that in both groups participants scored below the cut-off on the Initiation dimension.

Models at 6 months identified two clusters: as observed in previous time points, the largest group had generally lower apathy scores in every dimension, with only 10-13% impaired on the Initiation dimension. The smallest cluster, on the other hand, was characterised by higher apathy scores: up to 50% of the cluster obtained from self-rated scores was impaired on the Executive and Initiation dimensions. Similarly, the apathetic cluster identified from informant-rated scores revealed that up to 39% scored below the cut-off on the Executive dimension. The cluster presenting with more apathy was also more depressed and had greater disability when considering the informant-rated version of the test.

Analyses at 12 months identified similar subtypes of apathy presentation. For self-rated scores, the largest group with lower apathy scores had around 11% of participants impaired on the Initiation dimension, while most of the patients in the apathy group scored were impaired on the Executive dimension. Similarly to what observed at baseline and 30 days, almost half of participants in the group with higher apathy level was impaired on the Initiation dimension when considering informant-rated scores.

Generally, the study cohort seems to be characterised by a larger group of patients with lower apathy scores and a smaller group with higher scores on every DAS dimension. While analyses showed different characterisation of groups at the three timepoints considered, the majority of participants in the apathy group seemed to be impaired on the Initiation dimension. While a significant increase in apathy on this dimension could not be observed on longitudinal analyses, as showed in Chapter 3, the current findings seem to suggest that apathetic stroke survivors

mostly lack motivation for self-generation of thoughts or action, as measured by the DAS Initiation dimension (Radakovic and Abrahams, 2014). Interestingly, excluding associations between apathy and depression observed at different timepoints, no differences in clinical characteristics were observed between groups with higher and lower apathy scores.

A possible factor determining the belonging to these groups might be represented by the general level of apathy severity: as previously noted, in most cases these analyses revealed a smaller group of patients with higher apathy scores in every dimension. It could be argued that these findings might be exclusively due to patients presenting with more severe apathy. In a clinical setting, these results might also indicate that different dimension presentations can only be observed and measured in patients with similar levels of apathy as found in this study, making it difficult to generalise findings to patients with lower apathy levels. Future studies should replicate these analyses in a larger group of stroke patients to analyse the possible impact of apathy severity. This might help to identify more clearly the stratification of apathy dimension presentation based on overall apathy severity.

The type of modelling employed for these analyses allows a better characterisation of *post*-stroke apathy that takes into consideration subgroups variability. Impairment in one or more dimensions might be explained by different neurobiological mechanisms, such as lesions to brain areas or networks primarily responsible for each apathy dimensions. More studies are needed to combine this type of modelling with neuroimaging techniques that will allow a better understanding of neurobiological bases of apathy dimensions.

Identifying apathy subtype presentation holds clinical relevance: understanding the nature of apathy presentation in stroke patients might help with more accurate diagnosis. Understanding the pattern of symptoms might also provide with better interventions that are targeted at the specific dimensions affected in stroke instead of general apathy.

In the current study, depression was more common at baseline than 12 months and comorbidity with apathy was high at both time points. Moreover, when looking at longitudinal changes, depression scores did not significantly change over one year after stroke. These results are in line

with what previously described in literature, with studies showing that recovery from depression is high in stroke patients, despite presenting with heterogeneous recovery patterns (Dong *et al.,* 2021; Sagen-Vik *et al.,* 2022). The trajectory of *post*-stroke depression, therefore, appears to differ from that of apathy, as described in Chapter 3. Overall, these findings seem to confirm that apathy and depression have distinct prevalence rates, trajectories, and recovery rates (Hama *et al.,* 2007; Withall *et al.,* 2011).

Analysis looking at the relationship between depression and apathy dimensions found that greater Executive and Initiation apathy was associated with greater depression. However, the same relationship was not found with the Emotional dimension, confirming that apathy is characterized by neutral rather than low mood (Radakovic *et al.,* 2014; Tay *et al.*, 2021).

In conclusion, different patterns of apathy symptoms were identified in this study; these might help identify symptom presentation and impairment at different time points after stroke. The co-occurrence of apathy and depression was high in this cohort, despite depression scores remaining stable over time. In this study, patients with greater executive and initiation apathy generally presented with higher levels of depression.

Chapter 5: Effect of apathy on quality of life, disability, and cognition

Apathy in stroke has been associated with worse functional outcome, greater disability, and decreased Quality of Life (QOL) (Jorge *et al.,* 2010; Lopatkiewicz *et al.,* 2021). Basic activities of daily living, such as dressing, bathing, and eating, are also negatively affected by apathy (Santa *et al.,* 2008; van Dalen *et al.,* 2013). Generally, a slower functional recovery is observed in stroke patients with greater apathy over time (Matsuzaki *et al.,* 2015). The effect of apathy on outcome and recovery could, in turn, negatively affect physical and psychological rehabilitation, as decreased motivation could reduce engagement in rehabilitation activities (Hama *et al.,* 2011). Understanding the relationship between *post*-stroke apathy, disability, and outcome is important not only to clarify the mechanisms of motivational deficits, but also to plan optimal rehabilitation approaches.

Apathy is also associated with cognitive deficits and general worse cognitive functioning (van Dalen *et al.,* 2013). A systematic review reported that stroke patients with apathy scored 2.7 points lower in the Mini-Mental State Examination than non-apathetic patients (van Dalen *et al.,* 2013). Significant associations between apathy symptoms and reduced performance in tests of specific cognitive functions were also found in people with stroke. In particular, apathy seems to be associated with impairment in verbal learning, short- and long-term verbal recall, semantic fluency, abstract reasoning, attention, and concentration (Brodaty *et al.,* 2005; Caeiro *et al.,* 2013; Fishman *et al.,* 2018; Fishman *et al.,* 2019). Cognitive impairment itself may have an impact on functional outcome and specifically affect instrumental activities of daily living, such as cooking, cleaning, and managing finances (Brodaty *et al.,* 2005; Castellanos-Pinedo *et al.,* 2011). Other studies found that apathy is associated with higher risk of incident dementia, suggesting that it might be a prodromal symptom of vascular dementia (Onoda *et al.,* 2011; Tay *et al.,* 2020b).

As previously mentioned, a further complication in interpreting these results is the overlap of some symptoms between depression and apathy. Recent studies show that while patients may share some symptoms, the two are dissociable syndromes. In the context of stroke, they have

distinct prevalence rates, clinical phenotypes, neuroimaging correlates, and responses to treatment (Hollocks *et al.,* 2015; Matsuzaki *et al.,* 2015; Tay *et al.,* 2021; Tay *et al.,* 2023). Moreover, apathy and depression are reported to have different effects on outcome, disability, and cognition (Hama *et al.,* 2007; Matsuzaki *et al.,* 2015; Fishman *et al.,* 2018; Fishman *et al.,* 2019; Tay *et al.,* 2020a).

The goals here were to determine the association of apathy and depression with disability and quality of life. To do this, linear regression models were used to estimate the association between apathy scores soon after stroke, and QOL and disability at one year. Every apathy measure collected in the Apathy and Outcome after Stroke study was used in these analyses (AES self-rated, AES informant-rated, DAS self-rated, DAS informant-rated scores). QOL was measured with the Physical (SF36-PCS) and Mental Component Summary (SF36-MCS) scores obtained from the SF-36 (Ware and Sherbourne, 1992). The modified Rankin Scale (mRS) was used as a measure of disability at one year. Similar analyses were conducted with the depression subscale of the Geriatric Depression Scale (GDS-24) as a measure of depression.

Finally, the relationship of apathy and depression with cognition one year after stroke was investigated. Linear regression analyses were used to determine whether apathy scores at 30 days were associated with cognitive scores at one year. Global cognition was assessed with the Montreal Cognitive Assessment (MoCA) and the Brief Memory and Executive Test (BMET).

5.1 Methods

Study sample

The data analysed in this chapter was collected from the Apathy and Outcome after Stroke Study: 200 patients with ischaemic stroke were recruited and their mood and outcome measured at four time points over one year after stroke. Details of the study are reported in Chapter 2.

Measures

As previously described, the mRS is an instrument commonly employed in stroke survivors to measure the degree of disability or dependence in daily activities (Farrell *et al.,* 1991). The scale

scores indicate progressively greater disability, ranging from 0 (no disability or symptoms), to 6 (the individual is deceased).

The SF-36 is a self-report measure of health and quality of life, investigating physical health, social functioning, and mental health (Ware and Sherbourne, 1992). Each section of the test results in a score ranging from 0 to 100 – with higher scores reflecting better health. Mental Component Summary (MCS) and Physical Component Summary (PCS) scores are derived through aggregating scores of the eight subscales of the test. MCS and PCS are calculated by first obtaining z-scores from the subscales, multiplying these by the factor score of each summary score, and finally calculating T-scores (Taft *et al.,* 2001). The obtained T-scores were used in all the following analyses.

Depression was measured with the Geriatric Depression Scale (GDS) (Yesavage *et al.*, 1982). In particular, the GDS-24, that is the subscale identifying depression, was used here: this is a 24-item scale where higher scores indicate increasing levels of depression (Adams *et al.*, 2004). Cognition was assessed with the Montreal Cognitive Assessment (MoCA) (Nasreddine *et al.*, 2005) and the Brief Memory and Executive Test (BMET) (Brookes *et al.*, 2012). MoCA is a test of global cognition and appears to be more sensitive in assessing cognitive impairment than the Mini Mental State Examination in stroke patients (Dong *et al.*, 2010). The total possible score on this test is 30.

The BMET is a screening test to assess cognitive impairment in small vessel disease that includes tests of memory (immediate and delayed recall), space and time orientation, executive functions, and processing speed. Raw scores on the 8 subtests were recoded on a 0 to 2 scale based on normative age group data and thresholding. These were then used to generate the total score, ranging from 0 to 16 and describing the overall degree of cognitive impairment. A cut-off of ≤ 13 on the total score is used to define cognitive impairment. Two cognitive dimension scores were then identified by summing specific subtest scores. The executive functioning and processing speed category, from here on described as BMET-executive, included: letter-number matching, motor sequencing, letter sequencing, and number-letter sequencing. This dimension was specifically designed to be sensitive to the effects of SVD (Brookes *et al.,* 2015). The

orientation and memory category (BMET-orientation) was obtained by incorporating: orientation, 5-item repetition, 5-item recall, and 5-item recognition memory. Each subtest scores can range from 0 to 8. This dimension aids in discriminating stroke from other patient groups (Brookes *et al.,* 2012).

Association of apathy with Quality of Life and disability

Linear regression analyses were used to estimate whether apathy scores at 30 days (AES self-rated, AES informant-rated, DAS self-rated total, DAS informant-rated total, DAS self-rated and informant-rated Executive, Emotional, Initiation scores) were associated with QOL and disability at 12 months after stroke (SF36-MCS, SF-36-PCS, and mRS scores). Scores at 30 days were considered in the current analysis instead of baseline scores since the latter were deemed too close to the acute stage of stroke to accurately represent participants apathy: at this time, the presentation of apathy symptoms might be affected by external situations, such as being hospitalised. Assessing apathy at 30 days, on the other hand, might allow to better capture behaviours and mood relating to apathy. Participants who did not complete apathy measures at 30 days or SF-36 or mRS at 12 months were excluded from analysis. All outcome variables were standardized and analyses were controlled for age, sex, years of education, MoCA total score at baseline, NIHSS, acute infarct volume, and WMH volume. A *post*-hoc analysis was run to control the effect of depression (assessed with GDS-24 at 30 days) on the associations.

Association of depression with Quality of Life and disability

To assess whether depression predicts QOL and disability, the association between GDS-24 at 30 days and SF36-MCS, SF-36-PCS, and mRS scores 12 months after stroke was also estimated using linear regression analyses. Participants who did not complete GDS-24 at 30 days or SF-36 or mRS at 12 months were excluded from analysis. Analyses were adjusted for age, sex, years of education, MoCA total score at baseline, NIHSS, acute infarct volume, and WMH volume. A *post-hoc* analysis was run to control for the effect of apathy (measured with AES self-report score at 30 days) on the associations.

Apathy and cognition

The number of participants showing co-occurring apathy and cognitive impairment at baseline and 12 months was identified based on AES self-rated and MoCA cut-offs. Despite what explained above, here, baseline apathy scores were considered instead of those at 30 days: this decision was guided by the fact that no cognitive data was collected at 30 days, hence baseline apathy data was considered for completion with cognitive data. Odds ratios and 95% confidence intervals were calculated for apathetic and non-apathetic groups.

Furthermore, linear regression analyses were used to determine whether apathy scores at 30 days and 12 months were associated with cognitive scores at 12 months. As previously mentioned, scores at 30 days were considered in the current analysis instead of baseline scores since the latter were deemed too close to the acute stage of stroke to accurately represent participants apathy. Apathy measures included AES self-rated, AES informant-rated, DAS self-rated, DAS informant-rated scores. Cognitive scores included MoCA total score, BMET total score, BMET-executive, and BMET-orientation. Regression analyses were controlled for age, sex, and years of education.

Depression and cognition

To assess whether depression predicts cognition after stroke, the association of GDS-24 at 30 days and 12 months with cognitive scores at 12 months was estimated using linear regression models. Cognition was assessed with MoCA total score, BMET total score, BMET-executive, and BMET-orientation. Analyses were controlled for age, sex, and years of education.

5.2 Results

Association of apathy with Quality of Life and disability

Self-rated AES at 30 days was negatively associated with SF-36 MCS at 12 months ($t(142) = -5.27$, $p < 0.001$) (Table 6). This remained significant after adding co-variates to the model ($t(135) = -5.22$, $p < 0.001$), but not after including the GDS-24 in the model ($t(161) = -1.57$, $p = 0.119$). The informant rated version of AES at 30 days predicted SF-36 PCS at 12 months ($t(77) = -2.43$, $p = 0.017$), but was no longer significant after controlling for co-variates.

Self-rated DAS was negatively associated with both SF-36 MCS and SF-36 PCS ($t(145) = -5.24$, $p < 0.001$; $t(145) = -2.17$, $p = 0.031$). These were both significant after controlling for co-variates but lost significance when accounting for depression. Self-rated DAS Executive was negatively associated with both SF-36 MCS and SF-36 PCS ($t(145) = -7.33$, $p < 0.001$; $t(145) = -3.67$, $p < 0.001$, respectively). The association with SF-36 MCS was significant after including co-variates but no longer significant when including depression. On the other hand, the association with SF-36 PCS remained significant when including co-variates as well as GDS-24. Self-rated DAS Initiation was found to be significantly associated with SF-36 MCS ($t(145) = -3.28$, $p = 0.001$). The association was still significant after including co-variates, but no longer significant when controlling for depression.

DAS informant-rated was significantly negatively associated with SF-36 PCS ($t(78) = -2.24$, $p = 0.028$); however the association was no longer significant after including co-variates in the model. Informant-rated DAS Executive and Initiation both had a significant association with SF-36 PCS ($t(78) = -2.99$, $p = 0.004$; $t(78) = -2.14$, $p = 0.035$). While the Executive association remained significant after controlling for co-variates and depression, the association with Initiation lost significance after introducing co-variates in the model.

No associations were found between AES self-rated and SF-36 PCS, AES informant-rated and SF-36 MCS, DAS Emotional self-rated and SF-36, DAS Initiation self-rated and SF-36 PCS, DAS informant-rated and SF-36 MCS, DAS Executive self-rated and SF-36 MCS, DAS Emotional informant-rated and SF-36, DAS Initiation informant-rated and SF-36 MCS.

Both self-rated AES and DAS were positively associated with mRS at 12 months ($t(147) = 2.73$, $p = 0.007$; $t(150) = 3.26$, $p = 0.001$, respectively, Table 6). These remained significant after controlling for co-variates, but were no longer significant when including depression in the model. Self-rated DAS Executive and Initiation were positively associated with mRS at 12 months ($t(150) = 3.19$, $p = 0.002$; $t(150) = 2.76$, $p = 0.007$, respectively). Both associations remained significant when including co-variates in the model, but were no longer significant when including depression.

AES and DAS informant-rated were also positively associated with mRS (t(80) = 3.32, p = 0.001; t(81) = 3.77, p < 0.001). These remained significant after including co-variates but only DAS remained significant when controlling for depression. The effect of informant-rated DAS Executive and Initiation was statistically significant and positive (t(81) = 6.18, p < .001; t(81) = 3.83, p < 0.001). While DAS Executive remained significant after controlling for co-variates and depression, Initiation was no longer significant after including depression in the model. Self- and informant-rated DAS Emotional showed no significant associations with mRS at 12 months.

Table 6. Association of apathy scores at 30 days with QOL and disability at 12 months

	R^2	**DF**	**F**	***p*-value**	***p*-value***	***p*-value§**	**β**	**95%CI**
AES self-rated								
SF-36 MCS	0.16	1,142	27.76	< .001	< .001	.119	-0.55	-0.76, -0.34
SF-36 PCS	0.01	1,142	1.46	.230	.077	.922	-0.14	-0.36, 0.09
mRS	0.04	1,147	7.46	.007	.031	.246	0.03	0.00, 0.05
AES informant-rated								
SF-36 MCS	0.00	1,77	1.92	.170	.109	.799	-0.17	-0.42, 0.08
SF-36 PCS	0.06	1,77	5.92	.017	.099	.194	-0.32	-0.58, -0.06
mRS	0.11	1,80	11.05	.001	.005	.069	0.04	0.02, 0.06
DAS self-rated total								
SF-36 MCS	0.15	1,145	27.43	< .001	< .001	.216	-0.46	-0.64, -0.29
SF-36 PCS	0.02	1,145	4.71	.004	< .001	.104	-0.28	-0.46, -0.09
mRS	0.06	1,150	10.64	.001	.002	.164	0.03	0.01, 0.05
DAS self-rated Executive								
SF-36 MCS	0.27	1,145	53.70	< .001	< .001	.130	-1.29	-1.64, -0.94
SF-36 PCS	0.09	1,145	13.50	< .001	< .001	.001	-0.75	-1.15, -0.34
mRS	0.06	1,150	10.17	.002	.004	.420	0.06	0.02, 0.10
DAS self-rated Emotional								
SF-36 MCS	0.00	1,145	0.16	.694	.326	.342	-0.10	-0.60, 0.40
SF-36 PCS	0.09	1,145	13.50	< .001	< .001	.001	-0.75	-1.15, -0.34
mRS	0.06	1,150	10.17	.002	.004	.420	0.06	0.02, 0.10

Table 6 (continued).

	R^2	DF	F	*p*-value	*p*-value*	*p*-value§	β	95%CI
DAS self-rated Emotional								
SF-36 MCS	0.00	1,145	0.16	.694	.326	.342	-0.10	-0.60, 0.40
SF-36 PCS	0.00	1,145	0.56	.454	.183	.143	0.20	-0.32, 0.71
mRS	0.00	1,150	0.46	.497	.582	.615	0.02	-0.03, 0.07
DAS self-rated Initiation								
SF-36 MCS	0.07	1,145	10.73	.001	.004	.767	-0.61	-0.98, -0.24
SF-36 PCS	0.01	1,145	2.07	.152	.021	.182	-0.29	-0.68, 0.11
mRS	0.05	1,150	7.60	.006	.003	.055	0.05	0.01, 0.09
DAS informant-rated total								
SF-36 MCS	0.02	1,78	2.82	.097	.079	.962	-0.20	-0.44, 0.04
SF-36 PCS	0.05	1,78	5.00	.028	.069	.133	-0.27	-0.52, -0.03
mRS	0.14	1,81	14.18	< .001	< .001	.026	0.04	0.02, 0.06
DAS informant-rated Executive								
SF-36 MCS	0.05	1,78	3.84	.054	.060	.884	-0.58	-1.16, 0.00
SF-36 PCS	0.10	1,78	8.95	.004	.013	.028	-0.89	-1.49, -0.30
mRS	0.32	1,81	38.15	< .001	< .001	< .001	0.14	0.10, 0.19
DAS informant-rated Emotional								
SF-36 MCS	0.00	1,78	0.06	.809	.999	.478	0.08	-0.56, 0.71
SF-36 PCS	0.00	1,78	0.00	.955	.637	.489	0.02	-0.65, 0.68
mRS	0.01	1,81	1.13	.292	.610	.238	-0.03	-0.09, 0.03
DAS informant-rated Initiation								
SF-36 MCS	0.05	1,78	3.90	.052	.036	.446	-0.46	-0.93, 0.00
SF-36 PCS	0.06	1,78	4.59	.035	.094	.186	-0.52	-1.01, -0.04
mRS	0.15	1,81	14.64	< .001	< .001	.052	0.08	0.04, 0.12

P-values are shown before and after correcting for age, sex, years of education, MoCA total score at baseline, NIHSS, acute infarct volume, and WMH volume (*p*-value*). P-values are also shown after correcting for depression (GDS-24) (*p*-value§). Key: QOL, Quality of Life; AES, Apathy Evaluation Scale; SF-36 MCS, 36-Item Short Form Health Survey Mental Component Summary; SF-36 PCS, 36-Item Short Form Health Survey Physical Component Summary; mRS, Modified Rankin Scale; DAS; Dimensional Apathy Scale.

Association of depression with Quality of Life and disability

The GDS-24 was significantly, negatively associated with SF-36 MCS ($t(145) = -8.71$, $p < 0.001$), SF-36 PCS ($t(145) = -2.65$, $p = 0.009$), and mRS ($t(150) = 4.02$, $p < 0.001$) (Table 7). All associations remained significant when including co-variates and when controlling for apathy (AES self-report score).

Table 7. Association of GDS-24 at 30 days with QOL and disability at 12 months

	R^2	DF	F	*p*-value	*p*-value*	*p*-value§	β	95%CI
GDS-24								
SF-36 MCS	0.34	1,145	75.81	< .001	< .001	< .001	-1.53	-1.88, -1.18
SF-36 PCS	0.04	1,145	7.02	.009	.004	.016	-0.57	-0.99, -0.14
mRS	0.09	1,150	16.19	< .001	< .001	.006	0.08	0.04, 0.11

P-values are shown before and after correcting for age, sex, years of education, MoCA total score at baseline, NIHSS, acute infarct volume, and WMH volume (*p*-value*). P-values are also shown after correcting for apathy (AES self-rated at 30 days) (*p*-value§).

