Post-Stroke Apathy: Screening and Functional Impact

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Thesis Abstract: **Post-Stroke Apathy: Screening and Functional Impact**

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Background: Apathy, a disorder of motivation observed in up to 40% of stroke survivors, is likely to have a negative impact on stroke rehabilitation. It is often theorised to be a multidimensional construct yet frequently assessed using unidimensional measures. The Dimensional Apathy Scale (DAS, Radakovic & Abrahams, 2014) is a multidimensional assessment, with Executive, Emotional and Initiation Apathy subscales. The aims of this thesis were to examine the relationship between apathy and functional activity after stroke and assess the suitability of the DAS as a screen for post-stroke apathy (PSAp).

Method: A systematic review identified 8 papers investigating the associations between PSAp and functional activity. An online survey of 53 stroke, and 71 non-stroke participants investigated the psychometric properties and validity of the DAS in relation to a frequently used, unidimensional apathy measure and measures of depression and anxiety.

Results: The systematic review found that PSAp is associated with negative outcomes, including negatively affecting family life and later social reintegration and autonomy. The review highlights a negative relationship between PSAp and functional activity, although there were concerns regarding the quality of studies and the lack of multidimensional apathy assessment being utilised. The survey found that the DAS has good internal consistency, good convergent and divergent validity in stroke. Stroke survivors scored significantly higher on total apathy and all subscales than did non-stroke participants. Initiation and Executive Apathy were particularly prevalent, similar to previous DAS validation studies in neurogenerative diseases. Stroke survivors also had significantly higher levels of depression, but not anxiety, compared with non-stroke participants.

Conclusion: PSAp is common but under-researched. This thesis contributes to PSAp research, finding that PSAp is associated with functional disability and validating the DAS for use in stroke rehabilitation and research. Limitations and suggestions for future research are discussed.

Summary of Portfolio

Chapter 1: The first chapter provides a general introduction to the thesis, outlining the nature and importance of stroke and its consequences, including emotional and cognitive sequelae and impact on functional activities. It also introduces post-stroke apathy and theoretical models of apathy and PSAp.

Chapter 2: The second chapter presents a systematic review examining the association between apathy and functional activity after stroke. Eight articles, involving 1517 patients, were selected for review. Internal validity was rated ‘good’ in four studies, uncertainties and risk of bias affecting external validity were identified in all studies. PSAp was found to be prevalent and negatively associated with rehabilitation outcomes. Most studies used unidimensional measures of apathy, thereby failing to characterise apathy according to apathy subtype.

Chapter 3: The third chapter provides a bridge between the systematic review of the impact of PSAp on functional activities and an article on the first validation of a multidimensional assessment of apathy (the Dimensional Apathy Scale, DAS) in stroke. It provides an overview of theoretical models and research evidence on the dimensionality of apathy. It also covers methodological considerations regarding validation studies of clinical screening tools.

Chapter 4: The fourth chapter presents a validation study of the DAS in stroke. This scale has been validated for people with a range of neurodegenerative diseases, but not yet for stroke. The chapter discusses the scale and apathy as a multidimensional concept. This study is based on data from an online questionnaire, comparing stroke survivors and controls (people who had not experienced a stroke). The DAS showed high internal consistency and

good convergent and divergent validity with the Apathy Evaluation Scale (AES), Patient Health Questionnaire (PHQ-9) and Generalised Anxiety Disorder scale (GAD-7).

Chapter 5: The fifth chapter includes additional methods regarding assumptions for ANOVA and non-parametric data.

Chapter 6: The sixth and final chapter provides an extended discussion and critical appraisal to integrate and summarise the findings from this thesis.

CHAPTER 1 – General Introduction

Introducing stroke, apathy, post-stroke apathy and recovery

Word count excluding figures and tables: 5144

General Introduction

Introducing stroke, apathy, post-stroke apathy and recovery

Stroke

The word ‘stroke’ relates to the Greek word ‘apoplexia,’ which translates to ‘being struck with a deadly blow’ (Coupland, Thapar, Qureshi, Jenkins, & Davies, 2017). A stroke is a life-threatening medical emergency, which is the leading cause of disability, and the fourth most common cause of death in the UK (Stroke Association, 2017). There are over 100.000 new cases and 38.000 stroke related deaths each year, and an astonishing 1.2 million stroke survivors currently living in the UK (National Institue ofor Health and Care Excellence, 2019a). Stroke-related disability is costly on human, family and societal levels (Carod-Artal & Egido, 2009). In the UK, the total societal cost of stroke is estimated to be £8.9 billion a year, and the productivity loss due to death and disability is estimated to be £1.5 billion a year (Saka, Mcguire, & Wolfe, 2009).

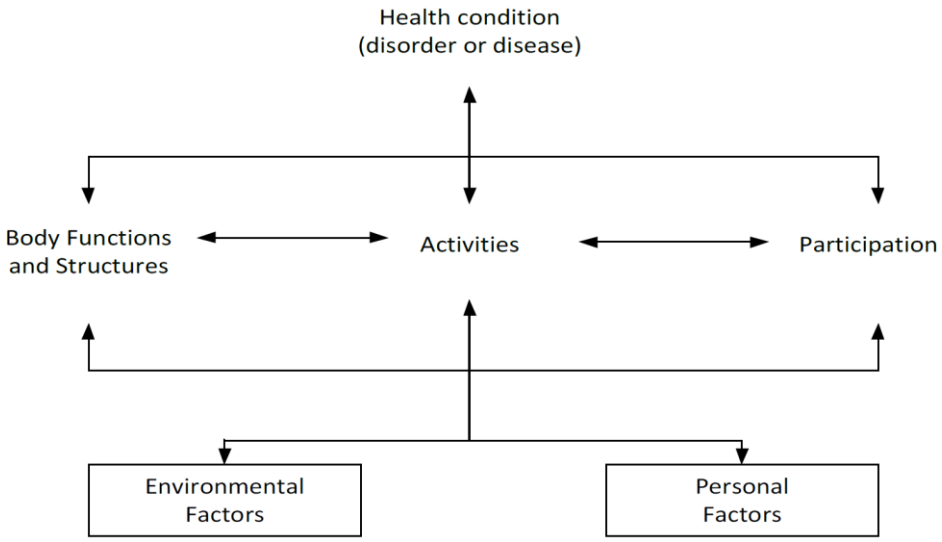
Stroke is a clinical syndrome, caused by an intracranial vascular event. The World Health Organisation define stroke as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin” (Sacco et al., 2013, p. 2065). There are two main types of stroke: Ischemic strokes are the most common (about 85% of all strokes), caused by a blocked blood vessel: Haemorrhagic strokes are caused by bleeding in the brain (Royal College of Physicians, 2016; Stroke Association, 2017). A Transient Ischemic Attack, or TIA, is a temporary blockage of the blood flow to the brain, lasting less than 24 hours, and is often referred to as a “mini-stroke” (Stroke Association, 2017). This is considered a warning sign but is not categorised as a major stroke.

The effects of a stroke can be extremely varied, depending on localisation in the brain, as well as the extent and severity of the damage (Stroke Association, 2017). The International

Classification of Functioning, Disability and Health (ICF) model, presented in Figure 1, shows how people might experience disabilities from any types of illness impacting sensation, movement, cognition, communication and emotion, and how these are affecting functional activities, which are in turn affecting social participation, mood and psychosocial adjustment (World Health Organisation, 2013).

Figure 1

The ICF Model: Interaction between ICF components, retrieved from World Health Organisation, (2013)



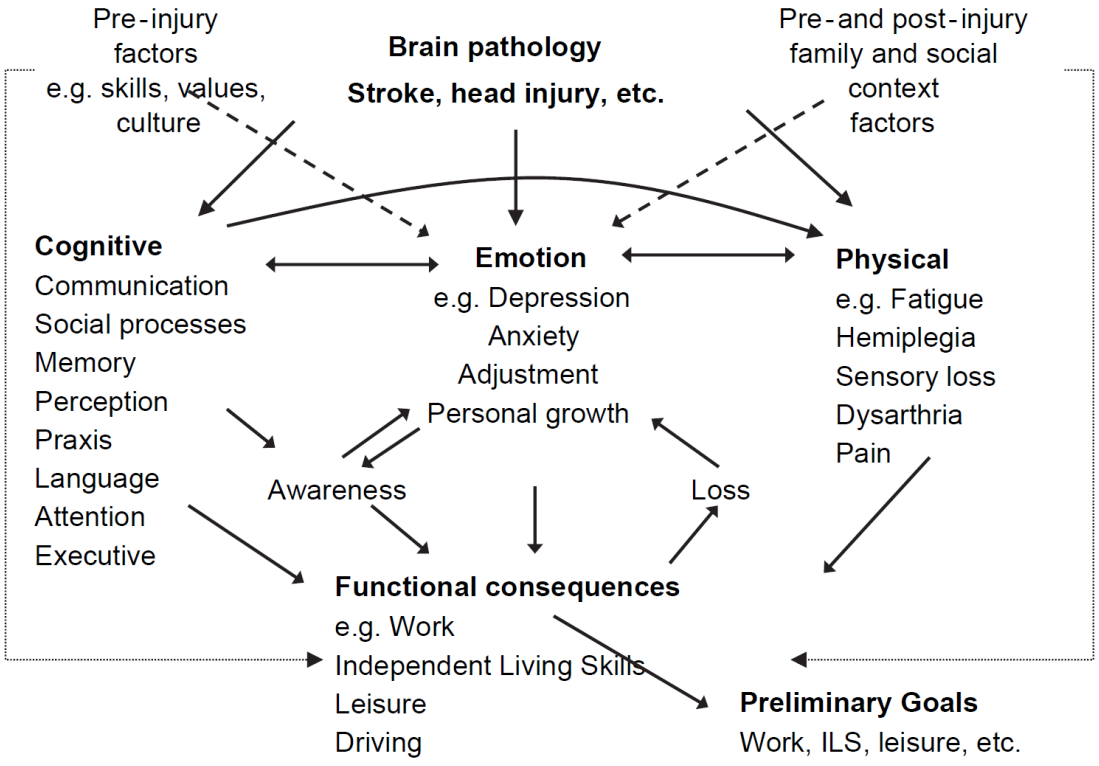
Body functions or structures can include various cognitive impairments, aphasia, emotional changes, incontinence, visual impairments, limb weakness, difficulties swallowing, motor impairments and balance problems, fatigue and pain (Stroke Association, 2017); they are notable factors which influence one's ability to participate in activities. Activities and participation refer to an individual's capacity and performance in any chosen activity. Environmental structures include family, friends, work, health care and rehabilitation services. Personal factors include age, gender, general health, and coping strategies (World Health Organisation, 2013). These contextual factors can be considered either to be

supportive, or work as barriers by inhibiting the ability to function and participate, they are related to one's functional abilities post stroke (World Health Organisation, 2013).

For health professional and teams working with the patient, it is helpful to provide a context for which one can understand the person, as well as the cognitive, emotional physical and communication consequences after brain injury such as stroke, (Wilson, Gracey, Evans, & Bateman, 2009). Figure 2 presents a model used at the Oliver Zangwill Centre, in Cambridge UK, encompassing biopsychosocial factors to help formulate the nature of the injury and its effect on the person, (Wilson et al., 2009). This model can be used to create an individual formulation for the person, to aid understanding and to identify strengths, weaknesses and needs, informing recovery goals, by considering internal as well as external factors.

Figure 2

A biopsychosocial model of the consequences of brain injury from the Oliver Zangwill Centre, retrieved from (Wilson et al., 2009)



Acute Treatment and Stroke Rehabilitation

In acute stroke care, emphasis is on medical stabilisation, assessment and rehabilitation, it is important for the latter to commence in acute care (Lynch, Mackintosh, Luker, & Hillier, 2019). In terms of treatment, the National Institute for Health and Care Excellence (NICE) recommends a thorough assessment and specialist care, with treatment from a multidisciplinary team approach supporting rehabilitation (NICE, 2019b). Rehabilitation can take place either in specialist multidisciplinary inpatient or outpatient services, dependent on the client's needs (Teasell et al., 2009). The main focus in rehabilitation is on the adaptation, restitution and neuroplasticity (Belagaje, 2017). Rehabilitation improves the person's immediate and long-term functioning (Lynch et al., 2019; Teasell et al., 2009).