Key: GDS-24, Geriatric Depression Scale – depression subscore; QOL, Quality of Life; SF-36 MCS, 36-Item Short Form Health Survey Mental Component Summary; SF-36 PCS, 36-Item Short Form Health Survey Physical Component Summary; mRS, Modified Rankin Scale.

Apathy and cognition

At baseline, 97 (48.9%) participants scored below the cut-off on MoCA and 47.6% of apathetic individuals showed cognitive impairment. At 12 months, 63 (31.8%) individuals were impaired on MoCA and 42.4% of apathetic individuals had co-occurring cognitive impairment.

There was no overlap between patients who were apathetic and had cognitive impairment; at baseline (OR = 0.93, 95% CI 0.37, 2.35) or at 12 months (OR = 0.84, 95% CI 0.37, 1.83).

Table 8 shows the associations between apathy scores at 30 days and cognitive measures at 12 months. Self-rated DAS Emotional, informant-rated AES, DAS total, DAS Emotional, and DAS Initiation were all negatively associated with BMET orientation ($t(148) = -2.06$, $p = 0.042$; $t(81) = -2.43$, $p = 0.017$; $t(82) = -2.39$, $p = 0.019$; $t(82) = -2.71$, $p = 0.008$; $t(82) = -2.12$, $p = 0.037$). The associations were no longer significant after adding the co-variates to the model. Informant-rated DAS total at 30 days was negatively associated with BMET total ($t(82) = -2.22$, $p = 0.029$), however the association was no longer significant after controlling for co-variates. Informant-rated DAS Emotional was negatively associated with BMET total and BMET executive ($t(82) =$

-3.04, p = 0.003; t(82) = -2.95, p = 0.004, respectively). Every association remained significant after adding the co-variates to the model. Informant-rated DAS Initiation was negatively associated with MoCA (t(75) = -2.55, p = 0.013). After introducing co-variates to the models, the association remained significant.

At 12 months, both informant-rated AES and DAS were associated with BMET, with all but one (AES - BMET Executive) associations remaining significant after introducing co-variates in the model (Table 9). When looking at associations with informant-rated apathy dimensions, DAS Executive was associated with MoCA, BMET total and BMET orientation (t(74) = -2.57, p = 0.012; t(82) = -2.36, p = 0.021; t(82) = -3.26, p = 0.002). DAS Emotional was associated with BMET total, BMET executive, and BMET orientation (t(82) = -3.39, p = 0.001; t(82) = -3.04, p = 0.003; t(82) = -3.19, p = 0.002). DAS Initiation was associated with MoCA and BMET orientation (t(74) = -2.03, p = 0.046; t(82) = -2.62, p = 0.010). All the associations remained significant after controlling for co-variates. Self-rated AES was associated with BMET total and BMET orientation (t(158) = -2.14, p = 0.034; t(158) = -2.22, p = 0.028), although the second association was no longer significant after controlling for age, sex, and education. DAS self-rated total and Executive were associated with MoCA, BMET total and orientation (DAS total: t(149) = -3.04, p = 0.003; t(158) = -2.28, p = 0.024; t(158) = -2.43, p = 0.016. DAS Executive: t(149) = -2.97, p = 0.004; t(158) = -2.22, p = 0.028; t(158) = -2.39, p = 0.018), with only DAS total remaining significant after introducing co-variates in the models. While self-rated DAS Emotional was associated with MoCA (t(149) = -2.56, p = 0.011), no associations were found with Initiation.

Table 8. Association of apathy at 30 days with cognitive scores at 12 months

	R^2	**DF**	**F**	***p*-value**	***p*-value***	**β**	**95%CI**
AES self-rated							
MoCA total	0.00	1, 138	0.18	.675	.587	0.02	-0.06, 0.09
BMET total	0.01	1,146	1.18	.279	.140	-0.04	-0.12, 0.04
BMET-executive	0.01	1, 146	1.68	.197	.104	-0.03	-0.07, 0.01
BMET-orientation	0.00	1, 146	0.50	.480	.282	-0.02	-0.06, 0.03
AES informant-rated							

Table 8 (continued).

	R^2	DF	F	*p*-value	*p*-value*	β	95%CI
MoCA total	0.04	1, 74	2.70	.105	.167	-0.05	-0.13, 0.01
BMET total	0.04	1, 81	3.65	.060	.173	-0.10	-0.21, 0.00
BMET-executive	0.02	1, 81	1.31	.256	.422	-0.03	-0.09, 0.02
BMET-orientation	0.07	1, 81	5.91	.017	.083	-0.07	-0.13, -0.01
DAS self-rated total							
MoCA total	0.00	1, 140	0.47	.496	.771	-0.02	-0.09, 0.05
BMET total	0.00	1, 148	0.49	.483	.280	-0.03	-0.10, 0.05
BMET-executive	0.00	1, 148	0.38	.538	.347	-0.01	-0.05, 0.03
BMET-orientation	0.00	1, 148	0.45	.502	.335	-0.01	-0.05, 0.03
DAS self-rated Executive							
MoCA total	0.01	1, 140	0.73	.394	.630	-0.06	-0.20, 0.08
BMET total	0.00	1, 148	0.00	.944	.791	0.00	-0.14, 0.15
BMET-executive	0.00	1, 148	0.02	.901	.697	0.00	-0.08, 0.07
BMET-orientation	0.00	1, 148	0.06	.805	.922	0.01	-0.07, 0.09
DAS self-rated Emotional							
MoCA total	0.01	1, 140	1.59	.210	.343	-0.11	-0.28, 0.06
BMET total	0.02	1, 148	3.28	.072	.150	-0.16	-0.34, 0.01
BMET-executive	0.01	1, 148	1.60	.209	.308	-0.06	-0.16, 0.03
BMET-orientation	0.03	1, 148	4.22	.042	.107	-0.10	-0.20, 0.00
DAS self-rated Initiation							
MoCA total	0.00	1, 140	0.20	.659	.546	0.03	-0.10, 0.16
BMET total	0.00	1, 148	0.09	.953	.484	0.00	-0.14, 0.13
BMET-executive	0.00	1, 148	0.02	.902	.477	-0.01	-0.17, 0.15
BMET-orientation	0.00	1, 148	0.00	.989	.569	0.00	-0.07, 0.08
DAS informant-rated total							
MoCA total	0.03	1, 75	2.17	.145	.053	-0.05	-0.11, 0.02
BMET total	0.06	1, 82	4.92	.029	.075	-0.11	-0.20, -0.01
BMET-executive	0.04	1, 82	3.02	.086	.140	-0.04	-0.10, 0.00
BMET-orientation	0.07	1, 82	5.73	.019	.064	-0.06	-0.11, -0.01

Table 8 (continued).

	R^2	DF	F	*p*-value	*p*-value*	β	95%CI
DAS informant-rated Executive							
MoCA total	0.00	1, 75	0.37	.545	.539	-0.05	-0.21, 0.11
BMET total	0.00	1, 82	0.07	.787	.962	-0.03	-0.28, 0.21
BMET-executive	0.00	1, 82	0.05	.820	.730	0.01	-0.11, 0.14
BMET-orientation	0.00	1, 82	0.52	.471	.661	-0.08	-0.18, 0.08
DAS informant-rated Emotional							
MoCA total	0.00	1, 75	0.01	.933	.415	0.00	-0.17, 0.19
BMET total	0.10	1, 82	9.27	.003	.011	-0.38	-0.63, -0.13
BMET-executive	0.10	1, 82	8.72	.004	.009	-0.20	-0.33, -0.06
BMET-orientation	0.08	1, 82	7.32	.008	.035	-0.18	-0.32, -0.05
DAS informant-rated Initiation							
MoCA total	0.08	1, 75	6.52	.013	.006	-0.16	-0.28, -0.03
BMET total	0.04	1, 82	3.71	.057	.092	-0.18	-0.37, 0.00
BMET-executive	0.03	1, 82	2.18	.144	.178	-0.08	-0.18, 0.03
BMET-orientation	0.05	1, 82	5.49	.037	.073	-0.11	-0.21, -0.01

P-values are shown before and after correcting for age, sex, and years of education (*p*-value*).
Key: AES, Apathy Evaluation Scale; MoCA, Montreal Cognitive Assessment; BMET, Brief Memory and Executive Test; DAS, Dimensional Apathy Scale.

Table 9. Association of apathy and cognitive scores at 12 months

	R^2	DF	F	*p*-value	*p*-value*	β	95%CI
AES self-rated							
MoCA total	0.02	1, 149	2.60	.109	.726	-0.05	-0.12, 0.01
BMET total	0.03	1, 158	4.57	.034	.044	-0.07	-0.14, 0.00
BMET-executive	0.02	1, 158	2.88	.092	.060	-0.03	-0.07, 0.00
BMET-orientation	0.03	1, 158	4.92	.028	.072	-0.04	-0.08, 0.00
AES informant-rated							
	R^2	DF	F	*p*-value	*p*-value*	β	95%CI
MoCA total	0.03	1, 74	2.40	.126	.112	-0.08	-0.18, -0.02
BMET total	0.11	1, 82	10.11	.002	.004	-0.16	-0.27, -0.06
BMET-executive	0.05	1, 82	3.88	.052	.066	-0.06	-0.11, 0.00
BMET-orientation	0.16	1, 82	15.45	< .001	< .001	-0.11	-0.16, -0.05

Table 9 (continued).

	R^2	DF	F	*p*-value	*p*-value*	β	95%CI
DAS self-rated total							
MoCA total	0.06	1, 149	9.27	.003	.041	-0.09	-0.14, -0.03
BMET total	0.03	1, 158	5.21	.024	.031	-0.07	-0.13, 0.00
BMET-executive	0.02	1, 158	3.05	.083	.058	-0.03	-0.06, 0.00
BMET-orientation	0.04	1, 158	5.90	.016	.040	-0.04	-0.07, 0.00
DAS self-rated Executive							
MoCA total	0.06	1, 149	8.79	.004	.074	-0.17	-0.29, -0.06
BMET total	0.03	1, 158	4.93	.028	.050	-0.14	-0.26, -0.02
BMET-executive	0.02	1, 158	2.81	.095	.097	-0.06	-0.12, 0.00
BMET-orientation	0.03	1, 158	5.70	.018	.052	-0.08	-0.15, -0.01
DAS self-rated Emotional							
MoCA total	0.04	1, 149	6.56	.011	.027	-0.20	-0.35, -0.05
BMET total	0.01	1, 158	2.03	.156	.226	-0.12	-0.29, 0.05
BMET-executive	0.01	1, 158	1.17	.281	.277	-0.05	-0.14, 0.04
BMET-orientation	0.01	1, 158	2.34	.128	.255	-0.07	-0.16, 0.02
DAS self-rated Initiation							
MoCA total	0.01	1, 49	1.82	.179	.448	-0.08	-0.21, 0.04
BMET total	0.01	1, 158	2.01	.158	.105	-0.09	-0.27, 0.04
BMET-executive	0.01	1, 158	1.27	.261	.141	-0.04	-0.11, 0.03
BMET-orientation	0.01	1, 158	2.17	.143	.133	-0.05	-0.13, 0.02
DAS informant-rated total							
MoCA total	0.05	1, 74	3.86	.053	.025	-0.08	-0.16, 0.00
BMET total	0.11	1, 82	10.35	.002	.003	-0.13	-0.21, -0.05
BMET-executive	0.05	1, 82	4.14	.045	.049	-0.05	-0.09, 0.00
BMET-orientation	0.16	1, 82	15.44	< .001	< .001	-0.09	-0.13, -0.04
DAS informant-rated Executive							
MoCA total	0.08	1, 74	6.60	.012	.005	-0.23	-0.40, -0.05
BMET total	0.06	1, 82	5.55	.021	.015	-0.23	-0.42, -0.04
BMET-executive	0.02	1, 82	1.27	.263	.195	-0.06	-0.16, 0.05
BMET-orientation	0.11	1, 82	10.64	.002	.001	-0.17	-0.27, -0.07

Table 9 (continued).

	R^2	DF	F	*p*-value	*p*-value*	β	95%CI
DAS informant-rated Emotional							
MoCA total	0.02	1, 74	0.20	.660	.747	0.06	-0.19, 0.31
BMET total	0.12	1, 82	11.50	.001	.003	-0.36	-0.57, -0.15
BMET-executive	0.10	1, 82	9.22	.003	.004	-0.17	-0.28, -0.06
BMET-orientation	0.11	1, 82	10.18	.002	.009	-0.19	-0.30, -0.07
DAS informant-rated Initiation							
MoCA total	0.05	1, 74	4.11	.005	.031	-0.18	-0.35, 0.00
BMET total	0.04	1, 82	3.60	.061	.088	-0.18	-0.36, 0.00
BMET-executive	0.01	1, 82	0.81	.372	.427	-0.04	-0.14, 0.05
BMET-orientation	0.07	1, 82	6.87	.010	.018	-0.13	-0.23, -0.03

P-values are shown before and after correcting for age, sex, and years of education (*p*-value*). Key: AES, Apathy Evaluation Scale; MoCA, Montreal Cognitive Assessment; BMET, Brief Memory and Executive Test; DAS, Dimensional Apathy Scale.

Depression and cognition

At 12 months, GDS-24 was associated with MoCA (t(149) = -2.21, p = 0.029), however the association was no longer significant when controlling for age, sex, and education (t(137) = -1.03, p = 0.304). There were no other significant associations of depression with cognitive scores at 12 months (Table 10).

Table 10. Association of depression with cognitive scores at 12 months

	R^2	DF	F	*p*-value	*p*-value*	β	95%CI
GDS-24 – 30 days							
MoCA total	0.00	1, 141	0.26	.611	.935	-0.04	-0.18, 0.11
BMET total	0.00	1, 149	0.01	.937	.755	-0.01	-0.16, 0.15
BMET-executive	0.00	1, 149	0.01	.924	.750	-0.01	-0.09, 0.08
BMET-orientation	0.00	1, 149	0.00	.960	.801	-0.01	-0.09, 0.08

Table 10 (continued).

	R^2	DF	F	*p*-value	*p*-value*	β	95%CI
GDS-24 - 12 months							
MoCA total	0.03	1, 149	4.88	.029	.305	-0.12	-0.22, -0.01
BMET total	0.01	1, 158	1.49	.224	.337	-0.07	-0.18, 0.04
BMET-executive	0.01	1, 158	0.82	.366	.445	-0.03	-0.09, 0.03
BMET-orientation	0.01	1, 158	1.77	.186	.218	-0.04	-0.10, 0.02

P-values are shown before and after correcting for age, sex, and years of education (*p*-value*).
Key: GDS-24, Geriatric Depression Scale – depression subscore; MoCA, Montreal Cognitive Assessment; BMET, Brief Memory and Executive Test; DAS, Dimensional Apathy Scale.

5.3 Discussion

It has been suggested that apathy relates to worse outcome, either by contributing to more severe neurological or cognitive deficit, and/or by impairing engagement with rehabilitation (Jorge *et al.,* 2010; Hama *et al.,* 2011). Of note, previous studies have suggested that both apathy and depression independently influence stroke outcome (Lopatkiewicz *et al.,* 2021; Matsuzaki *et al.,* 2015). Both AES and DAS as self-rated, and AES and DAS rated by informants were positively associated with mRS at 12 months. However, significance was reduced when depression was also entered with only the informant-rated DAS remaining significant. This raises the possibility that depressive symptoms may influence recovery, perhaps by impairing engagement with rehabilitation, either acting as a mediator of the association between apathy and disability, or representing a source of confounding.

Apathy was also associated with, and predicted, worse QOL one year after stroke. Significant associations were found between AES self-rated and the Mental Component of SF-36 and between the informant-rated version of AES and the Physical Component of SF-36. While the first association remained significant after adding co-variates to the model, the latter was no longer significant after controlling for co-variates. This suggested that depressive symptoms rather than apathy are likely to be more important in determining QOL for the stroke patient. Similar findings have been reported in other neurological conditions: for instance, studies investigating the presence and effect of depression in Alzheimer's and Parkinson's Disease have established a relationship between depression and QOL decline, making mood symptoms some of the most important variables in predicting lower quality of life (Barbe *et al.,* 2018; Su *et al.,* 2021). While the relationship between apathy and patient's quality of life has been investigated

in the current study, further studies are required to determine the effect of post-stroke apathy on carer quality of life which were not assessed here.

Post-stroke apathy is usually associated with cognitive deficits affecting both global cognition and specific domains, such as memory, processing speed, verbal learning, and semantic fluency (Caeiro *et al.,* 2013; Horne *et al.,* 2022; van Dalen *et al.,* 2013). In this study, almost half of apathy patients were impaired on the MoCA at baseline and 12 months. Interestingly, apathy rather than depression scores at 30 days seemed to predict worse cognitive functioning at 12 months. In particular, the informant-rated scores on the DAS Emotional and Initiation apathy seemed to predict lower scores on MoCA and BMET, including the orientation-memory and executive components. The GDS-24, on the other hand, did not significantly predict cognitive scores one year after stroke. Moreover, apathy measured at 12 months was associated with worse cognitive functioning, on both self- and informant-rated measures. On the other hand, depression at 12 months was associated with lower MoCA scores, however the association was no longer significant when controlling for co-variates such as age, sex, and education.

In this study, apathy seemed to predict worse cognitive functioning one year after stroke, however a causal relationship could not be established with the current methods. While apathy could contribute to worse cognitive deficits, as previously stated, it could be argued that more severe brain damage is associated with greater cognitive deficits, which in turn might bring about or worsen apathy symptoms. In particular, this might involve those aspects of apathy relating to executive functions and highlights the importance of choosing appropriate cognitive measures when evaluating apathy in neurological diseases. Further research should investigate the temporal and causal links between cognition and apathy, in order to better understand the direction of this association.

Taken together the results of this study seem to suggest that apathy rather than depression can be used as a predictor of cognitive functioning one year after stroke. Previous studies found that apathy is associated with a higher risk of incident dementia and that it may be a prodromal symptom of vascular dementia (Onoda *et al.,* 2011; Tay *et al.,* 2020b). These findings suggest that a timely and accurate assessment of apathy might therefore be informative for diagnosing

dementia. Further research is needed to investigate the inclusion of apathy in predictive models of vascular dementia and the relationship between apathy and dementia-related mortality.

As discussed in Chapter 3, a limitation to the results reported here is the multiple comparison problem, which might increase the likelihood of false positive results. This problem could be controlled by applying controls on the significance level or adopting a Bayesian approach (Lee and Lee, 2018; Sjölander and Vansteelandt, 2019).

Chapter 6: Association of apathy with lesion volume, lesion location, and disrupted structural networks

In order to clarify the neurobiological bases of apathy, attempts have been made to link symptoms to specific lesions or damage to brain regions, as described in Chapter 1. Levy and Dubois, for instance, attributed each category of symptom to specific and focal damaged brain regions in the prefrontal cortex and basal ganglia (Levy and Dubois, 2006). According to their model, emotional-affective symptoms would derive from damage to the orbito-medial prefrontal cortex and related regions. Cognitive symptoms would instead be mediated by the dorsolateral prefrontal cortex and related areas within the basal ganglia. Finally, auto-activation symptoms would be related to the internal segment of the globus pallidus. All these areas are traditionally believed to be core components of the goal-directed behaviour system (Levy and Dubois, 2006).

A different approach to the matter of neurobiological basis of apathy takes into consideration brain networks, hypothesizing that networks supporting goal-directed behaviour may be involved in the development of apathy symptoms. Tay and colleagues, for instance, suggest that network damage may produce a cascade of events eventually leading to apathy (Tay *et al.,* 2020a). According to this theory, *post*-stroke apathy would occur as a result of two phenomena: apathy can either be the consequence of a focal lesion affecting brain areas responsible for goal-directed behaviour, or of a peripheral lesion that would disrupt connections to these core areas. Focal ischaemic or haemorrhagic stroke would produce apathy because of damage occurring to the central areas of the network, whereas damage to white matter integrity might cause reduction or interruption of structural or functional connections. For instance, a 2019 study identified specific subnetworks that would be linked to apathy in Small Vessel Disease, comprising the parietal-premotor, occipitotemporal, and frontostriatal networks (Tay *et al.,* 2019).

Current findings seem to suggest that different types of stroke and cerebrovascular pathologies might be specifically associated with apathy symptoms through a variety of different mechanisms. However, questions regarding specific brain networks and regions involved in apathy syndrome remain unanswered and the novel models regarding apathy networks need to be further validated.

In the current study, I aimed at performing a comprehensive examination of neurobiological features of apathy in a cohort of ischaemic stroke patients, in an attempt to validate some of the theories reviewed above. In particular, this research had the following objectives:

1) Exploring the association between stroke type and apathy: one-way ANOVA and Kruskal-Wallis test were used to look at whether apathy symptoms were predicted by stroke type as defined by the TOAST classification (Adams *et al.,* 1993).
2) Analysing the relation of apathy symptoms with volume and location of acute infarct. Lesion volume was obtained with a semi-automatic drawing of lesion: this was then used in linear models to investigate the association with apathy scores at each time point. Acute infarct lesion maps were subjected to voxel-wise analysis to check for associations between lesioned areas and apathy scores. These analyses were performed for apathy scores at baseline and 12 months and were corrected for multiple comparisons.
3) Establishing whether an association between white-matter hyperintensity (WMH) and apathy exists: WMH volume was calculated with a semi-automatic process. Linear models were then used to explore the associations with apathy scores at each time point.
4) Checking the association between grey matter density in the brain and apathy scores: voxel-based morphometry was used here to assess whether apathy could be explained by a reduction in grey matter (GM). Two-sample t-tests were used to compare GM of apathetic and non-apathetic participants at baseline and 12 months.
5) Assessing the relation between disruption to white-matter networks and apathy, as well as replicating findings suggesting that damage to goal-directed behaviour networks would explain apathy symptoms. Two methods were used here. On the one hand, a white-matter (WM) atlas was used to identify the percentage of tracts affected by acute infarct and WMH lesions. On the other hand, tractography was performed on a healthy control dataset using lesion masks as seed. The resulting 'disconnected' maps were used in voxel-wise and region of interest (ROI) analyses with apathy scores at baseline and 12 months.

6.1 Methods

Study sample

The data analysed in this chapter was collected from the Apathy and Outcome after Stroke Study. Details of the study are reported in Chapter 2.
As previously described, an MRI scan of the brain was performed at baseline (2.1±2.9 days after stroke) as part of standard clinical care. T1, T2, T2*, T2-FLAIR, and DWI sequences were obtained. Scans were performed on a variety of scanners with different sequences. Resolution ranged from 0.94x0.94x4.40mm to 1.20x1.20x6.50mm for DWI images and from 0.47x0.47x5.20mm to 0.75x0.75x5.20mm for T2-FLAIR images. T1, DWI, and T2-FLAIR images were stripped of the skull using BET from the FSL software package (Smith *et al.,* 2002).

Association of apathy with stroke subtype

A one-way ANOVA or Kruskal-Wallis test was performed to compare the effect of TOAST classification on apathy scores. Analysis were repeated for AES self-rated, AES informant-rated, DAS self-rated, DAS informant-rated at baseline, 30 days, 6 months, and 12 months after stroke.

Association of apathy with acute infarct volume and white matter hyperintensity volume

Acute infarct and WMH lesions were identified for each participant with a semi-automatic drawing of lesions (Jim software, Xinapse Systems Limited) on DWI and T2-Flair scans, respectively. Lesion volumes were then calculated and raw volumes were transformed to z-scores to avoid scaling issues. Outliers were identified using the interquartile range (IQR) rule: the IQR was calculated and multiplied by 1.5, a constant used to discern outliers. The product was added to the third quartile and any score greater than this was considered an outlier and excluded. Similarly, the product was subtracted from the first quartile and any score less than this was excluded. Linear models were used to test associations with apathy (AES self-rated, AES informant-rated, DAS self-rated, DAS informant-rated) at baseline, 30 days, 6 months, and 12 months after stroke. Analyses were corrected for age and sex.

Voxel-based lesion symptom mapping

Acute infarct lesions masks were obtained from a semi-automatic drawing of lesions on DWI scans (Jim software, Xinapse Systems Limited). Lesion masks were registered to a common

space (the MNI152 standard space template) and binarised. Voxel-based lesion symptom mapping (VLSM) was conducted with the NiiStat software (https://www.nitrc.org/projects/niistat/) under MATLAB version R2019a (The MathWorks Inc., 2022). The analyses were conducted across the whole brain in voxels affected in at least 10% (n ≥ 16) of all participants. Voxels not affected by lesions were excluded from analysis. Statistical significance was set at $p < .05$ corrected for family-wise error (FWE) using Freedman-Lane permutation with 2000 permutations. The analysis was repeated by considering apathy scores on AES self-rated, AES informant-rated, DAS self- and informant-rated total score, DAS self- and informant-rated dimensions score, at baseline and 12 months after stroke. Participants who did not have an informant were excluded from analysis considering informant-rated AES and DAS.

Voxel-based morphometry

Brain tissue volume was estimated with SIENAX (Smith *et al.,* 2002), part of FSL (Smith *et al.,* 2004). Acute infarct lesions and WMH lesions were excluded from grey matter (GM) segments using Jim software (Xinapse Systems Limited) to obtain normal-appearing GM segment. Normal-appearing GM segments were then registered to the MNI152 standard space template. Voxel-based morphometry (VBM) analysis were conducted with the Statistical Parametric Mapping 12 tool (SPM12, Penny *et al.*, 2006) under MATLAB version R2019a (The MathWorks Inc., 2022). VBM involves creating spatially normalized images in which the intensity of each voxel relates to the local volume of a brain tissue, in this case GM. Two-sample t-tests were then used to compare GM of apathetic and non-apathetic participants. Statistical significance was set at $p < .05$ corrected for FWE. Analyses were repeated at baseline and 12 months considering every apathy test cut-off (AES self-rated, AES informant-rated, DAS self-rated, and DAS informant-rated) at baseline and 12 months. Participants who did not have an informant were excluded from the relevant analysis.

Apathy and disruption to white-matter networks

A white matter atlas was used to identify the percentage of tracts affected by lesions. The atlas by Catani and de Schotten (2008) was selected for this purpose. A list of tracts used for this analysis can be found in Box 1. A T1 scan from the cohort was selected as a template: the scan

was chosen as it represented the cohort mean GM, WM, and total brain volume. Atlas tracts were registered to the T1 template. Acute infarct masks and WMH lesion masks were transformed to the T1 template space, and the volume of tract affected by lesion was calculated as the overlap between lesions and tracts. Volumes were log transformed to account for skewed distributions and set to zero when < 10 mm^3. The association between apathy scores and volumes of affected tracts was explored with linear models. The full set of predictors was reduced to only include relevant predictors: Bayesian model selection was performed with the BAS package (Clyde, 2022) in R 4.2.3 (R Core Team, 2023). First, full models including all possible terms, *i.e*. every tract volume, were calculated. The Bayesian Information Criterion (BIC) was used to determine the optimal and simplified model with a reduced number of predictors, where a smaller BIC absolute value identified a better model. Once the relevant subset of predictors was identified, regression models were specified. All analyses were performed with apathy scores obtained at baseline and 12 months after stroke.

Box 1. List of tracts from the Catani and de Schotten atlas (2008) used in analysis

Anterior Commissure, Anterior Segment (Arcuate), Arcuate, Cingulum, Cortico Ponto Cerebellar, Corpus Callosum, Cortico Spinal, Fornix, Inferior Cerebellar Pedunculus, Inferior Longitudinal Fasciculus, Inferior Occipito Frontal Fasciculus, Internal Capsule, Long Segment (Arcuate), Optic Radiations, Posterior Segment (Arcuate), Superior Cerebellar Pedunculus, Uncinate.

Structural disconnectome mapping of apathy

To estimate the extent of structural disconnection, whole-brain tractography was performed on healthy control data. A subset of the CamCAN dataset (Shafto *et al.,* 2014) was selected based on matched age with our cohort (median age 57-75). A total of 185 CamCAN controls were identified: 4 were excluded for the presence of WMH and 1 was excluded for missing brain mask. For every participant, acute infarct lesions and WMH lesions were registered to each CamCAN control space. Probabilistic tractography was performed using acute infarct lesions and WMH as seeds with Probtrackx (Behrens *et al.,* 2007), as part of the FSL software (Smith *et al.,* 2004). The resulting tractograms were transformed to visitation maps, binarised, and registered to the FMRIB template. An overlap map was then produced by summing each point in the

normalised visitation maps. The resulting disconnectome maps indicated the probability that voxels were disconnected for each patient (Kolskår *et al.,* 2022). These 'disconnectome maps' were included in group-level analysis to investigate the association between structural dysconnectivity and apathy. Voxel-wise analyses were performed with the NiiStat software (https://www.nitrc.org/projects/niistat/) under MATLAB version R2019a (The MathWorks Inc., 2022), taking into account every apathy measure collected at baseline and 12 months. Only voxels affected in at least 10% ($n \geq 16$) of all participants were considered in the analysis. Statistical significance was set at $p < .05$ corrected for FWE using Freedman-Lane permutation with 2000 permutations. Region of interest (ROI) analysis was also performed with NiiStat, where the associations between apathy and the apathy subnetwork described by Tay were assessed (Tay *et al.,* 2019). A list of the areas considered in this analysis is presented in Box 2. Only voxels affected in at least 5% ($n \geq 8$) of participants were subjected to the analysis. The p-value was set at $< .05$ and was corrected for FWE using Freedman-Lane permutation with 2000 permutations.

Box 2. List of AAL areas used in ROI analysis

Anterior Cingulate Gyrus, Inferior Frontal Gyrus, Inferior Temporal Gyrus, Insula, Medial Superior Frontal Gyrus, Middle Cingulate Gyrus, Middle Occipital Gyrus, Middle Temporal Gyrus, Pallidum, Paracentral Lobule, Pericalcarine Cortex, Precuneus, Putamen, Superior Parietal Gyrus, Superior Temporal Gyrus, Supplementary Motor Area, Thalamus.

Key: AAL, Automated Anatomical Labeling (Tzourio-Mazoyer *et al.,* 2002).

6.2 Results

Figure 15 shows acute infarct lesion overlap in the whole sample. Figure 16 shows lesion overlap for apathetic and non-apathetic patients based on the self-rated AES cut-off at 30 days.

Figure 15. Lesion overlap of the whole sample (n = 200)

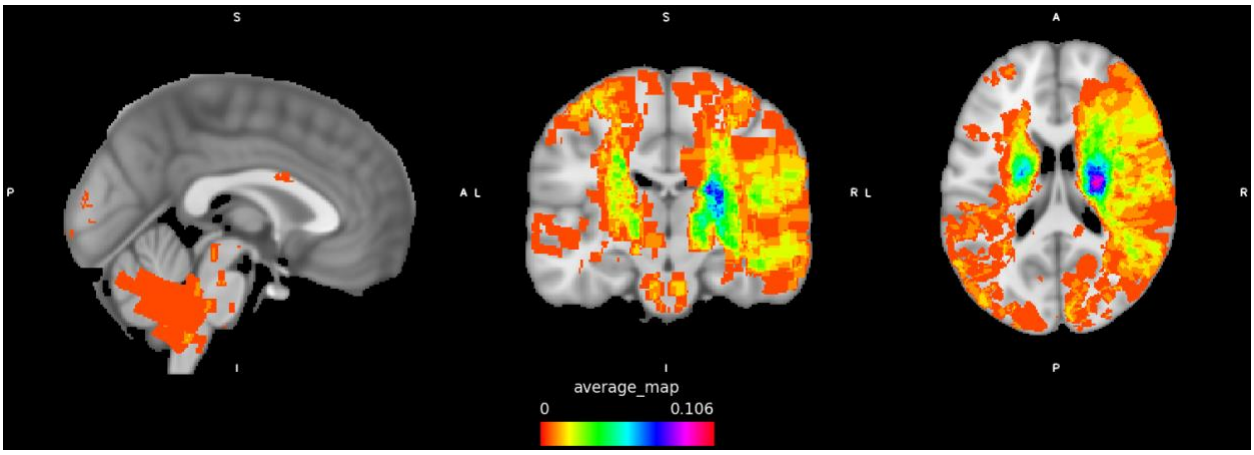
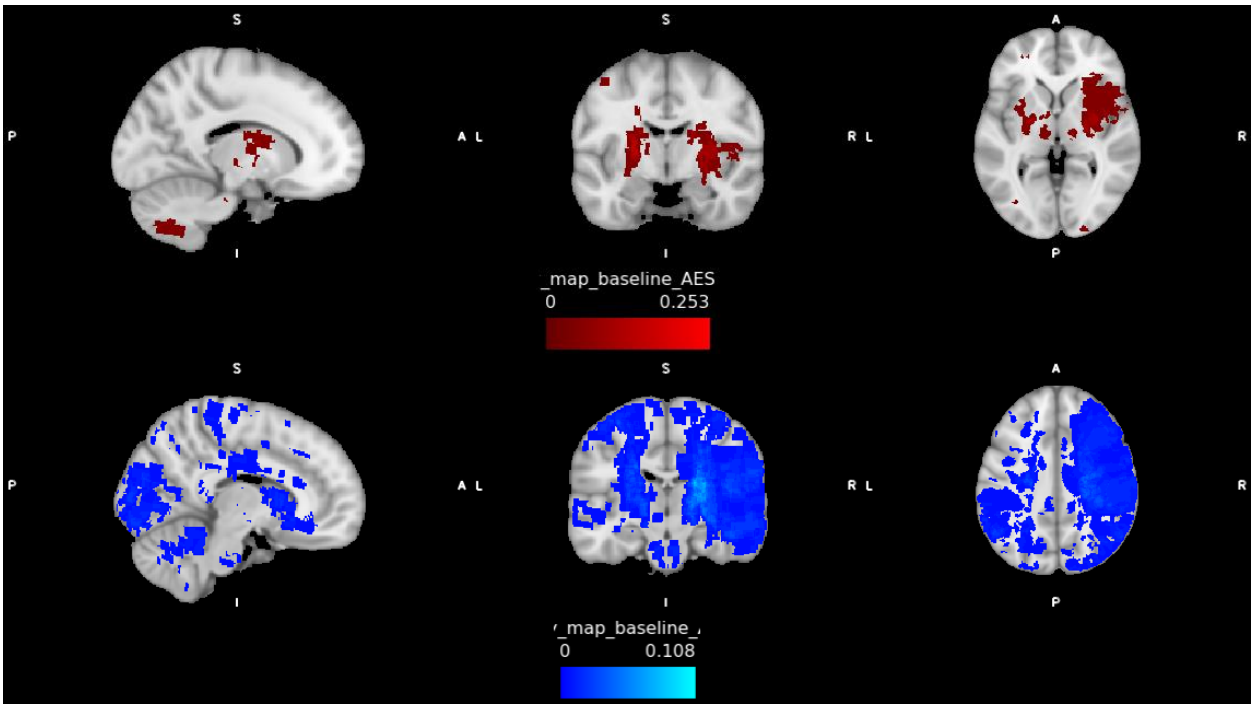


Figure 16. Lesion overlap of the apathetic group in red (n = 20) and non-apathetic group in blue (n = 178) at 30 days



Association of apathy with stroke subtype

A one-way ANOVA revealed that at baseline there was not a statistically significant difference in apathy scores between stroke subtypes when assessed with the TOAST classification (AES self-rated: $F(4, 190) = 0.368$, $p = 0.831$; AES informant-rated: $H(4) = 5.680$, $p = 0.225$; DAS self-rated: $H(4) = 4.188$, $p = 0.381$; DAS informant-rated: $H(4) = 4.981$, $p = 0.289$). Similarly,

analysis at 30 days found no significant differences in apathy scores based on stroke subtypes (AES self-rated: H(4) = 3.472, p = 0.482; AES informant-rated: H(4) = 3.965, p = 0.411; DAS self-rated: H(4) = 5.369, p = 0.252; DAS informant-rated: H(4) = 2.928, p = 0.570). At 6 months, no significant differences in apathy scores were found between stroke subtypes (AES self-rated: H(4) = 2.556, p = 0.635; AES informant-rated: F(4, 87) = 0.362, p = 0.835; DAS self-rated: F(4, 162) = 0.610, p = 0.656; DAS informant-rated: F(4, 89) = 0.371, p = 0.371). Similarly, no significant differences were found with apathy scores at 12 months (AES self-rated: H(4) = 2.510, p = 0.643; AES informant-rated: H(4) = 0.915, p = 0.922; DAS self-rated: H(4) = 5.819, p = 0.213; DAS informant-rated: H(4) = 1.424, p = 0.840).

Association of apathy with acute infarct volume and white matter hyperintensity volume

No significant associations of the different measures of apathy with acute infarct volume were found at baseline, 30 days, and 6 months (Table 11). Similarly, no significant associations of apathy measures with WMH volume were found at baseline, 30 days, and 6 months (Table 12). At 12-months, both the self- and informant-rated DAS were positively associated with WMH volume (β = 3.05, 95% CI [0.17, 5.93], t(140) = 2.09, p = 0.038; β = 5.51, 95% CI [0.62, 10.40], t(73) = 2.25, p = 0.028). While the self-rated scores were still significant when controlling for age and sex, the informant-rated DAS lost significance. Moreover, the informant-rated AES at 12 months was significantly associated with WMH (β = 4.73, 95% CI [0.95, 8.52], t(73) = 2.49, p = 0.015), even after introducing co-variates in the model.

Table 11. Association of apathy with acute infarct volume

	R^2	**DF**	**F**	***p*-value**	***p*-value***	**β**	**95%CI**
Baseline							
AES self-rated	0.00	1,167	0.11	.746	.537	-1.03	-7.30, 5.24
AES informant-rated	0.00	1,97	0.14	.704	.340	0.29	-1.24, 1.83
DAS self-rated	0.00	1,167	0.31	.579	.911	2.03	-5.19, 9.25
DAS informant-rated	0.02	1,96	1.70	.195	.102	1.11	-0.58, 2.81
30 days							
AES self-rated	0.00	1,146	0.01	.907	.551	-0.43	-7.75, 6.88
AES informant-rated	0.01	1,79	0.99	.321	.798	-1.64	-4.91, 1.63
DAS self-rated	0.00	1,146	0.29	.591	.813	2.09	-5.56, 9.73

Table 11 (continued).

	R^2	DF	F	*p*-value	*p*-value*	β	95%CI
DAS informant-rated	0.00	1,80	0.00	.949	.556	0.12	-3.53, 3.77
6 months							
AES self-rated	0.00	1,142	0.58	.447	.741	3.13	-4.98, 11,23
AES informant-rated	0.02	1,80	1.64	.205	.987	-1.75	-4.47, 0.97
DAS self-rated	0.01	1,142	1.64	.202	.378	5.85	-3.18, 14.88
DAS informant-rated	0.00	1,82	0.06	.805	.245	0.44	-3.12, 4.00
12 months							
AES self-rated	0.00	1,142	0.01	.926	.628	-0.42	-9.40, 8.56
AES informant-rated	0.00	1,73	0.00	.983	.723	0.09	-8.85, 9.04
DAS self-rated	0.00	1,142	0.62	.434	.603	4.01	-6.10, 14.13
DAS informant-rated	0.00	1,73	0.04	.844	.595	1.10	-10.02, 12.23

P-values are shown before and after correcting for age and sex (*p*-value*).
Key: AES, Apathy Evaluation Scale; DAS, Dimensional Apathy Scale.

Table 12. Association of apathy with white matter hyperintensity

	R^2	DF	F	*p*-value	*p*-value*	β	95%CI
Baseline							
AES self-rated	0.01	1,175	0.92	.340	.184	0.60	-0.64, 1.85
AES informant-rated	0.01	1,96	0.94	.335	.381	0.50	-0.52, 1.52
DAS self-rated	0.00	1,175	0.28	.599	.284	0.39	-1.07, 1.85
DAS informant-rated	0.01	1,97	0.56	.454	.430	0.44	-0.71, 1.58
30 days							
AES self-rated	0.00	1,146	0.36	.549	.932	-0.61	-2.60, 1.39
AES informant-rated	0.04	1,81	3.57	.062	.274	1.06	-0.06, 2.18
DAS self-rated	0.00	1,146	0.03	.853	.528	0.21	-2.05, 2.47
DAS informant-rated	0.02	1,82	1.37	.244	.318	0.73	-0.51, 1.96
6 months							
AES self-rated	0.01	1,140	1.17	.281	.146	1.29	-1.07, 3.65
AES informant-rated	0.00	1,79	0.08	.782	.798	0.15	-0.92, 1.22
DAS self-rated	0.00	1,140	0.58	.447	.255	1.02	-1.62, 3.66
DAS informant-rated	0.01	1,80	0.67	.414	.502	-0.56	-1.91, 0.79
12 months							
AES self-rated	0.01	1,140	1.86	.174	.096	1.74	-0.78, 4.25
AES informant-rated	0.08	1,73	6.21	.015	.039	4.73	0.95, 8.52
DAS self-rated	0.03	1,140	4.37	.038	.024	3.05	0.17, 5.93
DAS informant-rated	0.06	1,73	5.05	.028	.065	5.51	0.62, 10.40

P-values are shown before and after correcting for age and sex (*p*-value*).
Key: AES, Apathy Evaluation Scale; DAS, Dimensional Apathy Scale.

A *post-hoc* analysis was performed to assess the effect of lesion lateralisation. Participants were split based on whether the acute infarct occurred in the left or right hemisphere. Linear models were then used to test associations of WMH volumes with apathy at 12 months for left and right lesions. Models were controlled for age and sex. Full results are presented in Table 13. When looking at left hemisphere infarcts, the AES informant-rated was positively associated with WMH volume ($\beta = 7.33$, 95% CI [1.88, 12.78], $t(38) = 2.72$, $p = 0.010$). The association remained significant after introducing age and sex in the model. No other significant associations were found.

Table 13. Association of apathy at 12 months with WMH volume, based on lesion lateralisation

	R^2	**DF**	**F**	***p*-value**	***p*-value***	**β**	**95%CI**
Left hemisphere							
AES self-rated	0.02	1,69	1.11	.295	.165	2.11	-1.88, 6.10
AES informant-rated	0.16	1,38	7.42	.010	.014	7.33	1.88, 12.78
DAS self-rated	0.02	1,69	1.69	.198	.126	3.01	-1.61, 7.64
DAS informant-rated	0.10	1,38	3.99	.052	.046	7.46	-0.10, 15.01
Right hemisphere							
AES self-rated	0.01	1,80	1.01	.317	.243	1.64	-1.60, 4.88
AES informant-rated	0.03	1,41	1.24	.273	.382	2.80	-2.29, 7.89
DAS self-rated	0.04	1,80	2.93	.091	.086	3.21	-0.52, 6.94
DAS informant-rated	0.05	1,41	2.20	.146	.222	4.54	-1.64, 10.71

P-values are shown before and after correcting for age and sex (*p*-value*).
Key: WMH, White Matter Hyperintensity; AES, Apathy Evaluation Scale; DAS, Dimensional Apathy Scale.

Voxel-based lesion symptom mapping

VLSM was conducted across the whole brain in voxels affected in at least 10% of all participants. Analyses could not be performed considering apathy informant-rated scores, since lesions did not pass the 10% threshold.

In analysing self-rated apathy scores and lesioned voxels, VLSM found a significant association of DAS self-rated Executive (baseline) and Emotional (12 months) with right Corona Radiata: a cluster of only 5 voxels was found, the small size suggesting that further investigations are required to prove the validity of this finding.

Voxel-based morphometry

At baseline, there were no regions with significantly different grey matter volume in patients with apathy across all apathy tests.

Similarly, at 12 months, no apathy group showed different grey matter volume as compared to non-apathetic participants.