Much of a person's recovery often take place in the first few months following a stroke (Powers et al., 2018; Ramsey et al., 2017). Some stroke survivors will fully recover after stroke, whilst others will have to live with disabilities for the remainder of their respective lives (Boccuni et al., 2018). The level of paralysis and recovery of function in the first few days following a stroke predicts later treatment outcomes of motor-function recovery (Hendricks, Limbeek, & Geurts, 2002; Ramsey et al., 2017). Rehabilitation after stroke requires sustained efforts from the stroke survivor, a multidisciplinary team, as well as support from the stroke survivor's social network (Winstein et al., 2016).

NICE highlights the importance of smart-goals to guide the recovery process, these should be formed together with the stroke survivor, allowing consideration for a wide scope of factors, including severity, symptoms, available support, function before stroke etc. (NICE, 2019). Recovering from a stroke can be a lengthy process, requiring much motivation from the individual and their support system. A stroke can be, as mentioned above, a major event in one's life, requiring significant change and adaptation.

Strokes can have a high emotional impact, and many stroke survivors experience emotional difficulties following a stroke (Douven et al., 2018; Matsuzaki et al., 2015; Sagen et al., 2010). Rapid detection of factors delaying stroke rehabilitation is important to allow patients to fully utilise the offered rehabilitation programs (Lynch et al., 2019), and factors such as post-stroke depression (PSD) deserve greater focus in stroke given its negative influence on rehabilitation (Balkaya & Cho, 2019).

Emotional and motivational consequences of stroke

Depression is prevalent: it is observed in one third of stroke-survivors (Robinson & Jorge, 2016). PSD is associated with higher mortality rates and poorer rehabilitation outcomes (Towfighi et al., 2017; Williams, Ghose, & Swindle 2004). Physical disabilities, cognitive impairments, lack of family and social support, and premorbid depression are considered risk-factors for developing PSD (Robinson & Jorge, 2016; Towfighi et al., 2017). A comprehensive systematic review found that cognitive impairments, physical disability and stroke severity were predominant predictors for developing post-stroke depression (Hackett, Köhler, O'Brien, & Mead, 2014).

Approximately 50% of stroke survivors exhibit anxiety and depressive symptoms which continue several years after stroke (Bergersen, Frøslie, Stibrant Sunnerhagen, & Schanke, 2010). Post-stroke depression can be understood from a biopsychosocial perspective, where neurological changes following the stroke, psychological and environmental consequences and factors might emotionally impact the stroke-survivor at varying degrees, given their personal and unique context (Hackett, Hons, & Anderson, 2005).

There can be several consequences of a significant aversive life event, such as stroke, which might impact upon function and motivation. The emotional impact can be linked with the mourning of loss (of abilities) and coping with acceptance of disability, particularly when

individuals struggle or refuse to accept their new reality (Hama, Yamashita, Yamawaki, & Kurisu, 2011). It was argued that loss of identity and changes to the sense-of-self are common after stroke: subsequently, this can have a negative impact on one's self-esteem (Lapadatu & Morris, 2019). A study found that greater identity discrepancies between the actual and ideal self was associated with anxiety, depression and lower quality of life (Lapadatu & Morris, 2019).

Post-stroke anxiety is another common neuropsychiatric disorder in stroke survivors, and it is a frequently comorbid with PSD (Barker-Collo, 2007; Lincoln et al., 2013; Sagen et al., 2010). It is estimated that a quarter of stroke survivors will experience post-stroke anxiety (Hackett et al., 2014). Anxiety can be very disabling to the individual: fears can either be general or more specific, often related with incidents and situations such as fear of falling, stroke recurrence, fear of headaches, fear of physical exertion (such as exercise and having sex), and fear of being alone (Chun, Whiteley, Dennis, Mead, & Carson, 2018). These fears can impact one's activity levels and quality of life (Morris, Van Wijck, Joice, & Donaghy, 2013).

A stroke can be a very traumatic and life-threatening experience, some stroke-survivors develop Post Traumatic Stress Disorder (PTSD), (Merriman, Norman, & Barton, 2007). The prevalence varies in the literature, ranging from anything between 3-20% of stroke-survivors in the first year (Edmondson et al., 2013).

From a social perspective, a relative experiencing stroke can also impact on an entire family system and social environment: a sudden and unexpected disability in the family will often lead to changes in roles (e.g. changing from being a spouse to spouse and a carer), (Dam, Tonin, Casson, Ermani, & Pizzolato, 1993).

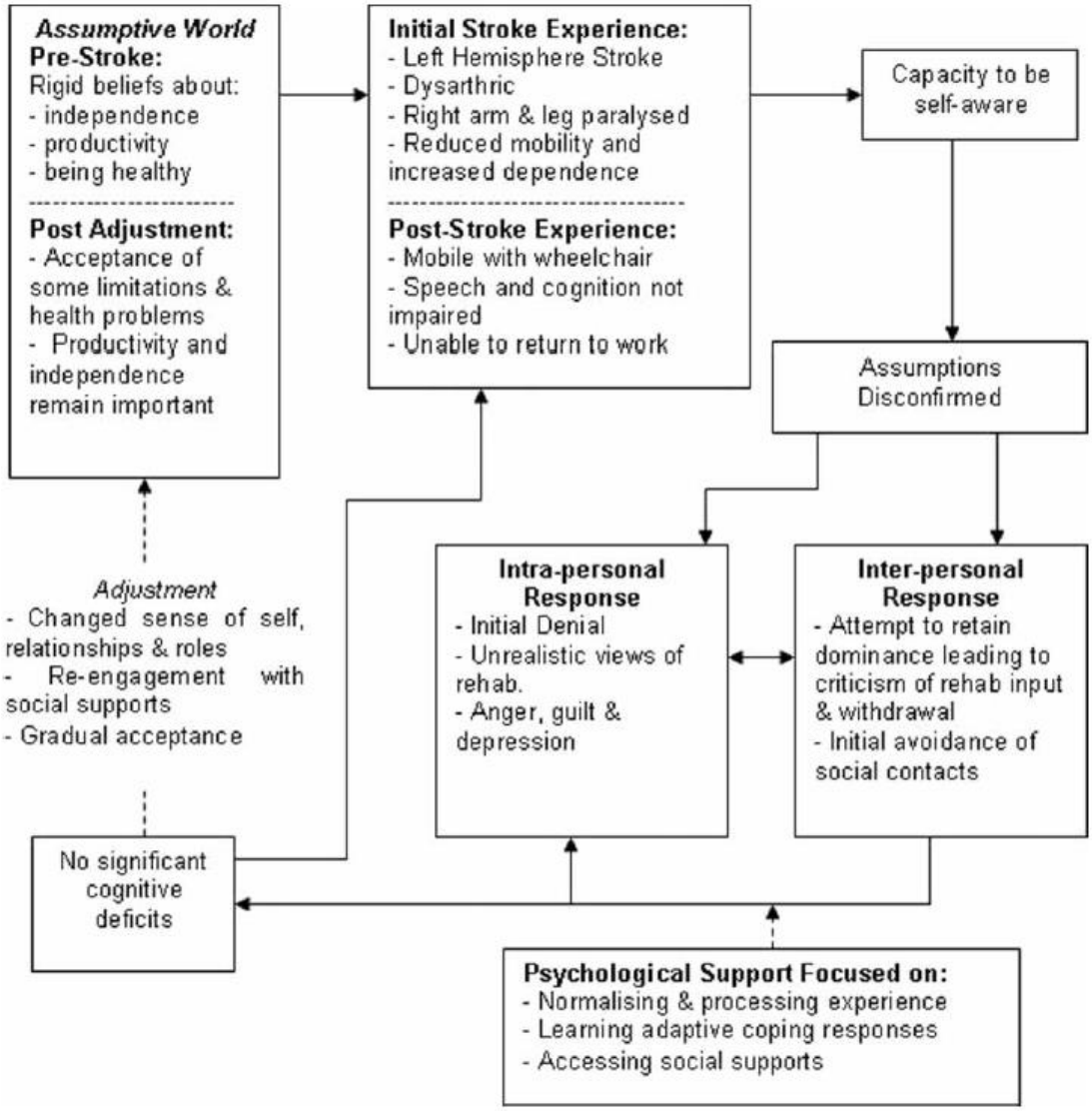
Emotionalism and emotional adjustment after stroke

Emotional disturbances are common after stroke and can affect social reintegration. These disturbances encompass a wide array of emotions, including anger, anxiety/fear, indifference, lack of emotional understanding and reduced emotional control (Ferro & Santos, 2019). Outbursts of involuntary crying and laughing (emotionalism) is a common consequence of stroke (McAleese, Guzman, O'Rourke, & Gillespie, 2019). The attribution of symptom origin is an important predictor for the stroke survivor's wellbeing when experiencing involuntary symptoms (McAleese et al., 2019).

There are great individual differences in terms of coping after stroke (Taylor et al., 2011). Difficulties with emotional adjustment is common amongst stroke survivors, and emotional adjustment is not a linear process (Smith et al., 2019; Taylor et al., 2011). Stroke survivors are frequently influenced by positive or negative triggering events, negative events might include set-backs (Smith et al., 2019). Taylor and colleges (2011) provided a Social Cognitive Transaction Model adapted for stroke, see Figure 3. This model shows the complex range of adjustment experiences that that the stroke survivor might alternate between (Taylor et al., 2011).

Figure 3

Social Cognitive Transition Model with a clinical example, retrieved from (Taylor et al., 2011).



Apathy

The word apathy stems from the Greek words: a (without) patos (passion), (Stuss, van Reekum, & Murphy, 2000), and can be defined as the lack of motivation for goal directed behaviours (Marin, Biedrzycki, & Firinciogullari, 1991). The term motivation has been defined as:

> A driving force or forces responsible for the initiation, persistence, direction, and vigour of goal-directed behaviour. It includes the biological drives such as hunger,

> thirst, sex, and self-preservation, and also social forms of motivation such as need for achievement and need for affiliation. (Colman, 2005, p. 224).

The strength of motivation can be considered as a continuum, with high motivation at one end and diminished motivation at the the other (Marin and Wilkosz, 2005). Apathy is considered to be a state of diminished motivation and falls towards the lower end of a motivation continuum, as do other disorders of motivation such as akinetic mutism and abulia (Marin, 1997; Marin et al., 2005). Apathy can have various causes and can be understood from situational and psychiatric approaches, such as depression, psychosis and schizophrenia (Konstantakopoulos et al., 2011), or neurological domains.

Apathy is highly prevalent across neurological disorders (Chase, 2011), it can be found in 43% of patients with mixed dementia (Mulin et al., 2011), and 30-80 % of Alzheimer's disease (Guimarães, Levy, Teixeira, Beato, & Caramelli, 2008). It is also common in amyotrophic lateral sclerosis (ALS), and has been found to be prognostic factor for ALS, as it is associated with disability and mortality (Caga et al., 2016). The prevalence of apathy is estimated to be around 60% in Traumatic Brain Injury (Starkstein & Pahissa, 2014), and often observed in stroke survivors (Brodaty et al., 2005; Hama et al., 2011). Apathy is also a common symptom in 'healthy' individuals, and becomes more prevalent as people age (Mehta et al., 2008). Symptoms of apathy are strongly associated with age in depression, and is more common in later-life depression (Groeneweg-Koolhoven et al., 2015).

Although relatively common, a wide variety of terms have been used to define apathy. Van Reekum and colleagues argued that a gold standard for the diagnosis of apathy was still needed (Van Reekum, Stuss, & Ostrander, 2005), and that research on apathy might be highly clinically relevant for helping informing patients, carers and clinicians (Van Dalen, Van Charante, Nederkoorn, Van Gool, & Richard, 2013). Stuss and colleagues argued that in cases

where the type of apathy is distinguishable, the rehabilitation and treatment should be tailored to address this (Stuss et al., 2000).

Levy and Dubois (2006) argued that there are three distinct subtypes of apathy: lack of initiation of activities; emotionally affective apathy, referring to inability to link behaviours with affective and emotional signals; and cognitive apathy, which refers to an inability to organise, manage and expand on plans. Several studies have supported these distinctions, finding multiple apathy syndromes related with distinct neurological and neuroanatomical correlates e.g. (Le Heron, Apps, & Husain, 2017; Starkstein & Leentjens, 2008)

A consensus in terms of diagnosis was only just reached about ten years ago. A taskforce of experienced researchers and clinicians within the field of apathy were consulted in 2008 (Robert et al., 2009), to decide upon the diagnostic criteria for apathy. The apathy criteria were reviewed in 2018 (Robert et al., 2018). See Table 1 for the diagnostic criteria for apathy.

Table 1

Apathy Diagnostic Criteria, retrieved from (Robert et al., 2018)

CRITERION A
A quantitative reduction of goal-directed activity either in behavioural, cognitive, emotional or social dimensions in comparison to the patient's previous level of functioning in these areas. These changes may be reported by the patient himself/herself or by observation of others.
CRITERION B
The presence of at least 2 of the 3 following dimensions for a period of at least four weeks and present most of the time
B1. BEHAVIOUR & COGNITION
Loss of, or diminished, goal-directed behaviour or cognitive activity as evidenced by at least one of the following:
General level of activity: the patient has a reduced level of activity either at home or work, makes less effort to initiate or accomplish tasks spontaneously, or needs to be prompted to perform them.
Persistence of activity: He/she is less persistent in maintaining an activity or conversation, finding solutions to problems or thinking of alternative ways to accomplish them if they become difficult.
Making choices: He/she has less interest or takes longer to make choices when different alternatives exist (e.g., selecting TV programs, preparing meals, choosing from a menu, etc.)
Interest in external issue: He/she has less interest in or reacts less to news, either good or bad, or has less interest in doing new things
Personal wellbeing: He/she is less interested in his/her own health and wellbeing or personal image (general appearance, grooming, clothes, etc.).
B2. EMOTION
Loss of, or diminished, emotion as evidenced by at least one of the following:
Spontaneous emotions: the patient shows less spontaneous (self-generated) emotions regarding their own affairs or appears less interested in events that should matter to him/her or to people that he/she knows well.
Emotional reactions to environment: He/she expresses less emotional reaction in response to positive or negative events in his/her environment that affect him/her or people he/she knows well (e.g., when things go well or bad, responding to jokes, or events on a TV program or a movie, or when disturbed or prompted to do things he/she would prefer not to do).
Impact on others: He/she is less concerned about the impact of his/her actions or feelings on the people around him/her.
Empathy: He/she shows less empathy to the emotions or feelings of others (e.g., becoming happy or sad when someone is happy or sad, or being moved when others need help).
Verbal or physical expressions: He/she shows less verbal or physical reactions that reveal his/her emotional states.
B3. SOCIAL INTERACTION
Loss of, or diminished engagement in social interaction as evidenced by at least one of the following:
Spontaneous social initiative: the patient takes less initiative in spontaneously proposing social or leisure activities to family or others.
Environmentally stimulated social interaction: He/she participates less or is less comfortable or more indifferent to social or leisure activities suggested by people around him/her.
Relationship with family members: He/she shows less interest in family members (e.g., to know what is happening to them, to meet them or make arrangements to contact them).
Verbal interaction: He/she is less likely to initiate a conversation, or he/she withdraws soon from it

Homebound: He /She prefer to stay at home more frequently or longer than usual and shows less interest in getting out to meet people.

CRITERION C

These symptoms (A - B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning.

CRITERION D

The symptoms (A - B) are not exclusively explained or due to physical disabilities (e.g. blindness and loss of hearing), to motor disabilities, to a diminished level of consciousness, to the direct physiological effects of a substance (e.g. drug of abuse, medication), or to major changes in the patient's environment.

As seen in the above table, symptoms of apathy might differ, affecting different dimensions including behaviour, emotion and social cognition. Radakovic and Abrahams provided a useful framework of apathy, by presenting the different dimensions in a comparison table. The table from their article is presented in Table 2, as this gives a useful overview of apathy dimensions as they are described in the literature.

Table 2

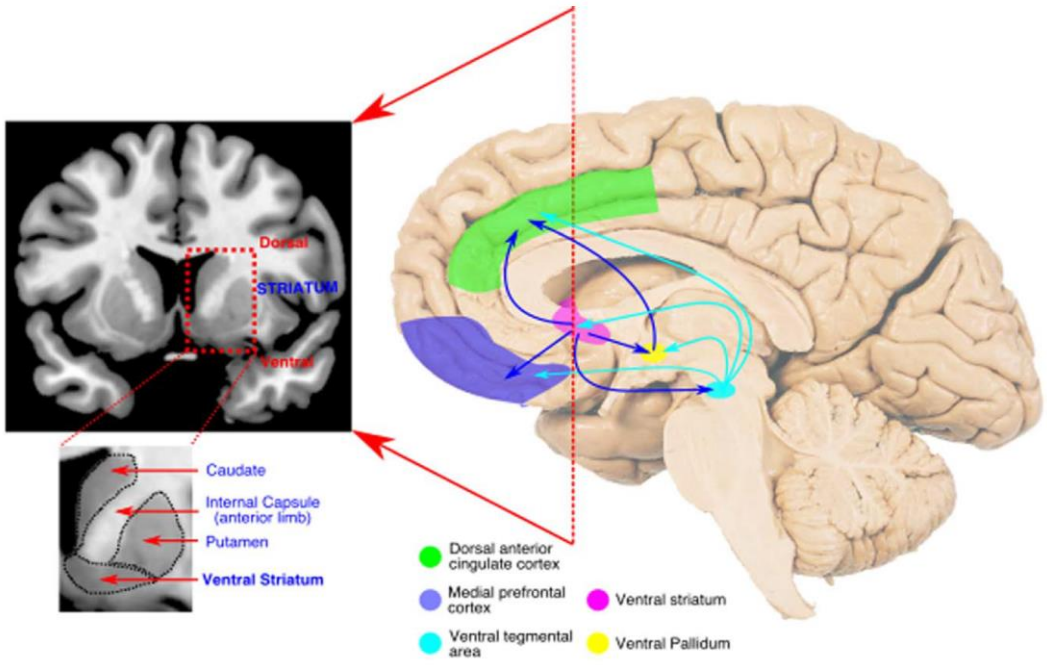
Presents the concepts of multidimensional apathy, retrieved from (Radakovic & Abrahams, 2018)

Author	Dimensions/ subtypes	Definition, symptoms/deficits
Marin, et al., (1991)	Behavioural	Decreased productivity, effortful actions, perseverance and lack of initiation behaviours.
	Cognitive	Decreased interest for learning new things, a lack of concern for oneself, inability to contribute value to recreation, social situations or being productive with tasks.
	Affective	Emotional flatness, lack of responsiveness to emotionally charged events (both good and bad) and an emotional blunting with unchanging affect
Cummings et al., (1994)	Initiative	Spontaneity is reduced for example does not start conversations or care about doing new things
	Enthusiasm	Enthusiasm for and involvement in activities, interests, and household chores
	Emotion	Reduced affect and emotions when compared to the individual's usual self and reduced interest in family members or friends
Robert et al., (2002)	Lack of initiative	Reduced conversation and decision making
	Lack of interest	Reduced interest in hobbies, other people or their family members and their interests
	Emotional blunting	Reduced affection and emotionally expression
Sockeel et al., (2006)	Intellectual curiosity	A lack of novelty seeking, interest and motivation along with a poor social life.
	Action initiation	Unproductive in day-to-day life and lessened initiative
	Self-awareness	'Meta-cognitive ability necessary to mediate information from a personal, social past and current history with projections to the future'
	Emotion	Emotional blunting of responses and diminished concern
Starkstein & Leentjens, (2008)	Goal-directed behaviours	A lack of energy of effort for daily activities and dependence on others for daily structuring
	Goal-directed cognition	A lack of interest in new experiences or in learning new things and concern for one's own well being
	Goal-directed behaviour concomitants	Flat affect and emotional unresponsiveness to positive or negative occurrences
Levy, (2012; Levy & Dubois, (2006)	Autoactivation	A lack of activity or initiation of goal-directed thoughts and actions, with a particular focus on self-initiation.
	Cognitive (Cognitive inertia)	A lack of ability to expand on plans, organization or management of goals
	Emotional affective	Inability to associate behaviours with emotion or affect, which extends to the interpretation of affective content and therefore experience of extreme affect.
Radakovic & Abrahams, (2014)	Initiation	Lack of motivation for self-generation of thought
	Executive	Lack of motivation for planning, organisation and attention
	Emotional	Lack of emotional motivation, indifference or emotional neutrality

As seen in the Table 1 and 2, the concept of apathy is complex, encompassing various symptoms, and understood through different neurological models. It has been proposed that there is a relationship between apathy and damage to prefrontal cortex, paralimbic areas, medial prefrontal cortex, anterior cingulate, and anterior temporal cortex, especially the amygdala and related subcortical structures (Levy, 2012; Radakovic & Abrahams, 2014). A reciprocally connected network model showing the brain regions associated with motivation and apathy is presented in Figure 4. This model displays the complexity of involved processes (Le Heron, Apps., & Husain, 2018). Damage to any of these areas or pathways may result in apathetic symptoms. The observed changes following such damage will inherently present different apathetic symptoms.

Figure 4

Model of the neuroanatomy for apathy, retrieved from Le Heron, Apps and Husain, (2018)



Apathy is underrepresented in research considering its negative associations with outcomes across patient groups and associations with negative rehabilitation outcomes (Konstantakopoulos et al., 2011). Stuss et al., (2000) argued that apathy receives very little

attention despite its prevalence as it is often viewed as a secondary symptom following other psychiatric or neurological disorders.

Post-stroke apathy

Post-stroke apathy (PSAp) is a common neuropsychiatric symptom after stroke (Caeiro, Ferro, & Costa, 2013). The prevalence of PSAp varies across studies, with prevalence estimates ranging between 22 and 40% (Brodaty et al., 2005; Mikami, Jorge, Moser, Jang, & Robinson, 2013).

PSAp is typically associated with more severe disability and long-term cognitive deficits that negatively influence several factors, including quality of life, functional recovery, maintaining daily activity, general health (Van Dalen et al., 2013), and chronicity of disability (Van Reekum et al., 2005). It is also considered to have a significant social impact and to be associated with increased caregiver burden (Van Dalen et al., 2013). Several studies have found a positive correlation between apathy scores, cognitive impairment and impairment of daily activities (Mikami, et al., 2013), more severe brain dysfunction (Sagen et al., 2010), disinhibition (Ricardo, Sergio, & Robert, 2010), and that patients with apathy tend to score lower on verbal intelligence (Santa et al., 2008).

An Australian study found that stroke survivors with apathy had reduced scores on attention, concentration, working memory, reasoning, and information processing speed, compared with non-apathetic stroke survivors (Brodaty et al., 2005). Individuals experiencing PSAp showed less cognitive and physical improvement after six months, compared with stroke-patients not experiencing apathy (Mikami et al., 2013). Older age also seems to influence apathy scores, as older individuals tend to rate themselves as more apathetic than their younger counterparts (Mikami et al., 2013; Sagen et al., 2010; Santa et al., 2008; Starkstein, Ingram, Garau, & Mizrahi, 2005).

PSAp is considered an independent phenomenon from post-stroke depression (Caeiro et al., 2013; Levy et al., 1998). Anhedonia, defined as the inability to feel pleasure, is an important symptom of depression recognised in diagnostic criteria (American Psychriatric Association, 2013). The distinction between anhedonia in the context of depression and apathy can be unclear (Hama et al., 2011). The relationship between apathy and depression is complex where lack of interest is a common overlapping feature in both syndromes; whereas the aspect of emotionality which is commonly seen in depression, is however considered a divergent factor from apathy (Radakovic, 2016).