Apathy and disruption to white-matter networks

Full linear models of association between apathy scores and volumes of affected tracts were calculated and reduced models selected based on lower absolute BIC value. At baseline, an optimal model with a BIC value of 1346.9 was identified for tracts affected by acute infarcts: the left Cortico Ponto Cerebellar and Cortico Spinal tracts, and right Long and Posterior Segment of the Arcuate fasciculus were significantly associated with AES self-rated ($t(190) = -3.08$, $p = 0.002$; $t(190) = 3.18$, $p = 0.002$; $t(190) = 2.72$, $p = 0.007$; $t(190) = -3.08$, $p = 0.002$), whereas no significant associations were found with the informant-rated version of the test. The right Long Segment of the Arcuate fasciculus and Inferior Fronto-Occipital fasciculus were significantly associated with DAS self-rated ($t(194) = 2.82$, $p = 0.005$; $t(194) = -3.80$, $p < 0.001$) (BIC 1429.4). A model with BIC value of 836.4 identified significant associations of informant-rated DAS with Fornix and Internal Capsule ($t(106) = 2.31$, $p = 0.023$; $t(106) = -2.74$, $p = 0.007$).

At 12 months, the self-rated AES was significantly associated with left Cortico Ponto Cerebellar, and Cortico Spinal tracts, and right Inferior and Superior Cerebellar tracts ($t(160) = -3.42$, $p < 0.001$; $t(160) = 3.67$, $p < 0.001$; $t(160) = -2.06$, $p = 0.041$; $t(160) = 4.10$, $p < 0.001$) (model BIC: 1213.3). AES informant-rated was associated with left Inferior Fronto-Occipital fasciculus and Cingulum, and right Inferior Longitudinal fasciculus and Optic Radiation ($t(83) = -2.07$, $p = 0.041$; $t(83) = 2.81$, $p = 0.006$; $t(83) = 2.24$, $p = 0.028$; $t(83) = -2.67$, $p = 0.009$). The model had a BIC value of 642.4. The left Cortico Ponto Cerebellar, Cortico Spinal, and right Superior Cerebellar tracts were significantly associated with self-rated DAS (BIC 1254.8) ($t(161) = -3.00$, $p = 0.003$; $t(161) = 3.24$, $p = 0.001$; $t(161) = 4.34$, $p < 0.001$, respectively). The model for informant-rated DAS identified significant associations with right Inferior Longitudinal

fasciculus and Optic Radiation (t(83) = 3.34, p = 0.001; t(83) = -2.80, p = 0.006), Internal Capsule (t(83) = -2.22, p = 0.029), and left Cingulum (t(83) = 2.17, p = 0.033) (BIC 683.7). A summary of significant associations between apathy and volumes of tracts affected by acute infarcts is shown in Table 14.

Tracts affected by WMH were also examined in linear models to check associations with apathy scores. At baseline, informant-rated AES was associated with right Inferior Fronto-Occipital fasciculus and Long Segment of the Arcuate fasciculus (t(106) = -3.21, p = 0.002; t(106) = 2.93, p = 0.004) with a BIC value of 801.4), while the self-rated test showed no significant associations. Both self- and informant-rated DAS were associated with the Arcuate fasciculus (self: (194) = -2.81, p = 0.005; informant: t(107) = 2.61, p = 0.010). The self-rated version also showed an association with the left Optic Radiation left t(107) = -2.44, p = 0.016 (BIC 840.8). AES self-rated at 12months was significantly associated with Fornix, right Cortico Spinal tract, and left Arcuate fasciculus (t(160) = -2.13, p = 0.035; t(160) = 2.14, p = 0.034; t(160) = -3.20, p = 0.002). The model had a BIC value of 1221.6. The self-rated DAS was significantly associated with left Anterior Segment and right Posterior Segment of the Arcuate fasciculus (t(162) = 3.12, p = 0.002; t(162) = -2.44, p = 0.016) (BIC 1259.7). Both AES and DAS informant-rated were associated with the Cingulum (t(86) = 2.63, p = 0.010; t(85) = 2.86, p = 0.005, respectively), and the DAS also showed association with the Anterior Commissure (t(85) = -2.11, p = 0.038) (BIC 682.3).

A summary of significant associations between apathy and volumes of tracts affected by WMH is presented in Table 15.

Table 14. Significant associations of apathy with volumes of tracts affected by acute infarcts

		***p*-value**
Baseline AES self-rated		
	Left cortico ponto cerebellar tract	.002
	Left cortico spinal tract	.002
	Right long segment of the arcuate fasciculus	.007
	Right posterior segment of the arcuate fasciculus	.002
Baseline DAS self-rated		
	Right long segment of the arcuate fasciculus	.005

Table 14 (continued).

		***p*-value**
	Internal capsule	.007
	Right inferior fronto-occipital fasciculus	< .001
Baseline DAS informant-rated		
	Fornix	.023
12-month AES self-rated		
	Left cortico ponto cerebellar tract	< .001
	Left cortico spinal tract	< .001
	Right inferior cerebellar tract	.041
	Right superior cerebellar tract	< .001
12-month AES informant-rated		
	Left inferior fronto-occipital fasciculus	.041
	Left cingulum	.006
	Right inferior longitudinal fasciculus	.028
	Right optic radiation	.009
12-month DAS self-rated		
	Left cortico ponto cerebellar tract	.003
	Left cortico spinal tract	.001
	Right superior cerebellar tract	< .001
12-month DAS informant-rated		
	Right inferior longitudinal fasciculus	.001
	Right optic radiation	.006
	Internal capsule	.029

Key: AES, Apathy Evaluation Scale; DAS, Dimensional Apathy Scale.

Table 15. Significant associations of apathy with volumes of tracts affected by white-matter hyperintensity

		***p*-value**
Baseline AES self-informant		
	Right inferior fronto-occipital fasciculus	.002
	Right long segment of the arcuate fasciculus	.004
Baseline DAS self-rated		
	Arcuate fasciculus	.005
	Left optic radiation	.016
Baseline DAS informant-rated		
	Left arcuate fasciculus	.010
12-month AES self-rated		
	Right cortico spinal tract	.034
	Fornix	.035
	Left Arcuate fasciculus	.002
12-month AES informant-rated		
	Left cingulum	.010

Table 15 (continued).

		***p*-value**
12-month DAS self-rated		
	Left anterior segment of the arcuate fasciculus	.002
	Right posterior segment of the arcuate fasciculus	.016
12-month DAS informant-rated		
	Left cingulum	.005
	Anterior commissure	.038

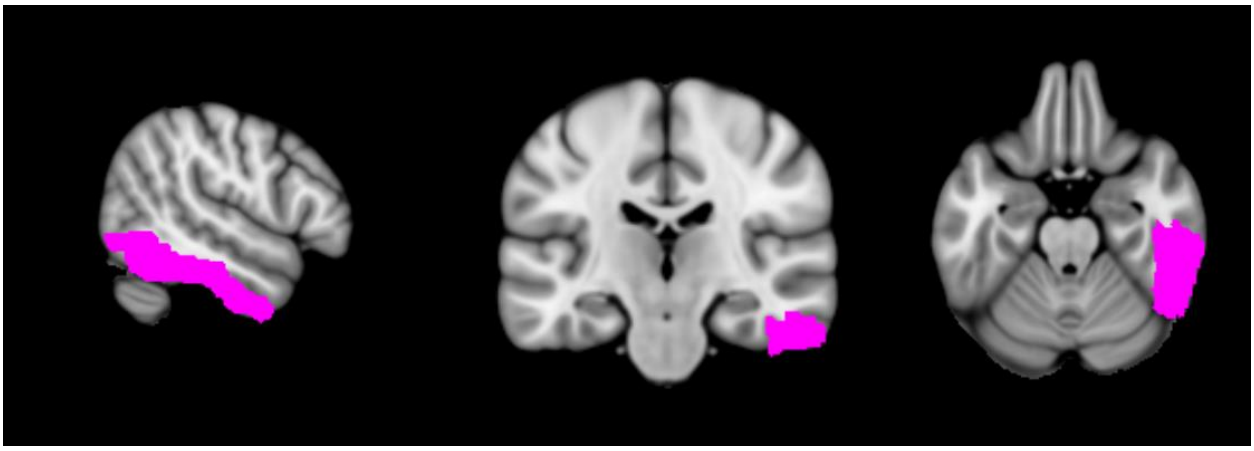
Key: AES, Apathy Evaluation Scale; DAS, Dimensional Apathy Scale.

Structural disconnectome mapping of apathy

Voxel-wise analysis did not identify any single voxels significantly associated with apathy scores at baseline or 12 months after stroke.

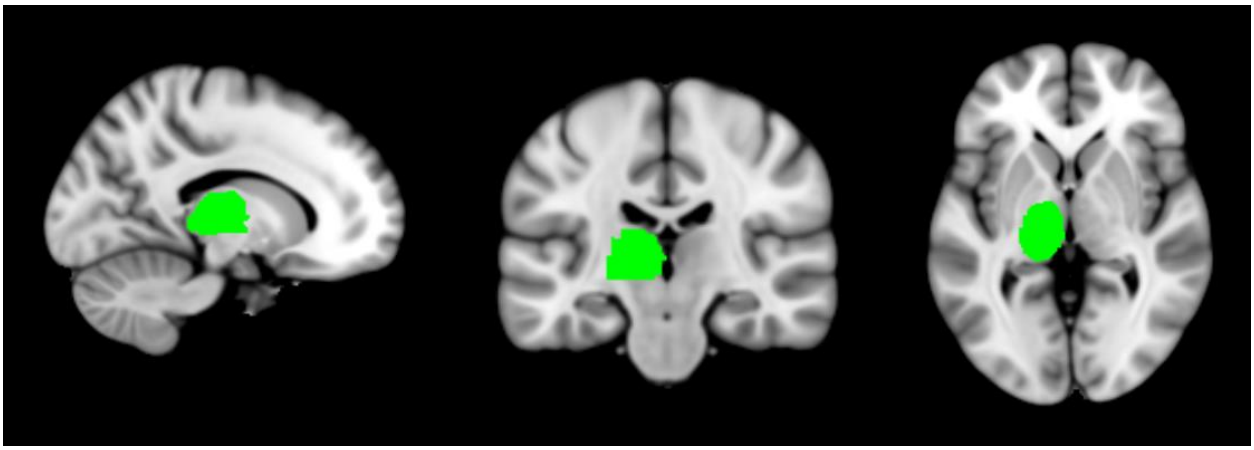
ROI analysis on acute infarct based disconnectome maps identified a significant association in the right Inferior Temporal Gyrus (MNI: 48, -17, -31, Figure 17) with self-rated DAS scores at baseline and in the left Thalamus (MNI: -9, -17, 6, Figure 18) with informant-rated DAS at 12 months.

Figure 17. Right Inferior Temporal Gyrus lesion associated with apathy symptoms



For all analyses, statistical inference was based on a random permutation test thresholded at p(FWE) < 0.05 at the cluster level.
Key: FWE, family-wise error.

Figure 18. Left Thalamus lesion associated with apathy symptoms



For all analyses, statistical inference was based on a random permutation test thresholded at p(FWE) < 0.05 at the cluster level. Key: FWE, family-wise error.

6.3 Discussion

Analyses were conducted to assess the association of apathy with stroke location, infarct volume, white-matter hyperintensity volume, and affected white-matter tracts using a variety of methods, including voxel-based morphometry, voxel-based lesion symptom mapping, and disconnectivity maps.

Results showed that apathy did not differ significantly based on the type of stroke, nor was it associated with greater lesion volume. Moreover, no significant associations between acute infarct location and apathy scores were found, despite apathy patients presenting lesions focused in specific areas of the right hemisphere, such as the basal ganglia, while non-apathy patients showed more widespread lesions.

Interestingly, WMH volume seemed to predict worse apathy scores at 12 months. These results are in line with what is previously described in literature, with studies showing that WM disruption is an important pathway to the development of *post*-stroke apathy (Clancy *et al.,* 2021; Martins-Filho *et al.,* 2023). As suggested by Tay, WMH could be linked to apathy through a reduction in WM network efficiency. The coupling of acute stroke and chronic WMH might eventually result in apathy (Tay *et al.,* 2020a).

Interestingly, results from this study show that an association with WMH could not be observed in the acute phase of stroke, but only one year later. This could suggest that WMH can be used as an indicator of apathy development, whereas other studies found the opposite to be true, that is apathy as a potential marker of small vessel disease progression among other more established markers (Clancy *et al.,* 2022). However, this hypothesis does not seem to contrast with the findings of the current study: a possible explanation is that apathy is initially caused by stroke and WMH limits recovery of the symptom (Tay *et al.,* 2020a). Hence, a correlation can only be observed later. It should be noted, however, that in order for the direction of this relationship to be fully explored, these results should be supported by a longitudinal assessment of WMH.

When considering hemispheric differences, associations between WMH volume and informant-rated apathy scores were found in the left hemisphere. Previous findings seem to support the association of apathy with right frontal region strokes because of the connections with subcortical structures involved in systems modulating arousal, motivation, and action-intention networks that sustain motor activity (Harciarek and Mańkowska, 2021; Horne *et al.,* 2022; Kos *et al.,* 2016). Studies in other patient populations, however, reported a greater involvement of the left hemisphere, likely due to different biological processes. For instance, Alzheimer's Disease patients with apathy were reported to have significantly greater cortical thinning in left regions as compared to non-apathetic patients (Tunnard *et al.,* 2010). The variety of findings might account for how different pathways to apathy exist (Kos *et al.,* 2016; Tay *et al.,* 2020a).

As previously argued, apathy has been strongly associated to network damage and subnetworks underlying action initiation and decision making have been previously identified as possible starting mechanisms of apathy (Tay *et al.,* 2019). Results of the current study found that damage to the thalamus brought on by acute infarct is associated with apathy. The thalamus is part of the key structures responsible for cognitive processing of effort-based decision-making in healthy individuals as part of a wider network (Le Heron *et al.,* 2018). According to some accounts, damage to one of these core areas, such as that caused by stroke, can cause a disfunction of the whole network, therefore causing apathy (Levy and Dubois, 2006). Previous studies also highlighted an association between lower thickness of the inferior temporal cortex and greater apathy in individuals with Mild Cognitive Impairment (MCI) and healthy controls (Guercio *et*

al., 2015). These findings were replications of previous studies building on the role of atrophy in the inferior temporal cortex as a predictor of greater apathy over time in early stages of dementia and Alzheimer's Disease (Donovan *et al.,* 2014; McDonald *et al.,* 2009).

Analysis on the association between white matter tract damage and apathy revealed numerous tracts involved with symptoms, including the Arcuate fasciculus, Fronto-Occipital tract, Cortico Spinal tract, and Cingulum. Interestingly, both apathy measures were associated with different lesioned tracts and heterogenous results were observed when considering apathy at different time points. Further studies using finer imaging methods, such as Diffusion Tensor Imaging (DTI), are necessary to shed light on the complex association between white matter damage and apathy symptoms.

Some limitations of the study need to be addressed. The main limitation of this study consisted in the quality of scans. The study set-up did not require a specific and standardised protocol for MRI images and most images were collected as part of a clinical scan that participants underwent during their admission in the acute stroke unit. This created a heterogenous set of scans and led to some participants having to be excluded from analysis because of missing specific sequence scans. Moreover, the lack of a standardised MRI protocol might have led the three recruitment sites to use different scanners and sequence settings, adding even more variability to the data.

A further limitation of this study consisted in the lack of systematic collection of details regarding the scanners used in the three study sites. As part of the study protocol, details concerning the number of scanners employed and relevant field of strength were not collected. The lack of data in this respect, as well as the heterogeneity of images, significantly impacted data harmonisation and results quality. Raw data quality might have affected the quality of registration to standard space and therefore impacted the outcome of any analysis following preprocessing steps. This resulted in heterogeneous images and required manual correction in few of the preprocessing passages described above, adding to the variability observed among images. This heterogeneity might also explain the variability found in results described in this Chapter. The number of apathy measures and time points considered for these analyses gave rise

to a series of multiple comparisons and findings that are difficult to summarise and interpret in light of previous findings and literature, making it especially challenging to understand and interpret them. This issue appears even more substantial when investigating individual white matter tracts.

Another major limitation for the analysis described was the lack of DTI in the original dataset. This made conducting detailed and advanced investigations into the structural connectivity patterns of the cohort challenging and required the use of more complex pipelines. The choice of investigating WM network connectivity in association with apathy despite the lack of DT images might have caused type II errors, allowing for a less than perfect identification of disrupted networks, eventually impacting the quality of results.

Chapter 7: Awareness of apathy

It has been often reported that patients with apathy might present low awareness of their symptoms when comparing self-rated and informant-rated versions of apathy measures (Marin *et al.*, 1991; Mehren *et al.,* 2018; Starkstein *et al*., 2010). Njomboro and Deb, for instance, reported that brain damaged patients evaluated their apathy symptoms significantly less than their informants (Njomboro and Deb, 2012). Similarly, this phenomenon was assessed by measuring interrater agreement between patients with Huntington's disease and their carers, finding that agreement was heavily affected by the cognitive status of the patient (Chatterjee *et al.,* 2005). A study conducted in a cohort of childhood-onset craniopharyngioma patients showed that apathy levels were judged to be higher by informants, indicating that many patients were not fully aware of their impairments (Mehren *et al*., 2018). Results from literature in this field seem to suggest that patients may not be fully aware of the behavioural and emotional changes related to apathy. These changes would, instead, appear more clearly to others, eventually leading patients to rate their apathetic symptoms significantly lower than their informants (Mehren *et al*., 2018).

This has implications for treatment, as patients might not be aware of any change in their life and might not be willing to undergo rehabilitation or interventions. Indeed, apathy is often reported by close relatives and patient carers, who might provide a different perspective on symptom changes and evolution (Marin *et al.*, 1991). This made necessary the development of appropriate tools to measure apathy both from the patient perspective and the perspective of an external informant, such as a carer or a clinician. As described in previous chapters, identical forms of DAS and AES exist to complement self-reported questionnaires and obtain an additional source of information. As described above, a discrepancy between patient and informant scores has been observed in various neurological disorders (Jacus *et al.*, 2022; Mehren *et al.*, 2018). It is unclear whether a similar phenomenon is observed in stroke survivors presenting with apathy and given the importance for most patients to attend rehabilitation, understanding the degree of symptom awareness is of significant benefit.

Here, the goal was to establish the degree of apathy awareness in a cohort of stroke survivors. To our knowledge, this is the first study to examine apathy awareness in stroke patients using a

patient-informant discrepancy method. Apathetic patients were first identified from the participants of the Apathy and Outcome after Stroke Study using informant data. An awareness score was then calculated based on the difference between self-rated and informant-rated apathy scores. This allowed us to obtain a 'scale of awareness', with positive scores indicating patients rating less apathy than the informant, suggesting greater lack of awareness.

7.1 Methods

Apathetic patients were identified as those scoring above a cut-off of 40 on the informant-rated version of the AES (Marin *et al.*, 1991). The concept of awareness was operationalised as interrater agreement between patients and their informants on the AES. This method was developed following the Subjective Rating Discrepancy detailed by Hannesdottir and Morris (2007): according to this method, the patient is asked to rate their ability to do certain activities, which is then compared to the ratings of an informant. In this study, interrater agreement was calculated by subtracting the total score of the self-rated test from the total score of the informant's version. In doing so, positive scores would identify a lack of awareness by the patients and a scale describing degree of loss of awareness could be generated. In order to adjust for scaling issues, awareness score was divided by the average of the two raters, which was calculated as the sum of the patient and informant total score divided by two. This takes into account that as levels of apathy increase generally, any differences between patient and informant may magnify simply due to measurement scaling. Equation 1 summarizes the formula used to calculate the scaled awareness score. The percentage of unaware apathetic patients was calculated as the number of patients who scored above zero on the AES scaled awareness scale. Analyses were run for AES scores at baseline, 30 days, 6 months, and 12 months after stroke.

Similarly, scaled awareness were calculated for DAS scores at baseline, 30 days, 6 months, and 12 months after stroke. Apathetic patients were identified as those scoring above a cut-off of 39 on the informant-rated version of DAS (Myhre *et al.*, 2022). Interrater agreement and scaled awareness scores were calculated with the formula described below (Equation 1). The percentage of unaware apathetic patients was calculated as the number of patients who scored above zero on the DAS scaled awareness scale.

Equation 1. Formula used to calculate interrater agreement

$$\frac{[informant - patient]}{[informant + patient]/2}$$

7.2 Results

As previously mentioned, 200 participants were recruited for this study: of these, 176 completed the 30-day assessment, 171 at 6 months, and 167 at 12 months. Moreover, 112 informants completed the assessment at baseline, 92 at 30 days, 95 at 6 months, and 89 at 12 months.

Analysis showed that 17 participants (15.6%) of patients were apathetic at baseline when considering the AES. All the patients were shown to report lower apathy scores than their informants (100% unaware of their symptoms). The mean difference between patient and informant rating was 12.2 ± 7.5. When considering the DAS cut-off, 7.3% of patients were apathetic and 87.5% of these rated their apathy lower than their informants. The mean difference in ratings was 15.8 ± 8.3.

At 30 days, 13 participants (14.8%) were apathetic on the AES and 100% of them reported lower apathy scores than their informants. The mean difference in apathy rating was 11.5 ± 8.3. On the DAS, 9% of patients were apathetic according to the cut-off. Of these, 7 were unaware of their symptoms, with a mean rating difference of 12.1 ± 15.3.

At 6 months, 12 patients were apathetic according to AES. 91.7% of these were shown to be unaware of their symptoms. The mean rating difference was 11.5 ± 6.2. On the DAS, 6 patients resulted apathetic and 83.3% of these rated their scores lower than their informants. The mean rating difference was 11.3 ± 10.3.