Comorbidity between apathy and depression has been observed in about 40 % of the cases (Caeiro, et al., 2013; Hackett et al., 2014), which further complicates the distinction. Fatigue is a diagnostic symptom of depression and can be associated with apathy. One might speculate that these overlaps cause diagnostic challenges.

Post-stroke apathy and rehabilitation

PSAp is considered a barrier to treatment in stroke survivors (Mayo, Fellows, Scott, Cameron, & Wood-Dauphinee, 2009; Sagen et al., 2010) and has been associated with poorer rehabilitation outcomes (Matsuzaki et al., 2015; Van Dalen et al., 2013). Due to its high prevalence, and potential interference with the rehabilitation process, it was proposed that the evaluation and identification of apathy should be included in acute and follow-up post-stroke assessments (Caeiro, et al., 2013). This will therefore be the focus of this thesis.

Overall aim for this thesis

Given the importance of motivation for stroke rehabilitation and secondary stroke prevention interventions, and the potential threat posed by PSAp to stroke recovery and the limited literature on PSAp; the overall aims of this thesis are to (1) explore the association between PSAp and functional outcomes, and to (2) validate a new, multidimensional measure

of apathy in this population. The validation study will further explore associations between apathy, depression and anxiety. Overall findings from both papers will then be discussed and concluded in the final chapters.

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CHAPTER 2 – Systematic Review

The Association of Apathy and Functional Activities After Stroke
A Systematic Review

Prepared for submission to The Clinical Neuropsychologist
(guidelines outlined in Appendix A)

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The Association of Apathy and Functional Activities After Stroke: A Systematic Review

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Abstract

Background: Rehabilitation is highly important to optimise functional outcomes after stroke. Apathy, a syndrome characterised by lack of motivation, is prevalent after stroke, bringing the risk that rehabilitation and functional outcomes may be affected, due to the lack of engagement in rehabilitation. **Objectives:** This systematic review aimed to investigate the association between apathy and functional activity after stroke. The protocol was registered on PROSPERO. **Method:** A systematic search for studies of stroke, apathy and functional recovery, published between 1985-2020, was conducted in five databases (Cochrane Library, EMBASE, MEDLINE, PsychINFO, and PubMed). Eight articles (N = 1517 stroke-patients) were selected for review. The NICE appraisal Checklist was used for quality assessment. A second reviewer screened, selected and assessed the risk of bias independently in 20% of the articles. **Results:** Apathy during hospital-based stroke rehabilitation affected functional activity negatively in 87.5% of studies reviewed. Apathy was only measured as a unidimensional construct. Seven studies were longitudinal (between three months and one year) and found that apathy remained relatively stable over time. The total internal validity was rated as good in four studies, uncertainties and risks of bias were however identified in all studies in terms of external validity. **Conclusion**: Apathy was common and negatively associated with rehabilitation outcomes. Studies used one dimensional measures of apathy, which fails to characterise the specific apathy subtype involved.

Keywords: apathy, apathy screening, stroke, functional recovery, rehabilitation

The Association of Apathy and Functional Activities After Stroke: A Systematic Review

Stroke can have a devastating impact, with up to forty percent of stroke survivors affected with moderate to severe disabilities (Duncan et al., 2005; Liang, Liang, Ungvari, & Tang, 2016). It can have very different functional outcomes and survivors might experience changes to their physical, psychological, and social functioning and well-being following a stroke (Hackett, Köhler, O'Brien, & Mead, 2014; Hansson, 2004; National Institute for Health and Care Excellence [NICE], 2019; Williams et al., 2004). These changes can limit independence in functional activities such as dressing, toileting, eating, drinking, mobility (walking and use of transport), socialising, hobbies, family responsibilities, housework and return to studies or work (NICE, 2019; Rhoda et al., 2014).

Rehabilitation plays a key role in increasing cognitive, psychological, social, and physical functioning and quality of life after stroke (Carod-Artal & Egido, 2009; Kristensen, Tistad, Von Koch, & Ytterberg, 2016). With 5% of NHS budgets dedicated to stroke treatment and rehabilitation, it is imperative to maximise rehabilitation and optimise outcomes (Saka, Mcguire, & Wolfe, 2009). Optimising functional outcomes through stroke rehabilitation however, requires effort and motivation on the part of stroke survivors (Langhorne, Bernhardt, & Kwakkel, 2011; Rapolienė, Endzelytė, Jasevičienė, & Savickas, 2018).

Apathy is common, observed in about one third of stroke survivors (Brodaty et al., 2005; Caeiro, Ferro, Pinho E Melo, Canhão, & Figueira, 2013; Van Dalen et al., 2013). It is defined as a lack of motivation, interest and concern for goal-directed behaviours (Levy & Dubois, 2006; Marin, Biedrzycki, Ruth, & Firinciogullari, 1991). The definition of apathy varies in the literature, depending on the theoretical model used to understand this concept.

Apathy is considered a multidimensional construct, with various subtypes or profiles (Levy et al., 1998; Marin et al., 1991; Radakovic & Abrahams, 2014; Robert et al., 2009).

Differences between apathy subtypes arise as a result of damage to different networks within the brain (Le Heron, Apps & Husain, 2018; Levy & Dubois, 2006). There can also be differences between the processes affected, which include deficits in choosing to pursue a certain behaviour, behavioural perseverance, and the evaluation of the costs and benefits of actions (Le Heron, et al., 2018).

Post Stroke Apathy (PSAp) is associated with damage to the brain, particularly to the prefrontal lobes, subcortical structures and basal ganglia systems (Levy & Dubois, 2006). Apathy can reduce motivation for participation in stroke rehabilitation and can be very disabling (Cosin et al., 2015; Mayo et al., 2015). If apathy is related with poorer outcomes, then this is of high clinical relevance and should be routinely screened for in stroke-populations. Given its prevalence, apathy has not received adequate attention in research (Hama, Yamashita, Yamawaki, & Kurisu, 2011; Sagen et al., 2010).

To our knowledge, there is currently no systematic review focusing on PSAp and its effect on functional outcomes in stroke rehabilitation. The focus of this systematic review is therefore to examine the association between apathy and functional activity following a stroke. We investigated if apathy affects functional activity and if so, how much, when and how does it affect some activities more than others? The focus will be on outcomes for people following a stroke instead of comparing specific interventions.

Methods

For this systematic review we investigated the association between apathy and functional activities after a stroke. Figure 1 presents our PICO definition, which helps to specify the research question by identifying (1) the Patient problem or Population, (2) the Intervention, (3) the Comparison, and (4) the Outcome(s) (Cooke et al., 2012). The primary outcomes were associated with level of functional activity after a stroke.

Figure 1

Our PICO Definition based on Cooke et al., (2012).

P	Does post-stroke apathy occur in adult stroke survivors
I	Undergoing acute or community-based stroke rehabilitation
C	- *No comparison* -
O	Affect recovery of functional activities

P= Population/problem, I= Intervention, C= Comparison, O= Outcome

We included studies with stated outcome measures for functional activity, such as The Barthel Index (Collin, Wade, Davies, & Horne, 1988; Mahoney & Barthel, 1965), and Functional Independence Measure (Linacre, Heinemann, Wright, Granger, & Hamilton, 1994).

We decided not to limit research based on their dimensional understanding of apathy. Apathy was measured using screening tools such as the Apathy Evaluation Scale (Marin et al., 1991), and the Apathy Inventory (Robert et al., 2002). Studies without any form of formal assessment of apathy were excluded from this systematic review.

There is agreement in terms of what constitutes a stroke, but there are differences when it comes to level of detail (neuroanatomical information, severity, frequency, age etc). We decided not to make restrictions in terms of stroke type, location or severity, given that it was indicated that literature in this area is scarce.

Search strategy

The systematic review protocol was registered on Prospero (https://www.crd.york.ac.uk/prospero/), which is sponsored by the National Institute for Health Research, UK. The PRISMA Guidelines (Moher et al., 2009), were used to guide the search strategy (see Figure 2). Four electronic bibliographic databases were searched: MEDLINE (Ovid), EMBASE (Ovid), PsycINFO (EBSCO), PubMed (EBSCO) and the

Cochrane Library. Studies published from 1985 onwards were included. Restrictions were applied to include only primary research, studies with human samples, in the English language, published in peer reviewed journals. Single case-studies, opinion articles and conference abstracts where the full text was not available were excluded.

A mixture of keywords and Medical Subject Headings (MeSH) was used to identify terms. The search terms used were: Apath* OR Amotivation OR Diminished motivation OR Avolition OR Athymhormia OR Indifference AND Stroke OR Ischemi* OR Infarct* OR Hemorrhag* OR Thrombo* OR Emboli* OR Cerebrovascular AND Functional Activity OR Recovery of function OR Recovery OR Improvement OR Functional recovery.

Data analysis

A narrative synthesis was carried out focusing on functional recovery in relation to apathy. Functional activity was the primary outcome measure. It was expected that publications in this area would be limited given the preliminary search conducted before the formal data search and extraction. A narrative synthesis was planned as meta-analysis was unlikely to be possible. Data were handled using reference manager Zotero and imported to Microsoft Excel. The studies were appraised using the NICE Appraisal Checklist. No formal statistical analysis was conducted.

Study Selection

All searches were carried out on 4th February 2020. The primary reviewer screened titles and abstracts. As advised by the PRISMA guidelines (Moher et al., 2009), a secondary reviewer screened titles and abstracts of 20% of articles and inclusion and exclusion were compared between reviewers. There were no issues in terms of agreement, as reviewers agreed in all cases. All articles meeting the inclusion criteria were examined using the quality assessment tool by both reviewers.

Information about study design, type of stroke, number of participants, measures and results was extracted. The screening process is visually presented in the flowchart below.

Quality Appraisal and Risk of Bias

Study quality was assessed using the NICE Quality Appraisal Checklist (see Appendix C), developed to support evaluation of the internal and external validity of correlational studies, in terms of study design, population, method, outcomes and analyses (NICE, 2012). These aspects of study quality are rated using five possible responses: 1) ++ indicates the study is designed to minimise risk of bias, 2) + indicates information is not clearly reported, 3) - indicates a significant source of bias, 4) Not reported (NR) indicates the study failed to report an aspect of methodology and lastly, 5) Not applicable (NA), where the section does not apply to the study due to study design (NICE, 2012). Studies are not given an overall numerical score in this checklist.

Results

Eight studies were identified for review following the searches, see Table 1 for summary.

Figure 2

Prisma flowchart

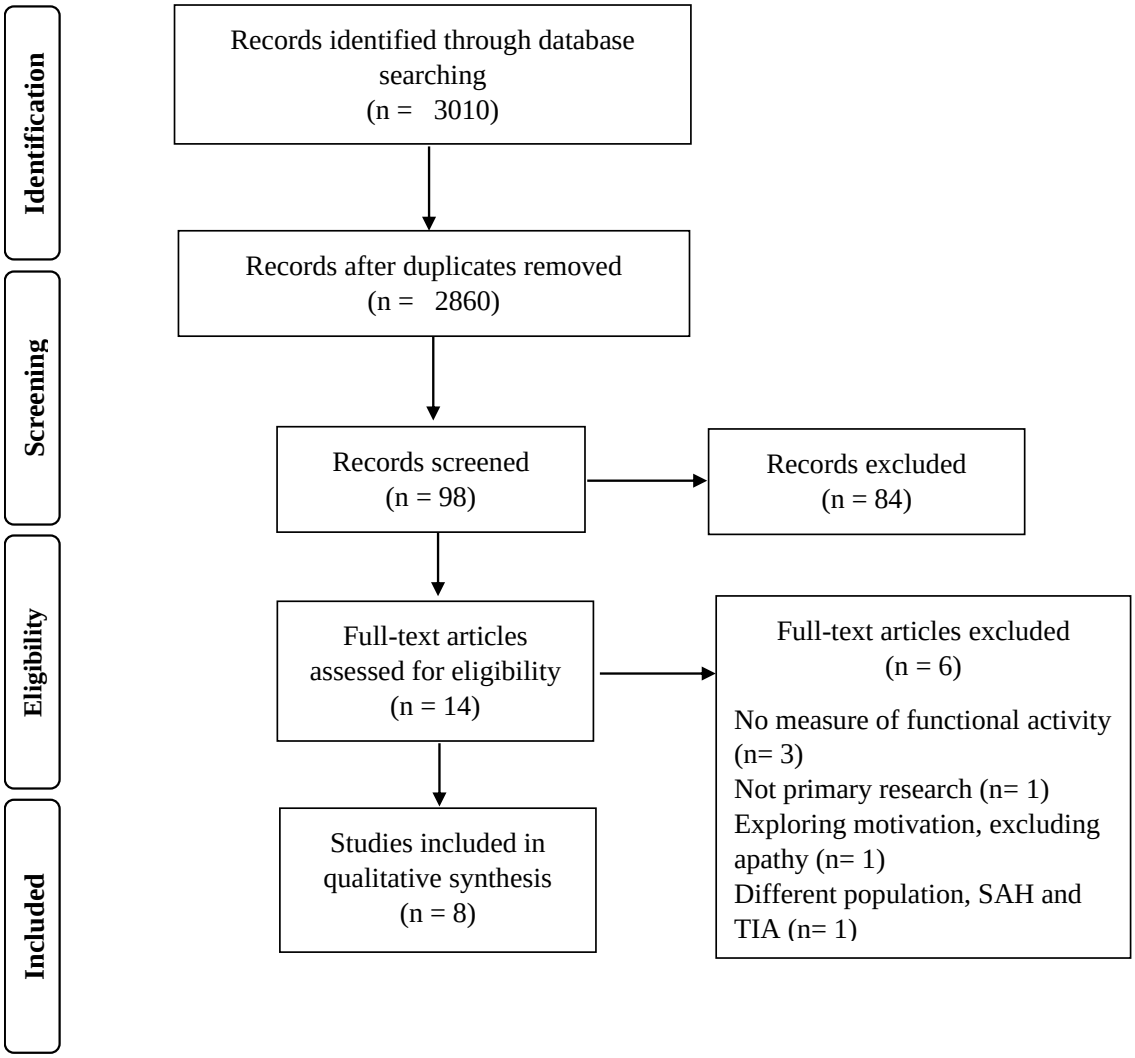

Table 1 *Summary of all 8 studies reviewed*

Author	Relevant Study Aims	Sample size	Age Mean (SD)	Females (%)	Type of stroke	Study design	Apathy Measure	Functional Activity measure	Relevant Findings
1. Bickerton et al., 2015	To examine the utility of the BCoS in discriminating cognitive profiles and recovery of function across stroke survivors.	657 Stroke patients (331 were reassessed after 9 months),100 matched controls.	69.31 (14.34)	43.29	Left (152) vs. right hemisphere (181) strokes as well as first ever (455) vs. repeated strokes (202)	Observational, Cross-sectional study	AES-S	NEADL, BI	Functional outcome at 9 months correlated with domain-level deficits in controlled attention, spatial attention, and praxis over and above initial dependency and concurrent levels of affect and apathy.
2. Hama, et al., 2007	To examine the effect of apathy on functional recovery after stroke	237 Stroke patients	65.1 (11.3)	34.2	Ischemic (128) and haemorrhagic (109)	Observational, Cross-sectional study	AS, NPI	FIM	Apathy correlated negatively with improvement in FIM after stroke.
3. Hama, et al., 2008	To examine the effect of acceptance of disability or 'insistence on recovery' in stroke patients: first on their functional improvement and second, on their psychological symptoms.	237 Stroke patients	66.3 (10.2)	29.87	Ischemic (136) and haemorrhagic (95)	Observational, Cross-sectional study	AS	FIM	“Insistence on recovery reduced apathy, resulting in enhanced improvement of disability after a stroke in elderly stroke patients.” AS scores decreased as insistence on recovery score increased.

Table 1 *Continued*

Author	Relevant Study Aims	Sample size	Age Mean (SD)	Females (%)	Type of stroke	Study design	Apathy Measure	Functional Activity measure	Relevant Findings
4. Harris, Elder, Schiff, Victor & Goldfine, 2014	To examine the effect of apathy and hypersomnia on outcome in acute rehabilitation.	213 Stroke patients	78.1 (range: 73.5-84)	59	Haemorrhagic stroke control patients	Cross-sectional design (retrospective) Correlational	Clinical diagnosis of apathy/ modified version of AS	FIM	Patients with apathy were 2.4 times more likely to go to a nursing home and had discharge FIM scores 12 points below the mean compared with non-apathetic stroke survivors.
5. Kennedy, Granato & Goldfine, 2015	To determine how the severity of apathy changes in the first weeks after stroke.	257 Stroke patients	72.8 (13.9)	Not stated	Ischemic and Haemorrhagic stroke, where 21% had persistent apathy	Observational, Cross-sectional study	AI-C	FIM	Apathy was present in 28% of patients undergoing inpatient acute rehabilitation for stroke. Apathy improved only modestly during the acute rehabilitation stay, and the majority of patients with apathy remained still had apathy at discharge.
6. Mikami, Jorge, Moser, Jang & Robinson, 2013	To examine the course of cognitive, physical, and social impairment among patients who developed apathy during the first year after stroke.	56 Stroke patients, (compared apathy vs. no apathy)	No apathy 62.1 (12.3), apathy 66.5 (14.9)	No apathy 36.6, apathy 34.8	Ischemic (no apathy 84.8, apathy:100) and haemorrhagic (no apathy: 15.2, apathy:0)	Observational, prospective cohort study	"Clinical diagnosis of apathy" and/or a modified version of AS	FIM, SFE	Apathy associated with less recovery in cognition and ADLs over the first year after stroke compared with similar non-apathic patients.

Table 1 *Continued*

Author	Relevant Study Aims	Sample size	Age Mean (SD)	Females (%)	Type of stroke	Study design	Apathy Measure	Functional Activity measure	Relevant Findings
7. Santa, et al., 2008	To examine the frequency of apathy after a first-ever stroke and to prospectively study the impact of apathy on functional recovery.	67, Stroke patients, measured at hospital admission and three months after stroke (apathy vs. no apathy)	Apathy 70.4 (2.6) no apathy 64.1(1.4)	Apathy 50, no apathy 42	Ischemic (Apathy: N=11, no apathy N= 24) and haemorrhagic (Apathy: N=3, no apathy N= 29)	Observational, prospective cohort study	AS	BI, FIM	Apathetic patients showed less improvement in the Barthel index or scores of functional independence measures than nonapathetic patients after rehabilitation.
8. Skidmore, Whyte, Butters, Terhorst & Reynolds, 2015	To examine the effects of strategy training, a behavioural intervention used to augment usual inpatient rehabilitation, on apathy symptoms over the first 6 months after stroke.	30 Stroke patients in acute inpatient rehabilitation. Strategy training vs usual inpatient rehabilitation. Admission, 3- and 6-months follow-up.	Strategy training group 64.87 (16.59), reflective listening 71.80 (13.19)	Strategy training groups, males: 9 (60), reflective listening 11 (73)	Strategy training Ischemic (19 (67), reflective listening, 11(73), Hemisphere right strategy training 10 (67), reflective listening 11 (73)	Secondary analysis of randomised control trial	AES (self-rating)	FIM	Correlations between apathy and function independence scores were nonsignificant, either at the 3-month or 6-month follow-up*

AES= Apathy Evaluation Scale (Marin et al., 1991), *AI=Apathy Inventory* (Robert et al., 2002), *AS= Apathy Scale* (Starkstein et al., 1992), *BCoS= Birmingham Cognitive Screen (Bickerton et al., 2015), BI= Barthel Index (Mahoney & Barthel, 1965), FIM= Functional Independence Measure* (Hamilton et al., 1994), *MHLC= Multidimensional Health Locus of Control (Wallston, Wallston, & Devellis, 1978), NPI-NH= Neuropsychiatric Inventory-Nursing Home* (Lange et al., 2004), *NEADL=Nottingham Extended Activities of Daily Living (Nouri & Lincoln, 1987), PSD= Post-stroke depression, SFE= Social Functioning Exam (Starr, Robinson, & Price, 1983). *Data were provided by the authors upon request and not past of the published article*

Quality assessment - External validity

As seen in Table 2, there were issues with external validity in all studies. All studies showed lack of information in terms of source population, and there is risk of bias in terms of generalisability and external validity. Five studies named the hospitals where data was collected (Hama et al., 2008, 2007; Harris et al. , 2014; Kennedy, Granato, & Goldfine, 2015; Mikami, Jorge, Moser, Jang, & Robinson, 2013; Santa et al., 2008), more detailed information about the sourcing of participants was however not provided.

There was generally little diversity in terms of location, with four studies conducted in the United States (Harris et al., 2014; Kennedy et al., 2015; Mikami et al., 2013; Skidmore, Whyte, Butters, Terhorst, & Reynolds, 2015), three in Japan (Hama et al., 2008, 2007; Santa et al., 2008) and one in the United Kingdom (Bickerton et al., 2015).

Quality assessment – Internal validity

As seen in Table 2, four of the eight studies were rated as having good internal validity based on the NICE quality appraisal checklist (NICE, 2012). All studies were based on observational data, with the exception of one study examining secondary data from a randomised controlled trial (RCT) (Skidmore et al., 2015). Only one study was rated as good in terms of theoretical basis of explanatory variables (Bickerton et al., 2015). Two studies provided sufficient psychometric information regarding their measures (Mikami et al., 2013; Skidmore et al., 2015), the remaining studies did not provide sufficient information. Only three studies sufficiently reported all important outcomes (Bickerton et al., 2015; Kennedy et al., 2015; Mikami et al., 2013).

In terms of follow-up time, three studies were rated as good (Hama et al., 2008; Mikami et al., 2013; Skidmore et al., 2015), follow-up time was too short in four of the studies (Bickerton et al., 2015; Harris et al., 2014; Kennedy et al., 2015; Santa et al., 2008).

All findings are summarised in Table 2, see Appendix C for more details about quality ratings.

Table 2

Summary of quality assessment of the 8 included studies, based on the NICE Quality Appraisal Checklist. Scoring key is available in Appendix B.

	Population			Method				Outcomes					Analyses					Summary	
Study	**1.1**	**1.2**	**1.3**	**2.1**	**2.2**	**2.3**	**2.4**	**2.5**	**3.1**	**3.2**	**3.3**	**3.4**	**3.5**	**4.1**	**4.2**	**4.3**	**4.6**	**Total Internal Validity**	**Total External Validity**
1. Bickerton, et al., 2015	+	-	+	NA	++	NA	++	NR	+	+	++	++	+	++	++	++	++	++	+
2. Hama, et al., 2007	+	++	+	NA	+	NA	+	NR	+	NA	+	NA	NA	++	++	NA	++	++	+
3. Hama, et al., 2008	+	+	+	NA	+	NA	+	NR	+	+	+	NA	++	++	++	+	+	+	+
4. Harris, et al., 2014	+	+	++	NA	+	NA	+	NR	+	NA	+	++	+	++	++	++	++	+	+
5. Kennedy, et al., 2015	+	++	+	NA	+	NA	++	NR	+	+	++	++	+	++	++	+	+	+	+
7. Mikami, et al., 2013	+	++	+	NA	+	NA	++	NR	++	NA	++	NA	++	+	++	++	-	++	+
8. Santa, et al., 2008	+	+	+	NA	NA	NA	+	NR	+	NA	+	NA	+	-	+	+	+	+	+
9. Skidmore, et al., 2015	+	+	+	+	+	+	+	NR	++	NA	+	++	++	+	++	++	++	++	+

++ indicates that for that particular aspect of study design, the study has been designed or conducted in such a way to minimise the risk of bias. + indicates that either the answer to the checklist question is not clear from the way the study is reported, or that the study may not have addressed all potential sources of bias for that particular aspect of study design. - should be reserved for those aspects of the study design in which significant sources of bias may persist. NR not reported should be reserved for those aspects in which the study under review fails to report how they have (or might have) been considered. NA not applicable should be reserved for those study design aspects that are not applicable given the study design under review.