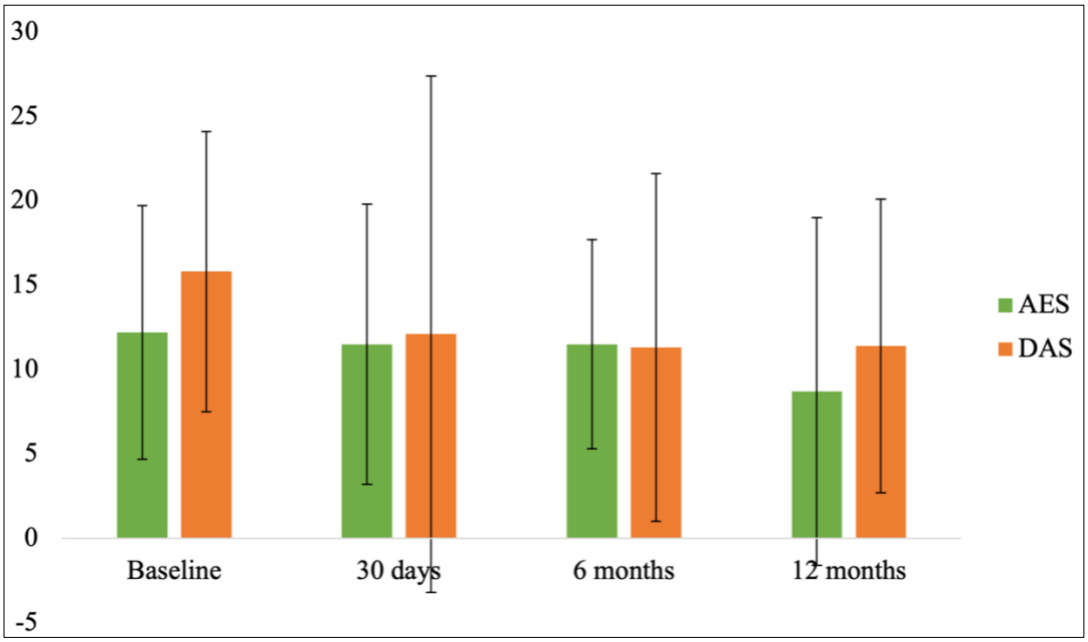
At 12 months, 11.5% of patients resulted apathetic when considering the AES cut-off. Out of these, 90% were unaware of their symptoms. The mean rating difference was 8.7 ± 10.3. On the DAS, 12.6% of patients were apathetic: of these, 81.8% showed lack of symptom awareness. The mean rating difference in this case was 11.4 ± 8.7.

Table 16 summarises the results described so far. These include the number of apathetic patients at each time point according to AES and DAS, as well as the percentage of patients showing a lower apathy score than what reported by their informant, *i.e.* the percentage of patients unaware of their symptoms. Figure 20 shows the scaled mean difference in apathy scores over time, for both AES and DAS; positive scores indicate a lack of patient's awareness.

Table 16. Patients unaware of apathy symptoms

	Baseline	30 days	6 months	12 months
AES				
Apathetic *n* (%)	17 (15.6%)	13 (14.8%)	12 (13.5%)	10 (11.5%)
Unaware *n* (%)	17 100%)	13 (100%)	11 (91.7%)	9 (90.0%)
DAS				
Apathetic *n* (%)	8 (7.3%)	8 (9.0%)	6 (6.6%)	11 (12.6%)
Unaware *n* (%)	7 (87.5%)	7 (87.5%)	5 (83.3%)	9 (81.8%)

Figure 19. Apathy scaled awareness scores over one year after stroke



The graph shows the mean difference in apathy ratings at four timepoints after stroke. Interrater agreement was calculated by subtracting the total score of the self-rated test from the total score of the informant's version and divided by the average of the two raters to adjust for scaling issues. Positive scores represent patient's lack of awareness.

Key: AES, Apathy Evaluation Scale; DAS, Dimensional Apathy Scale.

7.3 Discussion

In this prospective longitudinal study, the majority of apathetic patients were unaware of their symptoms, that is they rated apathy lower that their informants. This finding has clinical and research relevance. Clinically, it would seem important that multiple raters offer different assessments of apathy. As observed in previous chapters, informants might be able to offer a more accurate assessment of apathy symptoms, especially in the early stages after stroke. Moreover, the clinician perspective might help elucidate some behaviours and offer an objective assessment of symptoms.

Despite the patient being the focus of care and interventions, informants might have a different perspective and be equally affected by the symptoms. When planning and conducting apathy research, it is equally important to be aware of possible low awareness of apathy symptoms in stroke patients. When planning a new study, appropriate apathy measures should be considered as well as optimal, and possibly multiple, informants identified.

A limitation of these results is that the prevalence of apathetic patients in the current study was lower than what would be expected in a cohort of stroke survivors. This poses issues with the generalizability of findings when it comes to larger sample sizes. However, the current study provides a guide to what sample sizes might be needed for such research, which may involve screening and then exploring in more detail those who have apathy without awareness. More studies including larger samples of apathetic stroke patients and their informants are needed to replicate these findings as well as to better establish cut-offs for designating apathy awareness.

Another limitation of this study is represented by the formula used to determine apathy awareness. In particular, this method might be influenced by the accuracy of apathy questionnaires: future studies should aim at employing more objective measures of apathy in order to assess patient's awareness. Moreover, the formula used for these analyses is not standardised and was used here for the first time: future research might replicate the methods used for this study in a larger cohort to assess the validity of this method. Lastly, the formula to calculate awareness considers informants as the gold standard of objective apathy symptoms rating: however, it could be argued that diagnostic criteria, and not psychometric tests, should represent the gold standard for apathy symptoms assessment.

In conclusion, this study showed that apathetic patients seem to be mostly unaware of their symptoms, regardless of the test used to assess apathy. This finding has profound clinical implications and should be taken into consideration when designing and planning rehabilitation interventions, although larger sample sizes are needed to confirm these findings.

Chapter 8: Effect of apathy on carer burden and quality of life

As described in Chapter 1, apathy appears to be a common symptom not only following stroke, but also in small vessel disease (SVD) (Tay *et al* 2019). Cerebral SVD refers to various forms of pathologies affecting the small vessels of the brain and includes a group of heterogenous pathological processes that usually manifest radiologically as lacunes, white-matter hyperintensities (WMH), or microbleeds and that may result in cognitive impairment (Markus and de Leeuw, 2023; Pantoni 2010). Most SVD is related to ageing processes and vascular risk factors such as hypertension, however a small percentage of cases are caused by inherited disorders such as Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) (Markus and de Leeuw, 2023).

Carers play an important role in the physical and functional recovery after stroke and in a clinical context are considered as valuable members of the rehabilitation team (Lutz and Young, 2010). Together with physical impairment, neuropsychiatric symptoms may add to carer burden in the rehabilitation phase after stroke, resulting in a deterioration of their QOL (McCullagh *et al.,* 2005). In particular, there seems to be increasing evidence of the importance of caregivers in the long-term management of stroke patients as well as concomitant lack of carer support and emotional burden of caregiving (Anderson *et al.,* 1995; Blake *et al.,* 2003). Importantly, lower mood of carers seems to reduce the efficacy of patients' rehabilitation, while healthy carers are reported to improve general *post*-stroke recovery and rehabilitation process (Hunt and Smith, 2004). Carers' emotional state may correlate with poorer patient functional recovery and should be considered as a central factor in patient rehabilitation (Em *et al.,* 2017). Therefore, some authors suggested the need to shift the focus of stroke rehabilitation from a patient-focused to a combined patient-carer approach, since the latter is considered crucial in preserving the long-term wellbeing and rehabilitation of stroke patients (McCullagh *et al.,* 2005).

In the context of neuropsychiatric symptoms and carer burden, research for other conditions shows that apathy is among the most distressing neuropsychiatric symptoms for carers (de Vugt *et al.,* 2006; Feast *et al.,* 2016). Several studies involving patients with dementia found that carers report high distress scores related to apathy, with apathy levels especially associated with

worsening of the relationship between patient and carer (de Vugt *et al.,* 2003; de Vugt *et al.,* 2006). Similarly, studies conducted with Parkinson's disease patients and their carers indicate that carer distress is higher when neuropsychiatric symptoms such as apathy occur more frequently (Aarsland *et al.,* 2007). It is also well known that an increased carer burden leads to poorer QOL for the carer, which eventually results in a reduced ability to provide optimal care and in a negative outcome for both parties (Hiseman and Fackrell, 2017). Research in cerebrovascular diseases is still lacking in this regard and the relationship between *post*-stroke apathy, carer strain and QOL is yet to be fully understood.

A greater understanding of the impact of apathy on carer's wellbeing and QOL may also help the development of appropriate patient rehabilitation programs or carer interventions. Research addressing these issues may indeed identify the need to address different intervention targets, concerns or rehabilitation goals. To help clarify the relation existing among these factors, *post*-stroke rehabilitation research should therefore focus on apathy in relation to carer burden and wellbeing.

Based on the current knowledge and in the context of advancing the field of apathy treatments, it is hypothesised here that carers' QOL and wellbeing should be addressed when investigating new patient-focused and combined patient-carer interventions. The goal of this research was to examine how apathy affects the QOL of carers of patients with monogenic or sporadic forms of SVD. In particular, it is hypothesized that carers of SVD patients with apathy have greater distress and lower QOL as compared to carers of non-apathetic patients and that SVD patients with apathy present lower QOL than nonapathetic patients.
To our knowledge, this is the first study analysing the effect of apathy on carers of SVD patients.

8.1 Methods

Study design

A cross-sectional study was set up at Addenbrooke's Hospital Cambridge, UK, and SVD patients were recruited from the Stroke Unit. The Study was approved by the West of Scotland – Research Ethics Committee (REC reference: 22/WS/0010) and written informed consent was obtained from all patients and informants. Copies of approval letters from the Research Ethics

Committee and HRA can be found in an Appendix at the end of this thesis. The Appendix also contains copies of the Participant Information Sheet and Informed Consent Form which were approved for this study by the Research Ethics Committee.

Patients were recruited if they met the following inclusion criteria: radiology confirmed lacunar stroke (at least one month prior to recruitment) OR diagnosis of CADASIL, age ≥ 18 years, able to give informed consent, presence of a spouse, family member or other qualifying as a carer/informant willing to participate, sufficiently fluent in English to allow cognitive testing. As previously discussed, only patients with a monogenic or sporadic form of SVD were included in this study: this choice was guided by the lack of existing studies conducted in this population, making this study a novelty in the field. Participants were excluded if they had aphasia of a severity precluding consent or administration of cognitive tests, pre-existing clinical diagnosis of dementia, other major central nervous system or psychiatric disorders, or no identifiable carer or informant willing to participate.

With the study participant's consent, the carer's consent was also sought. Participants were then invited to a one-off assessment including cognitive testing, mood and neuropsychiatric assessment.

Patients were assessed with the AES – Clinician version (Marin *et al.,* 1991): a score ≥ 34 identified apathetic participants. The control group comprised non-apathy patients (*i.e.* those scoring below 34 on the AES – Clinician version), and their carers.

Sample size calculation

A study by Leroi comparing carer burden in Parkinson's Disease patients with and without apathy found significant greater burden in carers of participants with apathy. The sample size in the study included 22 patients (and their carers) in the apathetic group and 28 patients (and their carers) in the control group (Leroi *et al.,* 2012).

An a priori power analysis was conducted using Superpower version 0.2.2 (Lakens and Caldwell, 2021) for sample size estimation, based on data from the Leroi study (Leroi *et al.,* 2012). The

effect size in this study was 0.9, considered to be large using Cohen's criteria. With a significance criterion of $\alpha = .05$ and power = .80, the minimum sample size needed with this effect size was 38 for a two-sample t-test.

Recruitment started in May 2022 and is still ongoing. The results presented in the following sections include data collected up until September 2023.

Measures

Demographics, details of stroke, and past medical history (including CADASIL diagnosis and details) of patients were collected during the assessment. Current depressive symptoms were assessed based on DSM-5 diagnostic criteria (American Psychiatric Association, 2013).

Apathy was assessed with the clinician-rated version of the Apathy Evaluation Scale (AES) (Marin *et al.,* 1991). The test has been described in Chapter 2. Moreover, patients were asked to complete the Beck's Depression Inventory (BDI) (Beck *et al.,* 1961) to measure depressive symptoms. The BDI is a 21-item, self-report rating inventory that measures characteristic symptoms of depression: it includes items relating to hopelessness and irritability, feelings of guilt or being punished, and physical symptoms such as fatigue, weight loss, and lack of interest in sex (Beck *et al*., 1961). The BDI has been previously validated in stroke (Aben *et al.,* 2002).

Patient's functional outcome and QOL were measured with the Modified Rankin Scale (mRS) and 36-Item Short Form Health Survey (SF-36), respectively (Farrell *et al.,* 1991; Ware and Sherbourne, 1992). Cognitive functioning was assessed with the Montreal Cognitive Assessment (MoCA) (Nasreddine *et al.,* 2005) and the Brief Memory and Executive Test (BMET) (Brookes *et al.,* 2012). All the measures have been described in Chapter 2.

During the same assessment, carers demographics were collected. Carer's mood was assessed with the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983). The HADS contains 14 items measuring anxiety and depression symptoms and was firstly developed to use in a clinical hospital setting. Items are rated on a 4-point severity scale and two scales are produced, one for anxiety (HADS–A) and one for depression (HADS–D). The scale has been

extensively validated and can be administered in community settings and general practices (Bjelland *et al.,* 2002; Snaith, 2003).

Distress caused by apathy was measured with the Neuropsychiatric Inventory (NPI) (Cummings *et al.,* 1994). The NPI measures 12 common neuropsychiatric disturbances, including apathy and depression. Carers are asked to evaluate frequency and severity of each symptom and the distress caused by these. The NPI has been validated for stroke patients proving to be a suitable assessment tool (Angelelli *et al.,* 2004).

Carer burden was assessed with the Zarit Burden Interview (ZBI) (Zarit *et al.,* 1980). The ZBI is a self-report measure completed by carers to investigate stress related to caring for dementia patients: it comprises 22 items with scores ranging from 0 to 88, where 88 represents severe burden. Developed originally for carers of people with dementia, the scale has been used with stroke patients in different studies (Caro *et al.,* 2018; Elsheikh *et al.,* 2020; Imarhiagbe *et al.,* 2017).

Carers QOL was also measured with the SF-36 (Ware and Sherbourne, 1992).

Statistical analysis

Missing data were imputed via multiple-imputation using chained equations (van Buuren *et al.*, 2011). The number of datasets was generated and analysed in combination using Rubin's rules (Rubin, 1987). Analyses were considered significant when $p \leq 0.05$. All analysis was performed using R 4.2.3 (R Core Team, 2023).

Continuous variables were compared between groups using independent t-tests if normally distributed and Mann-Whitney U tests if not. Categorical or binary variables were compared with Chi squared test.

To test whether carers of apathetic patients experience greater distress and lower QOL, the mean difference of continuous scores on the NPI Caregiver Apathy Distress Scale, ZBI, SF-36 MCS, and SF-36 PCS were compared between the apathy and control group with independent t-tests or Mann-Whitney U tests.

Linear regression was also used to test the association between apathy and informant outcomes. First, univariate correlations between apathy and the variable of interest, *i.e.,* NPI Apathy Distress Scale, ZBI, SF-36 MCS, and SF-36 PCS were assessed using Pearson's or Spearman's correlations where appropriate. Multiple regression models were then used to further analyse the relationships between apathy and variables of interest while controlling for age and sex of patient and carer, mRS, MoCA total score, and carer QOL.

Furthermore, significant multivariate associations were used to carry out causal mediation analysis: this statistical technique is used to determine whether variance in the relationship between two variables can be explained by a third mediating variable (Imai and Yamamoto, 2013). Here, mediation analyses were conducted to identify variables that may explain significant multivariate associations between carer burden and apathy. Mediation analyses were conducted using the "mediation" package 4.5.0 (Tingley *et al.*, 2014) in R 4.2.3 (R Core Team, 2023).

8.2 Results

Study sample

In total, 24 patient-carer dyads were recruited. The apathy group comprised 12 dyads and did not differ from the control group in age, sex, education, ethnicity, functional outcome on the mRS, and cognitive functioning (Table 17).

The majority of patients in the apathy group had a diagnosis of CADASIL, whereas only one did in the control group ($p = 0.003$). Patients in the apathy group presented higher levels of apathy ($p < 0.001$) and depression ($p = 0.030$). Moreover, while 50% of apathy patients had a concurrent diagnosis of depression at the time of assessment, no control patients had co-occurring depression based on DSM-5 criteria. Apathetic patients had lower QOL on the Mental Component Summary ($p = 0.017$), but no other significant differences were observed in QOL. Carers in the apathy group showed higher anxiety levels on the HADS ($p = 0.049$) and distress caused by apathy symptoms ($p < 0.001$). Interestingly, no differences were found on the NPI depression distress scale ($p = 0.120$). Care burden was significantly higher in carers of apathetic patients ($p = 0.005$).

Table 17. Characteristics of the study sample

	Apathy (*n* = 12)	**Control (*n* = 12)**	**Apathy vs control *p*-value**
Age *M SD*			
Patient	64.8 ± 12.1	70.9 ± 10.9	.202
Carer	61.8 ± 14.2	69.4 ± 9.1	.140
Sex – female *n (%)*			
Patient	3 (25.0%)	3 (25.0%)	1.000
Carer	10 (83.3%)	10 (83.3%)	1.000
Years of education *M SD*			
Patient	14.3 ± 2.7	15.1 ± 3.7	.598
Carer	13.1 ± 3.1	14.3 ± 3.0	.280
Ethnicity patient *n (%)*			.368
Asian	0 (0%)	1 (8.3%)	
Black	1 (8.3%)	0 (0%)	
White	11 (91.7%)	11 (91.7%)	
Ethnicity carer *n (%)*			1.000
Asian	0 (0%)	1 (8.3%)	
White	12 (100%)	11 (91.7%)	
CADASIL *n (%)*	9 (75.0%)	1 (8.3%)	.003
Carer relationship to patient *n (%)*			.592
Partner/spouse	11 (91.7%)	10 (83.4%)	
Child	1 (8.3%)	1 (8.3%)	
Other informant	0 (0%)	1 (8.3%)	
AES *M SD*	49.8 ± 10.1	29.8 ± 4.8	< .001
BDI *M SD*	12.7 ± 6.5	6.4 ± 6.7	.030
mRS *Mdn (IQR)*	2.5 (1-3)	1 (0-2)	.116
SF-36 MCS *M SD*			
Patient	44.4 ± 9.1	52.7 ± 6.8	.017
Carer	43.3 ± 12.4	51.4 ± 9.7	.089
SF-36 PCS *M SD*			
Patient	33.6 ± 11.0	38.0 ± 14.8	.415
Carer	43.0 ± 12.1	45.0 ± 10.6	.672
MoCA total score *M SD*	22.2 ± 6.9	25.9 ± 3.8	.210
BMET total score *M SD*	9.3 ± 4.7	12.1 ± 3.3	.114
HADS anxiety *M SD*	9.1 ± 3.8	5.8 ± 4.3	.049
HADS depression *M SD*	6.1 ± 4.3	4.1 ± 3.1	.202
NPI carer distress – apathy *M SD*	2.4 ± 1.6	0.1 ± 0.3	< .001
NPI carer distress – depression *M SD*	1.6 ± 1.6	0.7 ± 1.2	.120
ZBI *M SD*	23.7 ± 15.3	7.8 ± 6.5	.005

The apathy group included patients with a score ≥ 34 on the AES – Clinician version (Marin *et al.,* 1991) and their carers. The control group included non-apathy patients, *i.e.* those with a score < 34 on the AES – Clinician version, and their carers. Years of education were calculated as the sum of compulsory and higher education (including full-time and part-time).

Key: M, mean; SD standard deviation; AES, Apathy Evaluation Scale – clinician-rated; BDI, Beck's Depression Inventory; mRS, pre-stroke Modified Rankin Scale; Mdn, median; SF-36 MCS, 36-Item Short Form Health Survey Mental Component Summary; SF-36 PCS, 36-Item Short Form Health Survey Physical Component Summary; HADS, Hospital Anxiety and Depression Scale; NPI, Neuropsychiatric Inventory; ZBI, Zarit Burden Interview; MoCA, Montreal Cognitive Assessment; BMET, Brief Memory and Executive Test.

Relationship of apathy with carer distress, burden, and QOL

Apathy was correlated with NPI Apathy Distress Scale and ZBI total ($r = .80$, $p < 0.001$; $r = .64$, $p < 0.001$). No significant associations were found with carer-rated SF-36 MCS or SF-36 PCS ($r = -.08$, $p = .725$; $r = .05$, $p = 0.813$). Multiple regression models were then used to further analyse the relationships of apathy with carer distress and burden while controlling for age and sex of patient and carer, mRS, MoCA total score, and carer QOL. Results revealed that after controlling for these variables, associations remained significant with both NPI and ZBI (Table 18). Given that mRS was significantly associated with NPI and patient sex, mRS, and SF-36 MCS were associated with ZBI, these variables were carried out and the possible mediating effect assessed in mediation models.

Table 18. Multivariate regression models with carer distress and burden as the outcome variable

	NPI – Apathy Distress Scale	**ZBI**
AES	**0.08 (0.001)**	**0.42 (0.016)**
Age patient	0.03 (0.41)	-0.52 (0.13)
Age carer	-0.07 (0.10)	0.35 (0.28)
Sex patient	-0.50 (0.64)	**20.05 (0.032)**
Sex carer	-1.12 (0.42)	16.52 (0.15)
mRS	**0.49 (0.011)**	**4.24 (0.007)**
MoCA	0.00 (0.99)	-0.16 (0.63)
SF-36 MCS	0.00 (0.93)	**-0.33 (0.042)**
SF-36 PCS	0.00 (0.83)	-0.15 (0.31)

Results are presented as unstandardised β (p).