Summary of Findings

Table 1 provides an overview of study aims, participant demographic information and main findings. As seen in Table 1, studies tended to focus on stroke patients in relatively early interventions at rehabilitation hospitals. Patients were assessed whilst admitted to acute rehabilitation hospital wards (Bickerton et al., 2015; Harris et al., 2014; Kennedy et al., 2015; Santa et al., 2008; Skidmore et al., 2015), or within less than three months after stroke (Hama et al., 2007; Hama et al., 2008; Mikami et al. 2015). A few studies also included a follow-up assessments 3 months after the initial point of assessment (Harris et al., 2014; Mikami et al. 2013; Santa et al., 2008; Skidmore et al., 2015), 6 months (Mikami et al. 2013; Skidmore et al., 2015), 9 months (Bickerton et al., 2015; Mikami et al. 2013), and one year after the baseline assessment (Mikami et al. 2013).

Two studies focused on how people with elevated apathy scores performed in activities of daily living (ADLs) at various times during hospitalisation compared with stroke patients without apathy (Mikami et al., 2013; Santa et al., 2008). ADLs refer to essential skills needed for independent self-care, including eating, grooming, dressing, toileting and mobility (Mlinac & Feng, 2016). Some studies focused on acute rehabilitation (Hama et al., 2008, 2007; Harris, Elder, Schiff, Victor, & Goldfine, 2014; Kennedy et al., 2015), whereas others had a longer follow-up period (Bickerton et al., 2015; Mikami et al., 2013; Santa et al., 2008). One study used secondary data from an RCT to investigate a new form of treatment targeting symptoms of apathy (Skidmore et al., 2015).

Assessment of apathy

The most frequently used screening tool was the self-rated version of the Apathy Scale (Starkstein, Mayberg, Andrezejewski, Leiguarda, & Robinson, 1992), which was used by four of the studies (Hama et al., 2008, 2007; Harris et al., 2014; Santa et al., 2008), see Table 1. One study (Hama et al., 2007) also used the Neuropsychiatric Inventory (Lange, Hopp, &

Kang, 2004), as an observer-rated measure for comparison with the self-rated score. Both AS and NPI give unidimensional apathy scores. One study (Mikami et al., 2013) based their apathy assessments on a modified clinician rated version of the AS, as well as clinical diagnosis. Diagnosis was based on the Robert et al., (2009) criteria for Alzheimer's disease. Harris et al., (2015) also based some of their apathy assessment on diagnosis. A diagnosis was given if patients were described in accordance with apathy descriptions by physical and speech and language therapists during rehabilitation. Finally, one study (Kennedy et al., 2015) used the clinician-rated version of the Apathy Inventory (Robert et al., 2002), which is a multidimensional measure. Findings were however presented based on the total scores; subscale scores were not presented.

Assessment of Functional Activity

The Functional Independence Measure (FIM, Hamilton, Laughlin, Fiedler, & Granger, 1994) was the most frequently used measure of functional activity, used by seven of the eight studies, (Hama et al., 2008, 2007; Harris et al., 2014; Kennedy et al., 2015; Mikami et al., 2013; Santa et al., 2008; Skidmore et al., 2015). The FIM is considered valid and reliable and is commonly used in clinical practice (Duncan et al., 2005). It is important to bear in mind, however, that this scale is not uniform or linear in terms of changes in the upper and lower extremes, as these represent different functional improvements (Harris et al., 2014). Two studies (Bickerton et al., 2015; Santa et al., 2008) used the Barthel Index (Collin et al., 1988).

Association between Post-Stroke Apathy and Functional Activity

Apathy was negatively associated with functional outcome after stroke in all the reviewed studies indicating that stroke survivors with apathy have worse prognosis in terms of recovery. Apathy was prevalent, ranging between 28 and 44% in the samples across studies, and they were found to remain relatively stable throughout rehabilitation, (Hama et al., 2008, 2007; Kennedy et al., 2015; Matsuzaki et al., 2015; Mikami et al., 2013; Santa et al., 2008).

Two studies found that stroke survivors with apathy were more than twice as likely to be discharged to a nursing home following hospitalisation (Harris et al., 2014; Kennedy et al., 2015). Although at a slower pace, improvements were also observed in stroke survivors with apathy, and it was suggested that all patients benefit from rehabilitation in terms of improvement of functional activities even when not being fully able to utilise the full potential of treatment (Matsuzaki et al., 2015; Santa et al., 2008).

Self-Report Measures

Five studies used self-rated apathy measures (Table 1). One of the studies, which also included the NPI as an observer-rated measure, found a significant difference between apathy scores (Matsuzaki et al., 2015). In this study, an additional eleven percent of the sample reached the threshold of a clinical diagnosis of apathy when rated by the clinician compared with self-rated scores (Matsuzaki et al., 2015). Unfortunately, the other study did not directly investigate the relationship between the observer- and self-rated scores, as the AS was only used in the follow-up analysis (Hama et al., 2007). The study using the clinician rated form (AI-C) chose this scale to include patients with aphasia and did not include a self-rated scale for comparison (Kennedy et al., 2015).

A concern was raised by two studies (Harris, 2014; Matsuzaki et al., 2015), regarding the apathy prevalence in stroke research, as scores are thought to be grossly underestimated. The use of self-rated scales on their own was criticised, due to limitations in terms of personal awareness following stroke. Both studies pointed to clinician rated versions of the scales as more reliable methods when assessing apathy.

Two studies argued that the use of self-report in research is potentially problematic since it might exclude stroke survivors with aphasia (Harris, et al., 2014; Kennedy et al., 2015). One study found that patients with aphasia are much more likely to experience apathy symptoms compared with stroke patients not experiencing language impairments (Harris, et

al., 2014). This finding was echoed by Kennedy and colleagues (2015), who also found a strong correlation between aphasia and apathy.

Apathy and Stroke Characteristics

Four studies included stroke characteristics in their analyses. An interesting finding was that hypersomnia and apathy, but not stroke severity was associated with poorer outcomes (Harris et al., 2014). One study found significant differences between apathy and repeated strokes, and that people suffering from multiple strokes had worse symptoms than people who had only experienced one stroke (Bickerton et al., 2015). Another finding from the same study was that apathy was more frequent in patients with damage to the right hemisphere than those with left hemisphere strokes. One study found that apathy was more prevalent in ischaemic strokes compared with haemorrhagic strokes, and that ischemic strokes were associated with poorer outcomes (Santa et al., 2008).

Post-stroke Apathy, Age and Functional Activities

There were inconsistencies in the association between apathy and confounding variables. Two studies found that older patients were significantly more apathetic (Santa et al., 2008), as well as being more cognitively impaired (Mikami et al., 2013). Another study found no significant association between apathy scores and age, days since stroke onset or years of education (Kennedy et al., 2015)**.**

Timing of Apathy Assessment

Almost all reviewed studies included a follow-up assessment of apathy in their research whilst patients were at hospital. None of the studies, however, followed patients longer than a year after stroke or provided post discharge follow-up assessments.

Discussion

This systematic review examined the association between PSAp and functional outcomes, identifying eight studies for analysis. This is not numerous considering the immense cost and patient and caregiver burden associated with stroke (Saka et al., 2009; Van Dalen et al., 2013), especially considering that about one third of stroke survivors experience apathy in the first year (Bickerton, et al., 2015; Hama, et al., 2007; Skidmore, et al., 2015). Quality assessment showed that there were issues in terms of the external validity of all the reviewed studies. This suggests that generalisability of findings cannot be assumed. Half of the studies had good internal validity, whilst there were uncertainties in relation with risk of bias in the remaining four.

Findings from this systematic review indicate that apathy was associated with poorer functional outcomes following stroke and remained relatively stable throughout rehabilitation. Stroke survivors with apathy were more likely to be discharged to nursing homes than survivors without apathy (Harris et al., 2014). Although at a slower pace, the studies reviewed found that stroke patients with apathy benefitted from rehabilitation and showed improvements on functional outcomes (Santa et al., 2008).

It is important to identify realistic goals in rehabilitation, to support and optimise functional recovery and quality of life (Dobkin, 2004). There are currently no evidence-based treatments targeting PSAp, and it is therefore important to gain better insight into this syndrome (Kennedy et al., 2015). It has been argued that it is the clinician's responsibility to test adjunct strategies on patients with apathy symptoms before concluding that there are no further gains to be made (Dobkin, 2004).

Six of the studies used unidimensional measures for apathy, which do not distinguish between apathy subtypes. This is problematic as apathy is considered a multidimensional

construct, with impairments in behavioural emotional and social interaction (Robert et al., 2018). The two studies (Bickerton et al., 2015; Skidmore et al., 2015) using multidimensional measures, did not fully utilise the potential of these, as they were only reporting severity of the total scores, and apathy profiles were not provided. This is a major issue, as apathy research indicates that there are distinct types of apathy associated with specific brain regions and pathways (Le Heron et al., 2017; Marin et al., 1991;Stuss, van Reekum, & Murphy, 2000). Post-stroke profiles of apathy would provide clinically relevant information informing rehabilitation planning. For example, a stroke survivor with initiation apathy might need different support to someone with emotional apathy. We predict that apathy subtype might be associated differently with functional outcomes.

In terms of prevalence, apathy was present in 28-44 % of stroke survivors, which concurs with PSAp literature, e.g. (Caeiro, Ferro, e Melo, Canhão, & Figueira 2013; Hollocks et al., 2015; Jorge, Starkstein, & Robinson, 2010), showing that apathy is common after stroke. The prevalence of apathy is much higher when also considering the more impaired part of the stroke population, compared with less impaired counterparts, as well as when considering issues concerning insight (Matsuzaki et al., 2015).

An identified difficulty with self-report measures of apathy, is that this sampling method does not allow access to a diverse and representative sample of real-life stroke populations. There are many stroke survivors living with severe cognitive impairments and aphasia that would struggle using these measures (Santa et al., 2008). This has also been previously raised in the literature on PSAp (Caeiro, et al., 2013). The use of self-report measures does however require less resource in terms of clinician time and training and is considered a non-intrusive form of data collection in terms of patient burden (Matsuzaki et al., 2015). Neither the AES-S (Marin et al., 1991), AS (Starkstein et al., 1992), NPI (Lange et

al.,2004) or AI (Robert et al., 2002), have been specifically validated for stroke. We argue that self-rating can still be useful as an apathy assessment –

the self-rated Dimensional Apathy Scale (Radakovic & Abrahams, 2014) has been utilised and validated in dementia patients, a group that is typified by cognitive impairment, and showed self-rated apathy/motivational impairments compared to controls (Radakovic, Davenport, Starr, & Abrahams, 2018).

Apathy is often evaluated later than other consequences of stroke, usually around three months after stroke (Cosin et al., 2015), which was also found to be the case in our review. People who had no apathy in the first week following stroke generally did not develop apathy at later points (Kennedy et al., 2015). Apathy can however develop or worsen in a few cases over time, and should be assessed and monitored throughout the intervention (Kennedy et al., 2015). It has been argued that there is no need to delay apathy assessment as apathy has been shown to be relatively stable and present at earlier stages of recovery (Cosin et al., 2015). By delaying early assessment of apathy, there is a risk of reducing the efficiency of early intervention.

In the reviewed articles, there were inconsistent findings regarding associations between demographic information such as age, education level and gender with apathy. The association of age and apathy with functional activity therefore remains unclear. Age has been found to be associated with greater cognitive impairments and apathy in other research (Sagen et al., 2010; Starkstein, Ingram, Garau & Mizrahi, 2005).

A study not included in the review, as it focused on Subarachnoid haemorrhage and TIA rather than stroke, found that apathy had a negative influence on outcome in terms of functional activities after transient ischemic attack or subarachnoid haemorrhage (Matsuzaki et al., 2015).