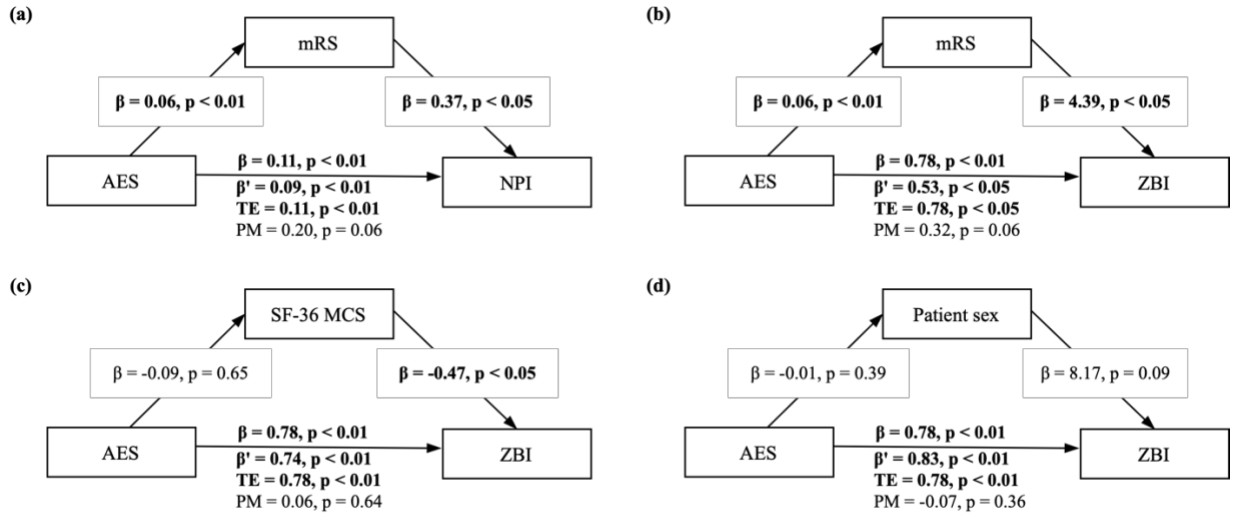
Key: AES, Apathy Evaluation Scale – clinician-rated; mRS, pre-stroke Modified Rankin Scale; MoCA, Montreal Cognitive Assessment; SF-36 MCS, 36-Item Short Form Health Survey Mental Component Summary; SF-36 PCS, 36-Item Short Form Health Survey Physical Component Summary.

Mediation analysis

Mediation models revealed that mRS partially mediated NPI and ZBI (Figure 21a-b). The SF-36 MCS also partially mediated ZBI (Figure 21c). No significant mediation effect was found for

patient sex (Figure 21d). The effect of apathy on NPI and ZBI remained significant after controlling for mediating variables.

Figure 20. Mediation analysis exploring the relationship of apathy with carer distress and burden



Modified Rankin Scale (mRS) partially mediates the association of apathy (AES, Apathy Evaluation Scale – clinician-rated) with Neuropsychiatric Inventory – Apathy Distress Scale (NPI) (a) and Zarit Burden Interview (ZBI) (b). The 36-Item Short Form Health Survey Mental Component Summary (SF-36 MCS) also partially mediates the association with ZBI (c). Patient sex does not mediate associations with ZBI (d).
Key: β, unadjusted coefficient; β', coefficient controlling for mediator; TE, total effect; PM, proportion mediated.

8.3 Discussion

Here, a new study was set up and analyses conducted to estimate the effect of apathy on carer's distress, burden, and QOL. To our knowledge, this is the first study conducted in a group of SVD patients and results are fundamental in better understanding outcomes of apathy and informing possible new interventions.

In comparing a group of apathy patients and non-apathy controls, the current results suggest that carers in the apathy group present higher distress and care burden. These results were still significant after controlling for possible factors influencing the relationship, such as patient's functional outcome and carer physical and mental QOL. However, mediation analyses also revealed that patient's functional outcome partially mediates the relationship of apathy with care distress and burden.

Interestingly, despite a high co-occurrence of apathy and depression in the study group, no significant differences were found between the apathy and control group in carer distress caused by depression symptoms. The current findings seem to suggest that apathy is a distinct symptom with different effects from depression. These results are in line with studies showing that *post*-stroke apathy and depression are dissociable syndromes with different effects on outcome (Caeiro *et al.,* 2013; Tay *et al.,* 2021; Withall *et al.,* 2011).

When looking at differences in QOL, results revealed that apathy patients had worse mental well-being, further confirming results presented in Chapter 5. Comparisons of carers QOL between the two groups, however, showed no significant differences. These results seem to differ from previous studies showing that carer's QOL and burden are associated (McCullagh *et al.,* 2005; van Exel *et al.,* 2005). An explanation for results in the current study might be the low sample size: as highlighted by the study's power analyses reported above, a larger sample might be needed to identify the effect in this population. Since the recruitment for this study is still ongoing, future analysis on the complete dataset might establish an association between apathy and carer's QOL.

A comparison of carer's mood showed that carers of apathy patients presented similar levels of depression but higher anxiety levels. This finding partly reflects previous findings showing that carer burden correlated positively with carer anxiety at 3 and 12 months after stroke (McCullagh *et al.,* 2005).

Importantly, the majority of apathy patients in the current study had a diagnosis of CADASIL. This might introduce a potential bias in the study, since results might represent differences between CADASIL and sporadic SVD, rather than identify different trends in apathy. Patients with CADASIL are reported to experience cognitive changes, mood, or behavior disturbances throughout the course of the disease (Chabriat and Lesnik Oberstein, 2022). These alterations might also involve motivation, social life, and relationship with external environment and stimuli. Therefore, it could be argued that the differences observed and reported in the current study might reflect a change intrinsic to CADASIL condition, rather than to the patients'

motivational status and relating to apathy as a symptom. Measures are in place to recruit an equal number of non-apathetic CADASIL patients in the current study so as to match the study and control group.
Despite the low sample size which might currently prevent the generalizability of conclusions, this study has a number of strengths. As previously mentioned, this is the first study to thoroughly assess carer's distress in a cohort of cerebrovascular patients by employing several validated measures, such as the Zarit Burden Interview and the Neuropsychiatric Inventory (Cummings *et al.,* 1994; Zarit *et al.,* 1980).

Results from this study hold clinical relevance and imply that attention should be directed to carers, as well as patients affected by apathy. Families might be the first to observe symptoms and lifestyle changes due to apathy, as well as being the ones affected the most by this syndrome. A possible limitation to this study is that the observation was limited to SVD patients, whereas other forms of stroke were excluded. While this allowed a specific analysis of this population, results might not be generalisable to the wider stroke population. Nonetheless, this study aims at providing a guide for future studies to be conducted in stroke cohorts and a reference for the sample size and methodology to be employed.

Moreover, these findings hold promising translational implications and should encourage future research to develop new and appropriate rehabilitation and educational interventions directed to carers and families of patients affected by apathy. Shifting the intervention goal from patient to families might reduce carer's burden and distress as well as have indirect positive consequences on patients.

In summary, results from the current seem to suggest that apathy has a significant and quantifiable impact on SVD patients' carers, including spouses and families. Efforts to develop new apathy interventions and management plans might therefore be directed towards tailoring programs for carers and families.

Chapter 9: Summary and future directions

This thesis has attempted to provide insight into the clinical characteristics of apathy and the relationship of this symptom with outcome in patients with cerebrovascular disease. These associations were examined in a longitudinal cohort of stroke survivors where apathy was assessed at four time points using validated mood and apathy questionnaires. Moreover, a cross-sectional study was conducted to examine the impact of apathy on quality of life and care burden in carers of patients with small vessel disease.

In this chapter, the main findings of this thesis are reviewed and their wider implications discussed. Moreover, future research is considered here in the context of the results of this thesis, as well as the broader topics connected to this field.

9.1 Summary of findings

This section summarises the main findings of this thesis and highlights any clinical and research implications.

1. **Apathy symptoms increased at the group and individual level over one year after stroke.** Over one year after stroke apathy seemed to worsen in a cohort of stroke survivors. Further analyses, however, revealed that while a larger group of patients was characterised by lower apathy scores, a smaller group presented worse apathy symptoms in every dimension. When looking at individual apathy dimensions, executive symptoms seemed to predominantly drive the general increase in apathy symptoms.

   While other studies found that apathy decreases or remains stable over time, this study found that the prevalence of apathy increases over one year, even though this applied to a minority of patients and was only found when looking at self-rated apathy scores (Brodaty *et al*., 2013; Caeiro *et al*., 2013; Mayo *et al.,* 2009; Withall *et al*., 2011). These findings may be due to an increased awareness of the psychological consequences of stroke in patients as the physical deficit improves, which might explain why informants did not register any differences in symptoms. Moreover, the differences in prevalence figures reported in this and other studies might be attributed to the timescale investigated and the measure used in other research (Lansdall *et al.*, 2017).

The different presentation of apathy at different timepoints, as presented in this study, might inform the examination of neurobiological and cognitive factors contributing to this symptom and might clarify how each factor impacts patients, therefore contributing to different symptom trajectories reported in this thesis.

2. **Apathy, but not depression, seems to predict worse cognitive functioning.** In this study, almost half of patients with apathy were impaired on the Montreal Cognitive Assessment (MoCA) and apathy scores at 30 days seemed to predict worse cognitive functioning at 12 months. Interestingly, the Geriatric Depression Scale (GDS)-24 depression subscore did not significantly predict cognitive scores one year after stroke. Previous studies found that post-stroke apathy is usually associated with cognitive deficits affecting both global cognition and specific domains, such as memory, processing speed, verbal learning, and semantic fluency (Caeiro *et al*., 2013; Horne *et al*., 2022; van Dalen *et al.,* 2013), however only some cognitive functions were found to be predicted by apathy in the current study. This might be explained by the fact that more severe brain damage is associated with greater cognitive deficits, which in turn might bring about or worsen apathy symptoms. However, a causal relationship could not be established with the current methods.
   Taken together, these results tie in with previous findings of apathy association with higher risk of incident dementia and might be helpful to clinicians and researchers in determining a timely assessment of apathy for the purposes of an accurate and early diagnosis of dementia (Onoda *et al.,* 2011; Tay *et al*., 2020b). Moreover, the results of this study might inform future models of cognitive functioning and conversion to dementia.

3. **Depression, but not apathy, seems to predict worse outcome.** In the context of outcome and quality of life (QOL), this study found that while apathy showed significant associations with the modified Rankin Scale (mRS) and the 36-Item Short Form Health Survey (SF-36) at 12 months, this relationship seemed to be mediated by depression. Depressive symptoms may influence recovery, by impairing engagement with

rehabilitation, or acting as a mediator of the association between apathy and disability, or representing a source of confounding.

Despite previous studies suggesting that both apathy and depression independently influence stroke outcome, the current findings suggest that depressive symptoms, rather than apathy, are likely to be more important in determining QOL in stroke patients (Lopatkiewicz *et al.,* 2021; Matsuzaki *et al*., 2015). Similar results depicting the importance of depression in determining QOL have been reported in other neurological conditions, such as Alzheimer's and Parkinson's Disease (Barbe *et al.,* 2018; Su *et al*., 2021).

These results seem to suggest that future studies should include depression measures in models predicting outcome and QOL.

4. **Stroke patients showed low awareness of apathy symptoms.** The majority of stroke survivors in this study did not show awareness of apathy and rated these symptoms lower than external informants. This finding has clinical and research relevance. Clinically, it would seem important that multiple raters offer different assessments of apathy: external informants might be able to offer a complementary assessment of apathy symptoms, especially in the early stages after stroke. Moreover, the clinician perspective might help elucidate some behaviours and offer an objective assessment of symptoms.

   Despite the patient being the focus of care and interventions, informants might have a different perspective and be equally affected by these symptoms. When planning and conducting apathy research, it is equally important to be aware of possible low awareness of apathy symptoms in stroke patients. When planning a new study, appropriate apathy measures should be considered as well as multiple informants identified.

   In conclusion, this study showed that apathetic patients seem to be mostly unaware of their symptoms, regardless of the test used to assess apathy. This finding has profound clinical implications and should be taken into consideration when designing and planning rehabilitation interventions, although larger sample sizes are needed to confirm these findings.

5. **Carers of patients with apathy experience greater burden and apathy- but not depression-related distress.** In a cross-sectional study of patients with small vessel

disease (SVD), carers of patients with apathy presented higher distress and care burden than carers of non-apathetic patients. These results were still significant after controlling for possible factors influencing the relationship, such as patient's functional outcome and carer's physical and mental QOL. However, mediation analyses also revealed that the patient's functional outcome partially mediates the relationship of apathy with care distress and burden. Interestingly, despite a high co-occurrence of apathy and depression in the study group, no significant differences were found between the apathy and control group in carer distress caused by depression symptoms. The current findings seem to suggest that apathy is a distinct symptom with discernible effects from depression. Comparisons of carers QOL between the two groups, however, showed no significant differences. These results seem to differ from previous studies showing that carer's QOL and burden are associated (McCullagh *et al.,* 2005; van Exel *et al*., 2005). Results in the current study might be explained by the low sample size of the cohort: as highlighted by the study's power analyses, a larger sample might be needed to identify the effect in this population. Nonetheless, this study aims at providing a guide for future studies to be conducted in stroke cohorts and a reference for the sample size and methodology to be employed.

Results from this study hold clinical relevance and imply that attention should be directed to carers, as well as patients affected by apathy. Families might be the first to observe symptoms and lifestyle changes due to apathy, as well as being affected the most by this syndrome.

Moreover, these findings hold promising translational implications and should encourage future research to develop new and appropriate rehabilitation and educational interventions directed at carers and families of patients affected by apathy. Shifting the intervention goal from patient to families might reduce carer's burden and distress, as well as have indirect positive consequences on patients.

9.2 Future directions

Here, some areas of future research are suggested and discussed, specifically in the context of the findings of this thesis and the questions which were left unanswered.

1. **Neurobiological bases of apathy in stroke.** While theories have been suggested in this respect, findings are still nonunivocal in detailing the neurophysiological causes of this symptom (Tay *et al.,* 2020a). From a methodological perspective, longitudinal studies might be useful in informing the progression of pathology by combining multiple assessments of apathy and repeated brain imaging. Studies using finer imaging methods, including Diffusion Tensor Imaging (DTI), might shed light on the complex association between white matter damage and apathy symptoms. Longitudinal studies might help explain why stroke patients present different symptom trajectories, as shown in this thesis, with some showing worse apathy after one year and others remaining stable throughout this time. Longitudinal studies exploring the growth of white matter hyperintensity (WMH) might also shed light on the association between increasing WMH burden and the trajectory of symptoms. Finally, future research is needed to clarify the possible role of hemispheric differences in apathy presentation.

2. **Role of apathy as an early marker of vascular dementia.** This thesis highlighted the association existing between apathy and cognition. Future studies might further explore this association by considering it in the wider context of vascular dementia. While it is well established that apathy is an early marker of dementia in patients with Alzheimer's Disease (Johansson *et al.,* 2019), Parkinson's Disease (Fitts *et al.,* 2015), and Frontotemporal Dementia (Malpetti *et al.,* 2021), only few studies suggested that apathy is an early indicator of dementia in small vessel disease patients and that assessing apathy might help identify individuals at risk of developing dementia (Onoda *et al.,* 2011; Tay *et al.,* 2020b). Further research is necessary to replicate these findings in patients with cerebrovascular disease: studies including larger groups of patients with different types of stroke might help clarify associations between apathy symptoms, subtypes of cognitive impairment, and trajectory of dementia. Specific modelling is also necessary to try and clarify the relationship between apathy and mortality in vascular dementia since studies conducted in dementia and community-dwelling populations found that apathy is associated with increased mortality (Eurelings *et al.,* 2018; Nijsten *et al*., 2017).
   A possible avenue for these studies would be to examine the association of apathy with specific cognitive functions by employing behavioural tasks assessing effort-based

decision making (Saleh *et al*., 2021). This may lead to a better understanding of the altered cognitive functions and mechanisms that specifically underlie apathy, including how small vessel disease and focal infarcts affect brain networks. More generally, a better understanding of apathy and its mechanisms might inform the understanding of goal-directed behaviour and motivation; this has important implications since motivation is a requirement to satisfy basic needs and a fundamental component of human interactions (Simpson and Balsam, 2016).

3. **Treatments and interventions for apathy.** Currently no gold standard treatment exists for apathy, and pharmacological medication does not appear to significantly affect apathy symptoms (Manera *et al*., 2020; Starkstein *et al.,* 2016; Whyte *et al.,* 2008). Future efforts should be directed at developing novel interventions and treatments. Among other possibilities, cognitive rehabilitation and training sessions have been considered and might represent a promising avenue (Mikami *et al.,* 2013; Skidmore *et al*., 2015). Importantly, when considering this type of approach, patient's symptom awareness should be taken into consideration. As showed in this thesis, most apathetic patients might be unaware of their symptoms and lack of awareness might affect adherence to rehabilitation programs (Resnick *et al*., 1998): this might result in worsening of the cognitive status which, in turn, might aggravate and reduce awareness (Derouesné *et al.,* 1999).

   A possible alternative avenue to cognitive interventions is to develop specific educational programs for carers to include informative sessions about apathy. Previous studies found that increased carer burden can result in reduced ability to provide optimal care and, eventually, in a negative outcome for both carer and patient (Hiseman and Fackrell, 2017). In patients with dementia, interventions for carers proved to reduce carer burden and improve QOL (McCullagh *et al*., 2005), and carer training was found to be significantly associated with delayed nursing home admission and reduced mortality (Brodaty *et al.,* 1993; Mittelman *et al.,* 1996). A review on progressive supranuclear palsy found that carer education and support is important in managing the cognitive and behavioural changes of patients, including apathy, however it noted that no evidence was found to support the use of carer education alone (Rittman *et al.,* 2016). Carer training

could be described as an educational approach to provide information about the patient's condition and apathetic behaviour and the learning of strategies to manage apathy symptoms: this type of training would involve family and carers in multi-disciplinary team meetings, goal setting and decision making, and could potentially reduce negative consequences of apathy (Braine, 2014; Manera *et al*., 2020). Future translational studies might compare such treatments and interventions in larger patient cohorts.

4. **Methodological aspects.** Some methodologies described in this thesis need further discussion and thorough consideration, especially when planning future studies in this area of research.

    4.1 *Multiple comparisons problem*. Various analyses described in this thesis were conducted by comparing multiple scales at different timepoints while correcting for multiple variables (Chapters 3 and 5). Multiple comparisons might cause a higher chance of finding false positive results. To address this issue, stricter controls on the significance level might be applied, by using a controlling procedure (such as controlling the family-wise error rate or the false discovery rate) (Lee and Lee, 2018). An alternative solution would be to adopt a Bayesian approach (Sjölander and Vansteelandt, 2019).

    4.2 *Quality of MRI scans*. The study set-up described in this thesis did not require a standardised protocol for MRI scans acquisition and most images were collected as part of a clinical scan that participants underwent during admission in the acute stroke unit (Chapter 2 and 6). This resulted in a heterogenous set of scans which also impacted data harmonisation. Moreover, greater data variability might have been caused by the use of different scanners and sequence settings in the different recruitment sites. Future studies should set a sequencing protocol *a priori* or systematically collect details about the different scanners used, including the number of scanners employed and the relevant field of strength.

4.3 *Diffusion Tensor Imaging (DTI) data*. This type of data might allow more detailed and advanced investigations into structural connectivity patterns. In the current study, the choice of investigating white matter network connectivity in association with apathy despite the lack of DT images might have caused type II errors, allowing for a less than perfect identification of disrupted networks, eventually impacting the quality and generalisability of results (Chapter 6).

4.4 *Formula used to determine apathy awareness*. The formula used to measure apathy awareness in this thesis was used here for the first time and has not been previously standardised (Chapter 7). Future research might replicate the methods used for this study in a larger cohort to assess the validity of this formula. It should also be noted that the formula considers informants as the best objective method to rate apathy symptoms: however, it could be argued that this is an approximation and that diagnostic criteria should be considered the gold standard to assess and measure apathy symptoms. The formula might also be influenced by the accuracy of apathy questionnaires and patients' response to these. Hence, future studies should aim at employing more objective measures of both apathy and patients' awareness.

4.5 *Sample size*. The analyses performed throughout this thesis should be replicated in larger sample sizes. This would be feasible using open-access databases or by combining data from multiple cohorts of stroke and SVD patients. The larger sample sizes would allow to further explore and analyse the effects of apathy on carer's QOL and burden.

9.3 Conclusion

In conclusion, we found that apathy tends to increase over one year in a cohort of ischemic stroke patients, although the majority of participants seemed to have stable or low levels of apathy. Moreover, apathy, but not depression, seemed to be a significant factor in determining carer's burden in a cohort of small vessel disease patients. Taken together, these results highlight the need to analyse individual trajectory of apathy in larger cohorts and continue investigating

the relation between apathy and carer's QOL and care burden, in order to establish better knowledge on mechanisms and treatments of apathy.

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Appendix

1. Apathy and Outcome after Stroke Study

1.1 Research Ethics Committee approval letter

NHS
Health Research Authority
East of England - Cambridge Central Research Ethics Committee

[redacted]

REDACTION: address has been removed for confidentiality reasons.

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

05 October 2016

[redacted]

REDACTION: name, address, and email address have been removed. Personal data removed for confidentiality reasons.

Dear [redacted],

Study title:	**Apathy and outcome of the stroke and its relationship to cerebral small vessel disease**
REC reference:	**16/EE/0333**
IRAS project ID:	**211282**

Thank you for your letter of 30 September 2016, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, [redacted]

REDACTION: name and email address have been removed for confidentiality reasons.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Mental Capacity Act 2005

I confirm that the committee has approved this research project for the purposes of the Mental Capacity Act 2005. The committee is satisfied that the requirements of section 31 of the Act will be met in relation to research carried out as part of this project on, or in relation to, a person who lacks capacity to consent to taking part in the project.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

REDACTION: name and email address have been removed for confidentiality reasons.