Strengths, limitations and future directions

It has been argued that stroke rehabilitation differs between healthcare systems, highlighting the importance of considering contextual differences in the evaluation of stroke rehabilitation programmes (Putman & De Wit, 2009). Most of the studies included in our review were conducted in hospitals in the USA and Japan. It is possible that hospital practices in these countries differ from UK and Europe. Another point is that none of the studies provided follow-up assessment beyond one year of treatment, it would be interesting to gain greater knowledge of the stability of PSAp exceeding this timeframe.

There are some concerns in terms of apathy assessment and prevalence. It is problematic that researchers base their understanding of apathy upon different models (some viewing apathy as a symptom of depression, others as a separate neurological syndrome). This is especially problematic when reviewing apathy based on clinical expertise from medical records, as there are several layers of nuances potentially lost in the translation of these transcripts. Research focusing on differential apathy diagnostics, including apathy subtypes and severity would be a valuable contribution and clinically relevant to PSAp research.

Conclusion

Despite the high prevalence of apathy, only eight studies were identified for review. Study quality was assessed with the NICE appraisal checklist. Interval validity was assessed as good in four studies. There were issues in terms of external validity in all studies. To conclude, apathy was commonly reported in these samples, with about one third of stroke patients above clinical thresholds of apathy across studies (Bickerton et al., 2015; Hama, et al., 2007; Mikami et al., 2013; Skidmore et al., 2015). The overall findings supported that apathy is associated with delayed recovery of functional activity. Studies frequently used self-report-based scales when screening for apathy, and limitations regarding language problems

and insight were raised and discussed. Patients with apathy benefit from rehabilitation programmes, even when apathy is not specifically targeted.

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CHAPTER 3 – Bridging the Systematic Review and Empirical Paper

Word count: 2062

Bridging the Systematic Review and Empirical Paper

The systematic review (SR) explored the association between post-stroke apathy (PSAp) and functional outcomes in stroke rehabilitation, finding a negative relationship between these. Stroke survivors with apathy were 2.4 times more likely to move to a nursing home following discharge compared with survivors without apathy (Harris et al., 2014). Optimising outcome in terms of functional activities after stroke is important, as this allows functional autonomy and social inclusion as the stroke survivor is able to look after his or herself and their home independently, return to work, studies, parenting etc. (Campos et al., 2019).

Despite the high prevalence of PSAp and its association with poor rehabilitation outcomes, the assessment of apathy is often delayed or absent in clinical settings (Cosin et al., 2015). It is also noteworthy that there are currently no recommendations or mention of PSAp in the NICE guidance on stroke (Royal College of Physicians, 2016).

The most frequently used apathy measure in the SR was the self-rated version of the Apathy Scale (Starkstein, Mayberg, Andrezejewski, Leiguarda, & Robinson, 1992), which provides a unidimensional apathy score. Apathy was also assessed using the Neuropsychiatric Inventory, NPI (Cummings et al., 1994), which has only a single item on apathy. Here, apathy is scored on a dichotomous yes/no basis, and does not provide nuances such as severity or elaboration in terms of apathy subtype (Robert et al., 2002). One study used a multidimensional measure in the SR: the clinician-rated version of the Apathy Inventory (Robert et al., 2002). The potential of the apathy subscale scores was however not used to characterise the nature of the apathy involved.

As discussed in the introduction chapter, apathy can present in different ways and is understood as a multifaceted syndrome: affecting constructs such as initiation (Cummings et al., 1994; Robert et al., 2002; Stuss, van Reekum, & Murphy, 2000), affect (Cummings et al.,

1994; Marin et al., 1991), goal-directed behaviours (Levy & Dubois, 2006; Starkstein & Leentjens, 2008), and intellectual curiosity and self-awareness (Sockeel et al., 2006). These constructs are associated with focal damage to different areas and pathways. Despite the prevailing view that apathy is a multidimensional phenomenon,(Le Heron et al., 2017; Levy, 2012; Radakovic & Abrahams, 2014; Robert et al., 2018) researchers are still relying on unidimensional measures, such as the Apathy Scale (Starkstein et al., 1992), as highlighted in the SR (Bickerton et al., 2015; Hama et al., 2008, 2007; Harris et al., 2014; Mikami et al., 2013; Santa et al., 2008; Skidmore et al., 2015).

Apathy Subtypes and Assessment

Levy and Dubois (2006) mapped their understanding of apathy on to Stuss' model for executive functioning (Stuss & Alexander, 2000), and proposed that there are three main apathy subtypes: lack of initiation of activities, emotionally affective apathy, and cognitive apathy - which refers to an inability to organise, manage and expand on plans (Levy & Dubois, 2006).

The Dimensional Apathy Scale, (DAS, Radakovic & Abrahams, 2014) was developed to provide a multidimensional assessment of apathy based on the neurocognitive model of Levy and Dubois (2006). It consists of three subscales. The executive subscale of the DAS (e.g. item 17 "When doing a demanding task, I have difficulty working out what I have to do") maps onto the cognitive apathy subtype in the Levy and Dubois model. This type of apathy could potentially affect functional outcome of stroke rehabilitation as patients may not be able to set or follow rehabilitation goals. The cognitive, behavioural and initiation subscale on the DAS maps onto Levy and Dubois's auto-activation subtype, focusing on behaviour, initiation and thoughts. "I try new things" is a reverse-scored item measuring this domain (Radakovic & Abrahams, 2014). Patients with this type of apathy may not initiate rehabilitation tasks. The emotional apathy subscale of the DAS refers to the integration of

emotional behaviour, where the outcome of this can be emotional blunting, neutrality and indifference (Radakovic & Abrahams, 2014). An example from the emotional apathy subscale on the DAS is “I feel indifferent to what is going on around me”. Each subscale consists of 8 items. Here patients may not be able to feel concern about their rehabilitation.

The DAS has been validated for use with people with neurogenerative disorders, such as Alzheimer’s Disease, Parkinson’s and Amyotrophic Lateral Sclerosis (ALS), (Radakovic & Abrahams, 2014, 2018; Radakovic, Stephenson, et al., 2016), but not for use with stroke survivors. For Parkinson's disease and Alzheimer’s Disease, the executive and initiation apathy subtypes of the DAS were most prominent (Radakovic et al., 2018; Radakovic, Stephenson, et al., 2017), whereas initiation apathy was the most prominent subtype for Amyotrophic lateral sclerosis (Radakovic, Stephenson, et al., 2016). The emotional apathy subtype was less prominent across all three conditions. The emotional apathy subtype has been found to be more prevalent in frontotemporal dementia compared with Alzheimer’s disease (Radakovic, Colville, et al., 2016; Wei, Irish, & Hodges, 2020). These findings suggest that apathy profiles vary across neurological conditions.

The validation of instruments prior to use in clinical practice and research is important to ensure they provide valid and reliable measures of the concepts targeted (Meader, Moe-Byrne, Llewellyn, & Mitchell, 2014). Methods used to validate measures usually involve assessments of validity and reliability. Validation studies provide guidance in terms of accurate and efficient methods for screening and assessment in research and clinical practice (Meader et al., 2014; Prisnie et al., 2016).

Evidence from the systematic review suggests that research and clinical practice does not often include any multidimensional assessment of apathy. Emotional, behavioural and cognitive domains of apathy have distinct neurocognitive correlates which could be overlooked when treating apathy as a unitary syndrome (Njomboro & Deb, 2014). Being

more specific about the nature of apathy will enable the development of more specific rehabilitation approaches to optimise functional outcomes.

A standard for the diagnosis of apathy is still needed (Van Reekum et al., 2005). If clinicians and researches choose to move to a more fine-grained, multidimensional assessment of PSAp, they would face the issue that there are no such measures validated for stroke. A validation study of the DAS in stroke populations is therefore considered to be of high clinical relevance, and subsequently the objective of the following empirical paper. The DAS is available in Appendix I.

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CHAPTER 4 – Empirical Paper

Profiling Apathy After Stroke

Prepared for submission to Neurological Sciences, (See guidelines in Appendix E)

Word count: 5764

Profiling Apathy After Stroke

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Abstract

Apathy, a disorder of motivation observed in up to 40% of stroke survivors, is negatively associated with stroke rehabilitation outcomes. Different apathy subtypes have been identified in other conditions, but there is currently no validated multidimensional measure of post-stroke apathy (PSAp). The Dimensional Apathy Scale (DAS) assesses apathy across three subtypes: Executive, Emotional and Initiation apathy (Radakovic & Abrahams, 2014). We aimed to test if the DAS is a valid and reliable tool to detect and characterise apathy in stroke. Fifty-three stroke survivors, (45.3% males, median age 54), and 71 in the non-stroke group (26.8% males, median age 45) completed measures of apathy (DAS, Apathy Evaluation Scale, AES), depression (Patient Hospital Questionnaire, PHQ-9) and anxiety (Generalised Anxiety Disorder scale, GAD-7) as part of an online survey. The DAS showed high internal consistency and convergent validity with the current gold standard unidimensional assessment for apathy (AES) and divergent validity with depression (PHQ-9) and anxiety (GAD-7). Stroke survivors scored significantly higher on the total score of DAS and all subscales, compared with controls. Stroke survivors scored significantly higher for depression, but not anxiety. Our results suggest the DAS is a valid and reliable screening tool to detect and characterise PSAp.

Keywords: apathy, stroke, Dimensional Apathy Scale, validity, reliability, depression

Profiling Apathy After Stroke

Apathy affects many stroke survivors and threatens to limit their recovery following stroke (Mayo, Fellows, Scott, Cameron, & Wood-Dauphinee, 2009; Mikami, Jorge, Moser, Jang, & Robinson, 2013).. Apathy is a disorder of diminished motivation, associated with a marked reduction of initiative, social interactions, activities, cognitive processes and emotional responsivity (Cummings et al., 1994; (Marin, Biedrzycki, & Firinciogullari, 1991; Robert et al., 2002). It is prevalent after stroke, affecting 22 – 41% of stroke survivors (Caeiro, et al., 2013; Matsuzaki et al., 2015; Van Dalen, Van Charante, Nederkoorn, Van Gool, & Richard, 2013). Post-stroke apathy (PSAp) has a negative impact on recovery (Hama, Yamashita, Yamawaki, & Kurisu, 2011; Kennedy, Granato, & Goldfine, 2015). It is associated with greater physical disability and impaired cognitive functioning and often associated with greater long-term impairment (Hama et al., 2007; Harris, Elder, Schiff, Victor, & Goldfine, 2014; Tang et al., 2015).

PSAp has important clinical implications, but is relatively under-researched (Brodaty et al., 2013). There are currently no recommendations or mention of PSAp in NICE guidance in the UK (NICE, 2019). Despite this, however, it is important to detect, and address PSAp given its association with stroke rehabilitation outcomes (Harris et al., 2014; Tang et al., 2015).

There are reported to be distinct subtypes of apathy affecting initiation, executive functioning and emotional neutrality (Le Heron, Apps, & Husain, 2017; Levy, 2012). Several apathy scales, such as the Apathy Scale (Starkstein, Mayberg, Andrezejewski, Leiguarda, & Robinson, 1992) and the Apathy Evaluation Scale (Marin et al., 1991) have in common, however, that they provide only a unidimensional score of apathy severity, on the assumption that apathy is a unidimensional phenomenon.

Based on the model of Levy and Dubois (2006) the Dimensional Apathy Scale (DAS, Radakovic & Abrahams, 2014) assesses three subtypes of apathy. The DAS consists of three subscales: Executive Apathy, or the lack of motivation for planning, organisation or attention: Emotional Apathy, or emotional indifference and neutrality; and Initiation Apathy, or the lack of motivation for self-generation of thoughts or actions (Radakovic & Abrahams, 2014). The DAS has been validated in Motor Neurone Disease (Radakovic et al., 2016), Parkinson's disease (Radakovic, Davenport, Starr, & Abrahams, 2018) and dementia (Radakovic & Abrahams, 2014). These validation studies have found positive intra-correlations between DAS subtypes. It is not yet, however, validated for acquired brain injuries, such as stroke.