If a sponsor wishes to contest the need for registration they should contact [redacted], the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Contract/Study Agreement [Template of the site agreement]		
Covering letter on headed paper		
Covering letter on headed paper		
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		
GP/consultant information sheets or letters		
IRAS Application Form [IRAS_Form_21072016]		21 July 2016
IRAS Application Form XML file [IRAS_Form_21072016]		21 July 2016
IRAS Checklist XML [Checklist_21072016]		21 July 2016
IRAS Checklist XML [Checklist_21072016]		21 July 2016
IRAS Checklist XML [Checklist_30092016]		30 September 2016
Letter from funder		
Other [clarification email from DL re independent review]		21 July 2016
Other [Statement of activities]		
Other [Schedule of events]		
Participant consent form [Carer consent form]	1.5	27 September 2016
Participant consent form [Stroke patient consent form]	1.6	27 September 2016
Participant consent form [Consultee consent form]	1.3	28 September 2016

Participant information sheet (PIS) [Carer PIS]	1.4	28 September 2016
Participant information sheet (PIS) [Stroke patient PIS]	1.5	28 September 2016
Participant information sheet (PIS) [Consultee PIS]	1.5	28 September 2016
Research protocol or project proposal	1.9	15 September 2016
Summary CV for Chief Investigator (CI)		
Validated questionnaire [Apathy Evaluation Scale - self report]		
Validated questionnaire [Apathy Evaluation Scale - carer for female patient]		
Validated questionnaire [Apathy Evaluation Scale - carer for male patient]		
Validated questionnaire [Dimensional Apathy Scale - self report]		
Validated questionnaire [Dimensional Apathy Scale - carer report]		
Validated questionnaire [Geriatric Depression Scale]		
Validated questionnaire [Modified Rankin Scale]		
Validated questionnaire [Frenchay Activities Index]		
Validated questionnaire [Quality of life]		
Validated questionnaire [Montreal Cognitive Assessment v 1]		
Validated questionnaire [The Brief Memory and Executive Test - left hand version]		
Validated questionnaire [Montreal Cognitive Assessment v 3]		
Validated questionnaire [Montreal Cognitive Assessment v 2]		
Validated questionnaire [The Brief Memory and Executive Test - right hand version]		
Validated questionnaire [Controlled Oral Word Association Test + Animal Fluency Test]		
Validated questionnaire [National Adult Reading Test – Restandardised]		
Validated questionnaire [Trail Making Test part 1]		
Validated questionnaire [Trail Making Test part 2]		
Validated questionnaire [WAIS IV Coding Test]		
Validated questionnaire [WAIS IV Forward Digit Span]		
Validated questionnaire [WMS IV Logic Memory]		
Validated questionnaire [WMS IV Visual Reproduction]		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

16/EE/0333	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely,

Chair

REDACTION: signature, names and email addresses have been removed.
Personal data removed for confidentiality reasons.

Email: [redacted]

Enclosures: "After ethical review – guidance for researchers"

Copy to: [redacted] *University of Cambridge*
Cambridge University Hospitals NHS Foundation Trust

1.2 HRA approval letter

NHS
Health Research Authority

[redacted]

Email: [redacted]

REDACTION: name, address and email addresses have been removed.
Personal data removed for confidentiality reasons.

13 December 2016

Dear [redacted]

Letter of HRA Approval

Study title:	**Apathy and outcome of the stroke and its relationship to cerebral small vessel disease**
IRAS project ID:	**211282**
REC reference:	**16/EE/0333**
Sponsor	**Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *"After Ethical Review – guidance for sponsors and investigators"*, issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to [redacted] REDACTION: email address has been removed for confidentiality reasons.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

IRAS project ID	211282

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please email the HRA at [redacted]
Additionally, one of our staff would be happy to call and discuss your experience of HRA Approval.

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HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

Your IRAS project ID is **211282**. Please quote this on all correspondence.

Yours sincerely

[redacted]
Assessor

Email: [redacted]

REDACTION: names and email addresses have been removed. Personal data removed for confidentiality reasons.

Copy to: [redacted] *University of Cambridge [Sponsor Contact]*
[redacted]
[redacted] *Cambridge University Hospitals NHS Foundation Trust [Lead NHS R&D Contact]*
[redacted]
NIHR CRN Portfolio Applications Team
[redacted]

1.3 Participant Information Sheet – stroke patient

UNIVERSITY OF CAMBRIDGE

Cambridge University Hospitals NHS
NHS Foundation Trust

PARTICIPANT INFORMATION SHEET – STROKE PATIENT

Study: Apathy and outcome after stroke

You are invited to participate in a research project we are running to find out whether apathy occurring soon after stroke is related to slower recovery and diminished quality of life of a person a year later. Before you decide whether to take part it is important that you understand why the research is being done and what it will involve. Please take time to read the following information sheet carefully and discuss it with friends, relatives, and your GP if you wish.

Do ask/contact us if there is anything that is not clear to you or if you would like more information. Please find contact details on the next page.

1. What is the purpose of the study?

People after stroke often experience apathy. Apathy can be described as reduction in initiative, interests, activity or emotional reactions. The occurrence of apathy after stroke may affect recovery. We are carrying out this study to find out whether individuals who develop apathy after stroke recover less well and experience more disability after a year than those who do not experience apathy. Two hundred participants are expected to take part in this study.

Apathy is especially common after strokes that affect small blood vessel in the brain. This is called small vessel disease. In this study we will also investigate whether small vessel disease, measured on a brain MRI scan, increases the risk of apathy after stroke.

2. Why have I been chosen?

You have been chosen because you have experienced stroke in the last 2 weeks.

3. Do I have to take part?

Your participation in the study is entirely voluntary. It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time without giving a reason. If you decide not to take part in the study or to withdraw, the standard of care you receive will not be affected.

4. What will happen to me if I take part?

If you agree to take part we will ask to see you, and carry out assessments, at four points after your stroke as outlined below. In addition we will ask some of those taking part in the study if they are happy to take part in an additional assessment which will involve a more advanced MRI scan.

1st time we will see you in the hospital just after stroke

We will collect details about your stroke and past medical history, carry out physical exam, ask you to fill in questionnaires about your mood and post-stroke possible feeling of apathy, and carry out memory tests. If you have not already had an MRI brain scan as a part of your routine care we will perform one; this takes about 30 minutes. Finally, we will take a blood sample (15ml).

2nd and 3rd time we will contact you at 1 month and 6 months after stroke

We will either see you in person or contact you via the phone or via post. We will ask you to complete questionnaires about your mood and possible feelings of apathy.

4th time we will see you in the hospital 1 year after stroke

We will complete questionnaires about your health, mood, possible apathy, daily activities and quality of life and carry out memory tests. Finally, we will take a blood sample (10ml).

3 months after stroke – more detailed MRI sub-study

You may be asked to take part in an optional sub-study which involves a more detailed research MRI scan. We will carry out a 40 minute advanced MRI scan in [insert the name of neuroimaging centre], additional memory testing and we will ask you to complete questionnaires about your mood, possible feelings of apathy, daily activities and quality of life.

What is an MRI scan?

The brain MRI scan takes pictures of your brain. This is a painless and safe brain scanning technique which takes place in an MRI scanner and takes about 30 minutes. It is often used in routine clinical care after stroke. An advanced MRI scan is more detailed than clinical MRI scan and takes about 45 minutes and allows us to observe more subtle characteristics of the brain. An experienced radiographer performs the scan. The radiographer will ask you to lie down very still in an MRI scanner for the period of the scan.

Carer involvement

If you live with a partner or other relative/friend or have a carer, with your permission we will ask him or her to consent to complete questionnaires about his or her perception of your feeling of apathy every time we contact you.

GP information

Your GP will be informed by letter of your participation in the study.

5. What will happen to my blood sample?

Your sample will firstly be stored at the hospital you visit and will later be transferred to the research centre at Cambridge University Hospitals for long term storage. It will be used to see whether any markers in the blood are related to apathy after stroke. Additionally, blood samples collected in the study will help us determine whether there are biological reasons (such as genetic factors) that mean some people are more likely to experience apathy after stroke.

6. What will happen to the data?

Anonymised study data will be securely sent, analysed and stored securely at the University of Cambridge.

7. What are the possible benefits of taking part?

There are no direct benefits to you from taking part in this study; however the results may help us understand the role apathy plays in stroke recovery and help people with stroke in the future.

8. What are the possible disadvantages and risks of taking part?

Blood sampling: some bruising and discomfort can occasionally occur after having blood taken. The blood sampling will be performed by trained staff.

MRI: some people find space in an MRI scanner limited. The scanner is, however, open at both ends. When you are in the scanner you can talk to the radiographer and the researcher between scanning sequences. You also have a buzzer to signal to the radiographer at any time during scanning if you need to. The scanner is loud so to protect you from the noise you are given soft foam ear plugs and ear defenders.

9. What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. If you have a concern about any aspect of the study, you should ask to speak to the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the Cambridge University Hospitals NHS Complaints Procedure by telephoning PALS on [redacted]. Details can also be obtained from the hospital. REDACTION: contact details have been removed for confidentiality reasons.

In the event that something goes wrong and you are harmed during the research, and this is due to someone's negligence, then you are protected by indemnity insurance provided by the University of Cambridge. Details of this insurance can be obtained from the University of Cambridge Insurance Section, [redacted].

REDACTION: contact details have been removed for confidentiality reasons.

[redacted] or by telephoning [redacted]. If you are harmed and negligence has not occurred the NHS complaints system will be available to you.

10. What will happen if there is a big change in my abilities during the year of follow up?

There is a small chance that the disease will progress or further strokes will occur resulting in a significant decline in cognitive abilities. If it is deemed at any point in the study, that your cognitive abilities have declined sufficiently to impair your ability to continue, you will be asked if you wish to carry on in the study. If you are unable to make this decision yourself, a legal representative will be consulted on your behalf. Once consulted the legal representative may implement withdrawal of consent on your behalf at any time.

In line with the Mental Capacity Act (2005), your representative will be asked to consider your feelings and wishes and decide whether you would wish to continue to participate in the study. During your first visit, you will be asked to provide contact information for an individual who may be asked to provide advice in this way.

11. Will my taking part in this study be kept confidential?

Your personal information will be accessed, used and stored in accordance with the Data Protection Act (1998). All information which is collected about you during the course of the research will be kept strictly confidential. Only the research team will have access to your personal details. Research data will be linked to a participant number for anonymous storage and analysis. Publications arising from this research will not identify individuals or present results in such a way that individuals could be identified from a combination of non-identifying details.

12. Expenses

We will be able to reimburse you for reasonable travel expenses when you come to the hospital for a visit regarding the research.

13. Who is organising and funding the study?

The study has been funded by the Stroke Association and the study has been reviewed by a number of experts selected by the Stroke Association. This study is being co-ordinated by Cambridge University Hospitals NHS Foundation Trust. The study has been approved by Research Ethics Committee – East of England – Cambridge Central. The research arose from patient involvement groups lead by the Stroke Association which highlighted the importance of apathy after stroke.

Thank you for taking time to consider participating in the study. If you agree to take part you will be given a copy of this information sheet and a copy of the signed consent form.

If you have questions about the study at any time please contact the local study organiser: [redacted], phone number: [redacted], e-mail address: [redacted]

REDACTION: name, email address and contact details have been removed for confidentiality reasons.

1.4 Participant Information Sheet – carer

UNIVERSITY OF CAMBRIDGE

Cambridge University Hospitals NHS
NHS Foundation Trust

PARTICIPANT INFORMATION SHEET – CARER

Study: Apathy and outcome after stroke

You are invited to participate in a research project we are running to find out whether apathy occurring soon after stroke is related to slower recovery and diminished quality of life of a person a year later. Apathy can be evaluated from the perspective of a patient as well as their carer. Before you decide whether to take part it is important that you understand why the research is being done and what it will involve. Please take time to read the following information sheet carefully and discuss it with friends and relatives if you wish.

Do ask/contact us if there is anything that is not clear to you or if you would like more information. Please find contact details on the next page.

1. What is the purpose of the study?

People after stroke often experience apathy. Apathy can be described as reduction in initiative, interests, activity or emotional reactions. The occurrence of apathy after stroke may affect recovery. We are carrying out this study to find out whether individuals who develop apathy after stroke recover less well and experience more disability after a year than those who do not experience apathy. We believe that carers of individuals with stroke have a unique perspective on a patient's apathy and can provide information leading to a fuller understanding of the patient's condition.

2. Why have I been chosen?

You have been chosen because a person in your care has experienced stroke in the last 2 weeks.

3. Do I have to take part?

Your participation in the study is entirely voluntary. It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time without giving a reason. If you decide not to take part in the study, the standard of care you receive will not be affected at any time.

4. What will happen to me if I take part?

You will complete questionnaires about apathy of the person in your care. You will do it on four occasions: just after the person in your care has had a stroke, subsequently 1 month, 6 months and 1 year after this event. In addition we will ask some of those taking part in the study if they are happy to take part in an additional assessment at 3 months after the event.

5. What will happen to the data?

Anonymised study data will be securely sent, analysed and stored securely at the University of Cambridge.

6. What are the possible benefits of taking part?

There are no direct benefits to you from taking part in this study; however the results may help understand the role apathy plays in stroke and help people with stroke and their carers in the future.

7. What are the possible disadvantages and risks of taking part?

There are no direct risks or disadvantages of taking part in the study.

8. What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. If you have a concern about any aspect of the study, you should ask to speak to the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain

formally, you can do this through the Cambridge University Hospitals NHS Complaints Procedure by telephoning PALS on [redacted]. Details can also be obtained from the hospital.

REDACTION: contact details have been removed for confidentiality reasons.

In the event that something goes wrong and you are harmed during the research, and this is due to someone's negligence, then you are protected by indemnity insurance provided by the University of Cambridge. Details of this insurance can be obtained from the University of Cambridge Insurance Section, [redacted] or by telephoning [redacted]. If you are harmed and negligence has not occurred the NHS complaints system will be available to you.

REDACTION: contact details have been removed for confidentiality reasons.

9. Will my taking part in this study be kept confidential?

Your personal information will be accessed, used and stored in accordance with the Data Protection Act (1998). All information which is collected about you during the course of the research will be kept strictly confidential. Only the research team will have access to your personal details. Research data will be linked to a participant number for anonymous storage and analysis. Publications arising from this research will not identify individuals or present results in such a way that individuals could be identified from a combination of non-identifying details.

10. Expenses

We will be able to reimburse you for reasonable travel expenses when you come to the hospital for a visit regarding the research.

11. Who is organising and funding the study?

The study has been funded by the Stroke Association and the study has been reviewed by a number of experts selected by the Stroke Association. This study is being co-ordinated by Cambridge University Hospitals NHS Foundation Trust. The study has been approved by Research Ethics Committee – East of England – Cambridge Central. The research arose from patient involvement groups lead by the Stroke Association which highlighted the importance of apathy after stroke.

Thank you for taking time to consider participating in the study. If you agree to take part you will be given a copy of this information sheet and a copy of the signed consent form.

If you have questions about the study at any time please contact the local study organiser: [redacted], phone number: [redacted], e-mail address: [redacted].

REDACTION: name, email address and contact details have been removed for confidentiality reasons.

1.5 Informed Consent Form – stroke patient

UNIVERSITY OF CAMBRIDGE

Cambridge University Hospitals NHS
NHS Foundation Trust

CONSENT FORM – STROKE PATIENT

Study: Apathy and outcome after stroke

Investigators: [redacted]

REDACTION: names have been removed for confidentiality reasons.

Please initial box:

1) I confirm that I have read and understood the information sheet dated 29-09-2016 (version 1.5) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2) I understand that my participation is voluntary and I am free to withdraw my consent at any time, without giving any reason, without my medical care or legal rights being affected. Should my capacity to participate or withdraw consent decline, I agree that a consultee named by me may implement withdrawal of consent on my behalf. ☐

3) I understand that relevant sections of my medical notes may be looked at by responsible individuals from the research team conducting this study or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

4) I understand that my GP will be informed of my participation. ☐

5) I agree to have a blood sample taken which will be used to investigate what causes apathy after stroke. ☐

6) I understand that my personal information will remain confidential to the researchers. ☐

7) I agree to take part in the above study ☐

8) Should my cognitive abilities significantly decline I wish to continue in the study provided that the consultee considers it to be in my best interest. YES/NO

Optional

9) I agree to take part in the advanced MRI brain imaging sub-study. ☐

10) I am happy for my partner/carer to be approached and complete questionnaires about my recovery from stroke. ☐

11) I am happy for my anonymised data and blood samples to be used in future studies. ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of the person taking consent (if different from Investigator)	Date	Signature
_____	_____	_____
Name of Investigator	Date	Signature

1.6 Informed Consent Form – carer

UNIVERSITY OF CAMBRIDGE

Cambridge University Hospitals NHS
NHS Foundation Trust

CONSENT FORM – CARER

Study: Apathy and outcome after stroke

Investigators: [redacted]

REDACTION: names have been removed for confidentiality reasons.

Please initial box:

1) I confirm that I have read and understood the information sheet dated 28-09-2016 (version 1.4) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2) I understand that my participation is voluntary and I am free to withdraw my consent at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3) I understand that my personal information will remain confidential to the researchers. ☐

4) I agree to take part in the above study. ☐

Optional

5) I am happy for my anonymised data to be used in future studies. ☐

_____	_____	_____
Name of Carer	Date	Signature
_____	_____	_____
Name of the person taking consent (if different from Investigator)	Date	Signature
_____	_____	_____
Name of Investigator	Date	Signature

2. Apathy and Quality of Life Study

2.1 Research Ethics Committee approval letter

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

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Personal data removed for confidentiality reasons.

[redacted]

West of Scotland REC 5

[redacted]

Date 24 February 2022

Direct line [redacted]
E-mail

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

Dear [redacted]

Study title:	**Apathy and Quality of Life Study**
REC reference:	**22/WS/0010**
Protocol number:	**Protocol version 1.1**
IRAS project ID:	**306418**

Thank you for your letter of 11 February 2022, responding to the Research Ethics Committee's (REC) request for further information on the above research and submitting revised documentation.

The further information was considered in correspondence by a Sub-Committee of the REC. A list of the Sub-Committee members is attached.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Good practice principles and responsibilities

The UK Policy Framework for Health and Social Care Research sets out principles of good practice in the management and conduct of health and social care research. It also outlines the responsibilities of individuals and organisations, including those related to the four elements of research transparency:

1. registering research studies
2. reporting results
3. informing participants
4. sharing study data and tissue

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or NHS management permission (in Scotland) should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All research should be registered in a publicly accessible database and we expect all researchers, research sponsors and others to meet this fundamental best practice standard.

It is a condition of the REC favourable opinion that **all clinical trials are registered** on a publicly accessible database within six weeks of recruiting the first research participant. For this purpose, 'clinical trials' are defined as:

- clinical trial of an investigational medicinal product
- clinical investigation or other study of a medical device
- combined trial of an investigational medicinal product and an investigational medical device
- other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice.

Failure to register a clinical trial is a breach of these approval conditions, unless a deferral has been agreed by the HRA (for more information on registration and requesting a deferral see: Research registration and research project identifiers).

If you have not already included registration details in your IRAS application form you should notify the REC of the registration details as soon as possible.

Publication of Your Research Summary

We will publish your research summary for the above study on the research summaries section of our website, together with your contact details, no earlier than three months from the date of this favourable opinion letter.

Should you wish to provide a substitute contact point, make a request to defer, or require further information, please visit: https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/

N.B. If your study is related to COVID-19 we will aim to publish your research summary within 3 days rather than three months.

During this public health emergency, it is vital that everyone can promptly identify all relevant research related to COVID-19 that is taking place globally. If you haven't already done so, please register your study on a public registry as soon as possible and provide the REC with the registration detail, which will be posted alongside other information relating to your project. We are also asking sponsors not to request deferral of publication of research summary for any projects relating to COVID-19. In addition, to facilitate finding and extracting studies related to COVID-19 from public databases, please enter the WHO official acronym for the coronavirus disease (COVID-19) in the full title of your study. Approved COVID-19 studies can be found at: https://www.hra.nhs.uk/covid-19-research/approved-covid-19-research/

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

After ethical review: Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study, including early termination of the study
- Final report
- Reporting results

The latest guidance on these topics can be found at https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/.

Ethical review of research sites

NHS/HSC sites

The favourable opinion applies to all NHS/HSC sites taking part in the study, subject to confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or management permission (in Scotland) being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS/HSC sites

I am pleased to confirm that the favourable opinion applies to any non-NHS/HSC sites listed in the application, subject to site management permission being obtained prior to the start of the study at the site.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering letter on headed paper [Cover letter]		
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Provisional insurance cover]		17 November 2021

IRAS Application Form [IRAS_Form_16122021]		16 December 2021
Letters of invitation to participant [Invitation letter]	1.0	10 December 2021
Other [Protocol v1.2 - tracked changes]	1.2	11 February 2022
Other [Response to REC provisional opinion]	NA	11 February 2022
Participant consent form [Patient consent form]	1.1	11 February 2022
Participant consent form [Patient consent form - tracked changes]	1.1	11 February 2022
Participant consent form [Carer consent form]	1.1	11 February 2022
Participant consent form [Carer consent form - tracked changes]	1.1	11 February 2022
Participant information sheet (PIS) [Patient information sheet]	1.1	11 February 2022
Participant information sheet (PIS) [Patient information sheet - tracked changes]	1.1	11 February 2022
Participant information sheet (PIS) [Carer information sheet]	1.1	11 February 2022
Participant information sheet (PIS) [Carer information sheet - tracked changes]	1.1	11 February 2022
Referee's report or other scientific critique report [NE Review form]	1	11 November 2021
Referee's report or other scientific critique report [SN Review form]	NA	06 December 2021
Research protocol or project proposal [Study protocol]	1.2	11 February 2022
Summary CV for Chief Investigator (CI) [CI CV]		10 December 2021
Summary CV for student [redacted] CV]		10 December 2021
Summary CV for supervisor (student research) [Supervisor CV]		10 December 2021
Validated questionnaire [Montreal Cognitive Assessment test]	7.1	
Validated questionnaire [BMET right handed version]	3.0	17 January 2017
Validated questionnaire [BMET left handed version]	3.0	17 January 2017
Validated questionnaire [Apathy Evaluation Scale - self-rated]		
Validated questionnaire [Apathy Evaluation Scale - Clinician form]		
Validated questionnaire [Apathy Evaluation Scale - informant-rated]		
Validated questionnaire [Beck's Depression Inventory]		
Validated questionnaire [Neuropsychiatric Inventory]		
Validated questionnaire [Hospital Anxiety and Depression Scale]		
Validated questionnaire [Zarit Burden Interview]		
Validated questionnaire [36-item Short Form Survey Instrument]		

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Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: https://www.hra.nhs.uk/planning-and-improving-research/learning/

IRAS project ID: 306418 Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely

[redacted]

for

[redacted]

Chair

REDACTION: signature, names and email address have been removed. Personal data removed for confidentiality reasons.

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments

"After ethical review – guidance for researchers"

Copy to: [redacted] Cambridge University Hospitals

Lead Nation - England: [redacted]

2.2 HRA approval letter

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

[redacted]

Email: [redacted]

REDACTION: names, addresses, and email addresses have been removed.
Personal data removed for confidentiality reasons.

22 March 2022

Dear [redacted],

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Apathy and Quality of Life Study**
IRAS project ID:	**306418**
Protocol number:	**Protocol version 1.1**
REC reference:	**22/WS/0010**
Sponsor	**Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document '*After Ethical Review – guidance for sponsors and investigators*', issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **306418**. Please quote this on all correspondence.

Yours sincerely,

[redacted]
HRA Approvals Specialist

Email: [redacted]

REDACTION: names and email addresses have been removed. Personal data removed for confidentiality reasons.

Copy to: [redacted]

2.3 Participant Information Sheet – stroke patient

UNIVERSITY OF CAMBRIDGE

Cambridge University Hospitals NHS
NHS Foundation Trust

PARTICIPANT INFORMATION SHEET – STROKE PATIENT

Study: Apathy and Quality of Life

You are being invited to take part in a research study. Before deciding whether to take part, you need to understand why this research is being done and what it involves. Please take time to read the following information carefully and talk to others about the study if you wish. Please ask us if anything is not clear or if you would like more information. Please take time to decide whether or not you wish to take part.

Section 1 tells you the purpose of this study and what will happen to you if you take part.
Section 2 gives you more detailed information about the conduct of the study.

Section 1: Purpose of the study and what will happen

1. What is the purpose of the study?
You are invited to participate in a research project we are running to find out whether apathy occurring after stroke is related to diminished quality of life in stroke patients and their carers and increased carer stresses. People after stroke often experience apathy. Apathy can be described as a reduction in motivation, interests, and social interactions. The occurrence of apathy after stroke may also affect carers.

2. Why have I been invited?
You have been invited to participate in this study because you have experienced stroke.

We plan to include 60 participants who experienced a stroke and their carers from Cambridge University Hospital Stroke Service.

3. Do I have to take part?
Participating in this study is completely voluntary. If you decide to participate you will be asked to sign an Informed Consent Form, however you are still free to change your mind and leave the study at any time without giving a reason. If you chose not to participate or to leave the study, your future medical treatment and normal standard of care will not be affected in any way.

4. What will happen to me if I take part?
If you are willing to participate in the study, you will sign the Informed Consent Form and be given a copy of this to take away and refer to later.

The researcher in charge of the study will then be in touch with you to perform a short screening interview whose result will determine which study group you will be assigned to. We will need to recruit an equal number of participants in each group, so it is possible that you might not be invited to continue the study if your group is already full. The researcher in charge of the study will confirm this to you.

If your participation to the study is confirmed, we will then ask to see you and your carer and carry out a one-off assessment. We will contact you via telephone or video call.

During this assessment we will collect details about your stroke and past medical history, ask you to fill in questionnaires about your health, mood and post-stroke possible feeling of apathy, and carry out memory tests.

If you live with a partner or other relative/friend or have a carer, with your permission we will ask him or her to consent to complete questionnaires about his or her perception of your feeling of apathy as well as questionnaires about his or her mood and quality of life.

The assessment for you and your relative will last approximately 1.5 hours: rest breaks will be provided when needed. No follow-up will be conducted.

5. What will I have to do?
If you decide to take part in the study you will be asked to visit the hospital for the assessment or join a remote call, in which case the material will be posted to you.

6. What are the possible disadvantages and risks of taking part?
There are no direct disadvantages of taking part in this study. Interviews might include sensitive topics: participants will be provided a comfortable and safe environment during the assessment and will be able to refuse to answer any questions at any time and without giving explanations.

All participants and carers taking part in the study will receive careful follow-up and the mood screening data acquired will be available to the treating clinicians to monitor your progress.

In case previously undetected findings are identified, this information will be communicated to your treating clinician who will advise you on how to proceed.

7. What are the possible benefits of taking part?
There is no guarantee that you will benefit from taking part in this study. However information collected as part of your participation in this study may benefit patients who experience apathy after stroke and their carers in the future.

8. Expenses & Payment
You will not receive any payment for participating in this study, however we can reimburse any reasonable travel and parking costs incurred by your participation in this study.

Section 2: Study Conduct

9. What if new information becomes available?
Sometimes during the course of a study, new information becomes available which might affect your decision to continue participating in this study. The study coordinator will contact you to discuss the new information and whether you wish to continue participating in the study. If you still wish to continue on the study, you will be asked to sign a new Informed Consent Form. The study sponsor, the regulatory authority or the study coordinator may decide to stop the study at any time. If that happens we will tell you why the study has been stopped.

10. What if I decide I no longer wish to participate in the study?
You are free to come off the study at any time without giving a reason and without affecting your future care or medical treatment. If you decide not to participate any further, no further tests will be performed on you. Any data already collected or results from tests already performed on you will continue to be used in the study analysis.

The study coordinators may also choose to withdraw you from the study if they feel it is in your best interests or if you are unable to comply with the requirements of the study. Reasons for study withdrawal could include inability to complete the visits or study documentation as required.

11. What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. If you have any concerns about any aspect of this study you should speak to the study researchers who will do their best to answer your questions.

In the event that something does go wrong and you are harmed by taking part in the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Cambridge University Hospitals NHS Foundation Trust or the University of Cambridge. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).The University has obtained insurance which provides no-fault compensation i.e. for non-negligent harm, you may be entitled to make a claim for this.

If you wish to complain or have any concerns about any aspect of the way you have been approached or treated during this study, you can do this through the NHS complaints procedure. In the first instance it may be helpful to contact the Cambridge University Hospitals NHS Complaints Procedure by telephoning the Patient Advice and Liaison Service (PALS) on [redacted]. REDACTION: contact details removed for confidentiality reasons.

12. Will my taking part in this study be kept confidential?

Cambridge University Hospitals NHS Foundation Trust (CUH) and The University of Cambridge are the Sponsors for this study based in the United Kingdom. They will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that they are responsible for looking after your information and using it properly. The Sponsor organisations will keep identifiable information about you for 10 years after the study has finished to ensure your safety and allow the study to be reviewed by the authorities after it is finished.

Your rights to access, change or move your information are limited, as the Sponsor organisations need to manage your information in specific ways in order for the research to be reliable and accurate. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how the Sponsors use your information using the information below:

- For Cambridge University Hospitals NHS Foundation Trust, please visit: https://www.cuh.nhs.uk/patient-privacy/ or email The Data Protection Officer at: [redacted] REDACTION: email address removed for confidentiality reasons.

- For University of Cambridge, please visit: https://www.medschl.cam.ac.uk/research/information-governance or email The Information Governance team at: [redacted] REDACTION: email address removed for confidentiality reasons.

The Stroke Research Group at Addenbrooke's Hospital, Cambridge University Hospital NHS Foundation Trust, will collect your name, NHS number and contact details to contact you about

this study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from the CUH NHS Foundation Trust/University of Cambridge and regulatory organisations may look at your medical and research records to check the accuracy of this study. The Stroke research Group will pass these details to the Sponsors along with the information collected from you and/or your medical records. The only people in the Sponsor organisations who will have access to information that identifies you will be people who need to contact you in relation to this study and to audit the data collection process. Cambridge University Hospitals will keep identifiable information about you from this study for 10 years after the study has finished.

All information collected about you as a result of your participation in the study will be kept strictly confidential. Your personal and medical information will be kept in a secured file and be treated in the strictest confidence. Confidentiality of your information might be broken should the researcher become aware of any information whose disclosure to relevant authorities is essential for effective safeguarding or is required by the law.

Once you have agreed to participate in this study you will be allocated a Study ID Number. This is a unique study number which will be used on all your study documentation along with your date of birth. Your date of birth is considered to be personal information. We collect this personal information on study documentation to help ensure that the data we receive as part of your study participation is correctly allocated to you. By cross checking these two unique references we can ensure the integrity of the data.
The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details. Only anonymous study data, without any personal information, will be published at the end of the study.

Will my data be transferred to any third party?
When you agree to take part in this study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

Your information could be used for research in any aspect of health or care, and could be combined with information about you from other sources held by researchers, the NHS or government. Where this information could identify you, the information will be held securely with strict arrangements about who can access the information. The information will only be used to contact you about future opportunities to participate in research. It will not be used to make decisions about future services available to you, such as insurance. Where there is a risk that you can be identified your data will only be used in research that has been independently reviewed by an ethics committee.

13. What will happen to the results of the study?
The results of the study will be anonymous and you will not be able to be identified from any of the data produced. When the results of this study are available they may be published in peer reviewed medical journals and used for medical presentations and conferences. They will be shared with the funding body. Anonymous datasets from the study may also be made available to other researchers in line with national and international data transparency initiatives. If you would like to obtain a copy of the published results please contact the study coordinator directly who will be able to arrange this for you.

Study documents and collected data will be kept for 10 years following the closure of the study for secondary analysis and for comparison with future studies. After which point they will be destroyed or ethical approval sought to continue using them. Paper based forms will be stored securely with access only available to those in the research team. Databases will be stored on university computers. Details kept on computers will be saved securely, and requiring password access to each database.

14. Who is funding the study?
The study is being funded by the Stroke Association.

15. Who has reviewed this study?
All research within the NHS is reviewed by an independent group of people called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the West of Scotland REC 5.

16. Further information and contact details
If you have questions about the study at any time please contact the local study organiser: Ms [redacted] phone number: [redacted], e-mail address: [redacted]

REDACTION: name, contact details, and email address removed for confidentiality reasons.

2.4 Participant Information Sheet – carer

UNIVERSITY OF CAMBRIDGE

Cambridge University Hospitals NHS
NHS Foundation Trust

PARTICIPANT INFORMATION SHEET – CARER

Study: Apathy and Quality of Life

You are being invited to take part in a research study. Before deciding whether to take part, you need to understand why this research is being done and what it involves. Please take time to read the following information carefully and talk to others about the study if you wish. Please ask us if anything is not clear or if you would like more information. Please take time to decide whether or not you wish to take part.

Section 1 tells you the purpose of this study and what will happen to you if you take part.
Section 2 gives you more detailed information about the conduct of the study.

1. What is the purpose of the study?

You are invited to participate in a research project we are running to find out whether apathy occurring after stroke is related to diminished quality of life in stroke patients and their carers and increased carer stresses. People after stroke often experience apathy. Apathy can be described as a reduction in motivation, interests, and social interactions. The occurrence of apathy after stroke may also affect carers and result in a reduction of quality of life and increased care stresses. We are carrying out this study to find out whether carers of individuals who develop apathy after stroke present greater distress and lower quality of life as compared to carers of non-apathetic participants.

2. Why have I been invited?

You have been invited to participate in this study because a person in your care has experienced a stroke.

We plan to include 60 participants who experienced a stroke and their carers from Cambridge University Hospital Stroke Service.

3. Do I have to take part?

Participating in this study is completely voluntary. If you decide to participate you will be asked to sign an Informed Consent Form, however you are still free to change your mind and leave the study at any time without giving a reason. If you chose not to participate or to leave the study, yours and your relative future medical treatment and normal standard of care will not be affected in any way.

4. What will happen to me if I take part?

If you agree to participate in the study, you will sign the Informed Consent Form at the end of this document and be given a copy of this to take away and refer to later.

We will then ask to see you and your relative and carry out a one-off assessment. We will contact you via telephone or video call.

During this assessment we will ask you to complete questionnaires about possible apathy symptoms of the person in your care and questionnaires about your quality of life, mood, and care related stress.

The assessment for you and your relative will last approximately 1.5 hours: rest breaks will be provided when needed. No follow-up will be conducted.

5. What will I have to do?
If you decide to take part in the study you will be asked to visit the hospital for the assessment or join a remote call, in which case the material will be posted to you.

6. What are the possible disadvantages and risks of taking part?
There are no direct disadvantages of taking part in this study. Interviews might include sensitive topics: participants will be provided a comfortable and safe environment during the assessment and will be able to refuse to answer any questions at any time and without giving explanations.

All participants and carers taking part in the study will receive careful follow-up and the mood screening data acquired will be available to the treating clinicians to monitor your progress.

In case previously undetected findings are identified, this information will be communicated to your treating clinician who will advise you on how to proceed.

7. What are the possible benefits of taking part?
There is no guarantee that you will benefit from taking part in this study. However information collected as part of your participation in this study may benefit patients who experience apathy after stroke and their carers in the future.

8. Expenses & Payment
You will not receive any payment for participating in this study, however we can reimburse any reasonable travel and parking costs incurred by your participation in this study.

Section 2: Study Conduct

9. What if new information becomes available?
Sometimes during the course of a study, new information becomes available which might affect your decision to continue participating in this study. The study coordinator will contact you to discuss the new information and whether you wish to continue participating in the study. If you still wish to continue on the study, you will be asked to sign a new Informed Consent Form.
The study sponsor, the regulatory authority or the study coordinator may decide to stop the study at any time. If that happens we will tell you why the study has been stopped.

10. What if I decide I no longer wish to participate in the study?
You are free to come off the study at any time without giving a reason and without affecting yours or your relative future care or medical treatment. If you decide not to participate any further, no further tests will be performed on you. Any data already collected or results from tests already performed on you will continue to be used in the study analysis.
The study coordinators may also choose to withdraw you from the study if they feel it is in your best interests or if you are unable to comply with the requirements of the study. Reasons for

study withdrawal could include inability to complete the visits or study documentation as required.

11. What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. If you have any concerns about any aspect of this study you should speak to the study researchers who will do their best to answer your questions.

In the event that something does go wrong and you are harmed by taking part in the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Cambridge University Hospitals NHS Foundation Trust or the University of Cambridge. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).The University has obtained insurance which provides no-fault compensation i.e. for non-negligent harm, you may be entitled to make a claim for this.
If you wish to complain or have any concerns about any aspect of the way you have been approached or treated during this study, you can do this through the NHS complaints procedure. In the first instance it may be helpful to contact the Cambridge University Hospitals NHS Complaints Procedure by telephoning the Patient Advice and Liaison Service (PALS) on [redacted]. REDACTION: contact details removed for confidentiality reasons.

12. Will my taking part in this study be kept confidential?

Cambridge University Hospitals NHS Foundation Trust (CUH) and The University of Cambridge are the Sponsors for this study based in the United Kingdom. They will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that they are responsible for looking after your information and using it properly. The Sponsor organisations will keep identifiable information about you for 10 years after the study has finished to ensure your safety and allow the study to be reviewed by the authorities after it is finished.

Your rights to access, change or move your information are limited, as the Sponsor organisations need to manage your information in specific ways in order for the research to be reliable and accurate. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how the Sponsors use your information using the information below:

- For Cambridge University Hospitals NHS Foundation Trust, please visit: https://www.cuh.nhs.uk/patient-privacy/ or email The Data Protection Officer at: [redacted] REDACTION: email address removed for confidentiality reasons.

- For University of Cambridge, please visit: https://www.medschl.cam.ac.uk/research/information-governance or email The Information Governance team at: [redacted] REDACTION: email address removed for confidentiality reasons.

The Stroke Research Group at Addenbrooke's Hospital, Cambridge University Hospital NHS Foundation Trust, will collect your name and contact details to contact you about this study, and to oversee the quality of the study. Individuals from the CUH NHS Foundation Trust/University of Cambridge and regulatory organisations may look at your research records to check the

accuracy of this study. The Stroke research Group will pass these details to the Sponsors along with the information collected from you. The only people in the Sponsor organisations who will have access to information that identifies you will be people who need to contact you in relation to this study and to audit the data collection process. Cambridge University Hospitals will keep identifiable information about you from this study for 10 years after the study has finished.
All information collected about you as a result of your participation in the study will be kept strictly confidential. Your personal and medical information will be kept in a secured file and be treated in the strictest confidence. Confidentiality of your information might be broken should the researcher become aware of any information whose disclosure to relevant authorities is essential for effective safeguarding or is required by the law.

Once you have agreed to participate in this study you will be allocated a Study ID Number. This is a unique study number which will be used on all your study documentation along with your date of birth. Your date of birth is considered to be personal information. We collect this personal information on study documentation to help ensure that the data we receive as part of your study participation is correctly allocated to you. By cross checking these two unique references we can ensure the integrity of the data.
The people who analyse the information will not be able to identify you and will not be able to find out your name or contact details. Only anonymous study data, without any personal information, will be published at the end of the study.
When you agree to take part in this study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

Your information could be used for research in any aspect of health or care, and could be combined with information about you from other sources held by researchers, the NHS or government. Where this information could identify you, the information will be held securely with strict arrangements about who can access the information. The information will only be used to contact you about future opportunities to participate in research. It will not be used to make decisions about future services available to you, such as insurance. Where there is a risk that you can be identified your data will only be used in research that has been independently reviewed by an ethics committee.

13. What will happen to the results of the study?
The results of the study will be anonymous and you will not be able to be identified from any of the data produced. When the results of this study are available they may be published in peer reviewed medical journals and used for medical presentations and conferences. They will be shared with the funding body. Anonymous datasets from the study may also be made available to other researchers in line with national and international data transparency initiatives. If you would like to obtain a copy of the published results please contact the study coordinator directly who will be able to arrange this for you.

Study documents and collected data will be kept for 10 years following the closure of the study for secondary analysis and for comparison with future studies. After which point they will be destroyed or ethical approval sought to continue using them. Paper based forms will be stored securely with access only available to those in the research team. Databases will be stored on university computers. Details kept on computers will be saved securely, and requiring password access to each database.

14. Who is funding the study?
The study is being funded by the Stroke Association.

15. Who has reviewed this study?
All research within the NHS is reviewed by an independent group of people called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the West of Scotland REC 5.

16. Further information and contact details
If you have questions about the study at any time please contact the local study organiser: Ms [redacted], phone number: [redacted], e-mail address: [redacted]

REDACTION: name, contact details, and email address removed for confidentiality reasons.

2.5 Informed Consent Form – stroke patient

UNIVERSITY OF CAMBRIDGE

Cambridge University Hospitals NHS
NHS Foundation Trust

INFORMED CONSENT FORM – STROKE PATIENT

Study: Apathy and Quality of Life

Investigators: [redacted]

REDACTION: names removed for confidentiality reasons.

Participant Number:

If you agree with each sentence below, please initial the box:

1.	I have read and understood the Participant Information Sheet version _, dated _ _ / _ _ / _ _ _ _ for the above study and I confirm that the study procedures and information have been explained to me. I have had the opportunity to ask questions and I am satisfied with the answers and explanations provided.	
2.	I understand that my participation in this study is voluntary and I am free to withdraw at any time, without giving a reason and without my medical care or legal rights being affected.	
3.	I understand that once I have consented a screening assessment will be performed and the continuation of my participation to the study is not guaranteed.	
4.	I understand that personal information about me will be collected and used in accordance with this information sheet. This information will be kept in the strictest confidence and none of my personal data will be published.	
5.	I understand that sections of my medical notes or information related directly to my participation in this study may be looked at by responsible individuals from the sponsor, regulatory authorities and research personnel where it is relevant to my taking part in research and that they will keep my personal information confidential. I give permission for these individuals to have access to my records.	
6.	I have read and understood the compensation arrangements for this study as specified in the Participant Information Sheet.	
7.	I understand that the investigators in charge of this study may close the study, or stop my participation in it at any time without my consent.	
8.	I have read and understood my responsibilities for the study as listed in section 5 of the Information Sheet.	
9.	I am happy for my partner/carer to be approached and complete questionnaires about my recovery from stroke.	
10.	I am happy for my anonymised data to be used in future studies.	

I agree to take part in this study:

_____	_____	_____
Name of Participant	Signature	Date
_____	_____	_____
Name of the person taking consent	Signature	Date

1 copy for the participant, 1 copy for the study team, 1 copy to be retained in the hospital notes.

2.6 Informed Consent Form – carer

UNIVERSITY OF CAMBRIDGE

Cambridge University Hospitals NHS
NHS Foundation Trust

INFORMED CONSENT FORM – CARER

Study: Apathy and Quality of Life

Investigators: [redacted]

REDACTION: names removed for confidentiality reasons.

Participant Number:

If you agree with each sentence below, please initial the box:

1.	I have read and understood the Carer Information Sheet version _, dated _ _ / _ _ / _ _ _ _ for the above study and I confirm that the study procedures and information have been explained to me. I have had the opportunity to ask questions and I am satisfied with the answers and explanations provided.	
2.	I understand that my participation in this study is voluntary and I am free to withdraw at any time, without giving a reason and without my medical care or legal rights being affected.	
3.	I understand that personal information about me will be collected and used in accordance with this information sheet. This information will be kept in the strictest confidence and none of my personal data will be published.	
4.	I have read and understood the compensation arrangements for this study as specified in the Carer Information Sheet.	
5.	I understand that the doctors in charge of this study may close the study, or stop my participation in it at any time without my consent.	
6.	I have read and understood my responsibilities for the study as listed in section 5 of the Information Sheet.	
7.	I am happy for my anonymised data to be used in future studies.	

I agree to take part in this study:

_____	_____	_____
Name of Participant	Signature	Date
_____	_____	_____
Name of the person taking consent	Signature	Date

1 copy for the participant, 1 copy for the study team, 1 copy to be retained in the hospital notes.