Given the high prevalence and clinical importance of PSAp (Hama et al., 2011; Van Dalen et al., 2013; Withall, Brodaty, Altendorf, & Sachdev, 2009), we aimed to investigate the psychometric properties and validity of the DAS against a 'gold-standard' unidimensional measure of apathy and to assess its associations with depression and anxiety in stroke survivors and a non-stroke group. Based on the above literature, the research questions for this study were as follows:

Research question 1: Does the Dimensional Apathy Scale show adequate validity and internal consistency in stroke?

- Hypothesis 1a: It is hypothesized that the DAS will show adequate internal consistency when completed by stroke survivors and the DAS subscales will be positively inter-correlated with each other, as found in previous validation studies in other conditions (Radakovic & Abrahams, 2018; Radakovic, Starr, et al., 2017; Radakovic et al., 2016; Radakovic, Stephenson, et al., 2017).
- Hypothesis 1b: In line with previous research, (e.g. Radakovic et al., 2016) it is hypothesized that there will be a positive correlation, or convergent validity, between

DAS and AES total scores, as both are measures of apathy. It is also hypothesized that the emotional aspects of PHQ-9 and GAD-7 for depression and anxiety will be negatively correlated with apathy, and therefore show divergent validity for DAS.

Research question 2: How do the DAS profiles differ between stroke survivors and non-stroke survivor groups?

- Hypothesis 2: It is hypothesized that the stroke survivor group will have a higher prevalence of all three dimensions of apathy compared with the control group.

Method

Design

This is a cross-sectional observational study, with a 2x3 mixed factorial design (e.g. a two-level between participants factor of group and a three-level within participants factor of DAS subscale). The chosen design is in line with the design used in previous studies validating the DAS in other neurological disorders, allowing validation and comparison of profiles (Radakovic & Abrahams, 2018; Radakovic, Starr, et al., 2017; Radakovic et al., 2016; Radakovic, Stephenson, et al., 2017).

Participants

Our primary focus was on adult stroke survivors. The inclusion criteria for our stroke survivor group were: being 18 years or older and having experienced a stroke that required hospital attendance at age 18 or above. The inclusion criteria for the non-stroke survivor group were: being 18 years and older. The exclusion criteria for the stroke group were major medical, neurological, or psychiatric co-morbidities unrelated to stroke (e.g. neither a potential risk factor nor consequence of stroke). The exclusion criteria for the non-stroke group were major medical, neurological, or psychiatric conditions. These exclusion criteria

were applied to allow the study to focus on apathy caused by stroke rather than other conditions.

We included participants with anxiety and depression, as these are frequent consequences of stroke and we aimed to recruit a representative sample of stroke survivors. Depression and anxiety were screened using the GAD-7 and PHQ-9 in the questionnaires to enable us to characterise the divergent validity of the DAS in relation to other disorders.

Procedure

Stroke survivors and non-stroke participants were recruited to an online survey via Twitter and Facebook. Stroke charities (e.g. Headway, Stroke Association UK, Stroke Association NI) were contacted to increase visibility of the study. Bristol online surveys was used to collect data. All participants were given an option to enter a prize draw of five £25 Amazon vouchers. This study was granted ethical approval from the University of East Anglia Faculty of Medicine and Health Sciences Research Ethics Committee and followed the General Data Protection Regulation (GDPR) guidelines (Information Commissioner's Office, 2018). Participants gave informed consent in line with the Declaration of Helsinki (World Medical Association, 2013).

The research team, consisting of people with expertise in stroke psychology and apathy research, independently reviewed whether participants met inclusion or exclusion criteria, based on the information provided about their health in the survey. This was followed by a discussion to reach consensus where there were inconsistencies. Participants were excluded on the basis of declaring a health condition unrelated to stroke but with a known association with apathy, to ensure that the current study measured apathy due to stroke rather than due to another condition. A few examples of medical conditions forming the basis of exclusion from both groups were: idiopathic intracranial hypertension, traumatic brain injury,

congenital cervical stenosis, epilepsy, spina bifida, ongoing cancer, bipolar 1 disorder, and ongoing substance abuse.

Measures

Demographic and clinical data on age, gender, years of education, occupation, marital status, age when admitted to hospital for stroke and other mental or physical health conditions were collected at the beginning of the survey.

Apathy

The Dimensional Apathy Scale (DAS, Radakovic & Abrahams, 2014) is a 24-item, three-dimensional scale for assessment of apathy subtypes. It has three subscales, each with 8 items. All items are rated on a 4-point Likert-scale, ranging from 0 (Almost always) to 3 (Hardly ever). Overall scores range from 0-72, higher scores indicate more apathy. Cut-off scores for abnormal scores are: Total ≥ 39, Executive subtype ≥ 14, Emotional subtype ≥ 15 and Initiation subtype ≥ 16 (Radakovic & Abrahams, 2014). The measure was found to have acceptable internal consistency for Parkinson's disease (Cronbach's α=.84, Radakovic et al., 2018), Alzheimer's disease (α=.85, Radakovic, Starr, & Abrahams, 2017) and ALS (α=.86, Radakovic, Stephenson, et al., 2017). Informant/carer-rated and self-versions are available. The self-rated version was used.

The Apathy Evaluation Scale (AES, Marin et al., 1991) comprises of 18 items measuring general apathy. Each item is rated on a 4-point Likert-scale, ranging from 1 (Not at all) to 4 (A lot). The scale has good internal consistency (α=.86-94), and test-retest reliability (α=.76-94), (Marin et al., 1991). There are three versions of this scale, for clinicians, informants and self-rated versions. The version used in this study was the self-rated version. Scores range from 18 to 72, higher scores indicate abnormal levels of apathy.

Depression

The Patient Health Questionnaire (PHQ-9, Kroenke, Spitzer, & Williams, 2001) is a

screening tool for depression, based on the DSM-IV criteria., validated for post-stroke depression (Prisnie et al., 2016). Each item is rated on a 4-point Likert-scale, ranging from 0 (Not at all) to 3 (Nearly every day). Distribution of scores in terms of depression severity is as follows: minimal = 0-4, mild = 5-9, moderate = 10-14, moderately severe = 15-19 and severe = 20-27 (Kroenke et al., 2001). PHQ-9 has excellent internal validity (α=.89) and test-retest reliability (Kroenke et al., 2001). Individuals scoring 10 or higher on the scale have a 88% chance of meeting diagnostic criteria for depression (Kroenke et al., 2001).

Anxiety

The Generalised Anxiety Disorder (GAD-7, Spitzer, Kroenke, Williams, & Löwe, 2006) is a 7-item screening tool for anxiety, based on the DSM-IV criteria, validated for stroke. GAD-7 has excellent internal validity (α=.92), with good test-retest reliability (intraclass correlation coefficient =.82) (Spitzer et al., 2006). Each item is rated on a 4-point Likert-scale, ranging from 0 (Not at all) to 3 (Nearly every day). The distribution of GAD-7 scores in terms of level of anxiety severity is as follows: minimal = 0-4, mild = 5-9, moderate = 10-14 and severe = 15-21 (Spitzer et al., 2006).

Statistical Analysis

To explore how all variables of interest is associated with each other across all conditions, G*Power 3.1.9.4 (Faul, 2007), was used to calculate required sample size for the mixed design ANOVA. A medium effect size is considered a conventional estimate, which yielded an estimated sample size of 44 participants. The power calculation is available in *Appendix D.*

IBM SPSS v.25 was used for data analysis. The analysis plan included checking for missing data and and replacing missing values using median imputation, and to assess distributions across variables. Parametric or non-parametric tests were planned as appropriate to test internal consistency and the associations between measures in the stroke group to

validate the measure, to test effects of group, subscale and interaction between them to characterise apathy in the two groups and then give the details of tests in the results.

Results

Characteristics

One-hundred-and-forty people completed the online questionnaire. Altogether 53 stroke survivors and 71 people who have not experienced stroke were included in the analysis. Seven stroke survivors and nine people who have not experienced stroke were excluded from further analysis on medical, psychiatric and neurological grounds. Only 43% of stroke survivors and 81% of the participants without stroke completed the questionnaire. As seen in Table 1, the two groups were matched on gender, living arrangements, and years of education, but differed significantly on age and occupational status.

Table 1

Demographic Characteristics for Stroke Survivors (N=53) and the Non-stroke Group (N=71)

Factor	Stroke survivors	Non-stroke group	U	χ^2	*df*	*p*
Age, Median (IQR)	54 (14)	45 (27)	1327.5			**.005**
Gender male (N %)	24 (45.3)	19 (26.8)		5.13	2	.077
In employment or studies N (%)	23 (43.4)	63 (88.7)		35.67	1	**.001**
Living arrangement, N (%)				2.06	6	.915
Single	12 (22.6)	18 (25.4)		122	1	.727
Married/ partnership	37 (68.7)	36 (50.7)		136	1	.712
Divorced/ separated	3 (5.7)	4 (5.6)		123	1	.726
Other	1 (1.9)	2 (2.8)		.04	1	.834
Years of education, Median (IQR)	13 (3)	13 (2)	2077.0			.230
Having a University degree, N (%)	31 (58.5)	52 (73.2)		3.51	1	0.61

IQR= Interquartile Range, significant findings are indicated in bold.

As seen in Table 2 ischemic strokes were the most common stroke type. Strokes in left and right hemispheres were almost equally represented, but 43% of stroke survivors did not specify stroke-location. Relatively few stroke survivors had experienced repeated strokes.

In our stroke group there where were no significant correlations (Spearman's Rho) between age and apathy on the DAS (DAS total score, $r_s(51) = .138$, $p = .328$; DAS Executive Apathy, $r_s(51) = -.222$, $p = .110$; DAS Initiation Apathy, $r_s(51) = -.212$, $p = .127$); and DAS Emotional Apathy, $r_s(5)1 = .156$, $p = .263$). The correlation between age and the DAS total score control group was non-significant $r_s(69) = -.166$, $p = .127$).

Table 2

Clinical Characteristics for Stroke Survivor Participants (N = 53).

Clinical Characteristics	
Age at first hospital admission, mean (SD)	47.50 (12.7)
Types of strokes N (%)	
Ischemic	28 (52.8)
Haemorrhagic	19 (35.9)
Type of stroke not specified	6 (11.3)
Stroke location N (%)	
Right hemisphere	15 (28.3)
Left hemisphere	14 (26.4)
Hemisphere not specified	24 (45.3)
Frontal lobe	4 (7.6)
Parietal lobe	2 (3.8)
Temporal lobe	2 (3.8)
Occipital lobe	0 (0.0)
Cerebellar	3 (5.7)
Subcortical (e.g. basal ganglia, thalamic)	6 (11.3)
Mixed locations	4 (7.6)
Stroke location not specified	32 (60.4)
Multiple strokes, N (%)	6 (10.0)
Average number of multiple strokes, mean (SD)	2.6 (55)

SD= standard deviations

Data Preparation

Missing data were handled using median imputation (Acuña & Rodriguez, 2004; Tabachnick & Fidell, 2013). Where possible non-parametric tests were used. A 2x3 mixed ANOVA with a Greenhouse Gleiser correction testing differences between groups and subscales on the DAS and the interaction between these factors, see details in Chapter 5.

Psychometric Properties of DAS in Stroke

Internal Consistency of the DAS

Overall, the DAS had a good level of internal consistency for stroke survivors (α=.84) and an acceptable level for people who have not experienced stroke (α=.76). Internal consistency was acceptable for the initiation apathy (α=0.79) and executive apathy subscales (α=0.74), but questionable for the emotional subscale (α=0.64) for the stroke group.

Convergent Validity of the DAS

As seen in Table 3, the DAS total scores had a strong, positive correlation with the AES. The Initiation and Executive Apathy subscales were also strongly positively correlated with the AES and the emotional subscale showed a moderate positive correlation with the AES. These findings support the convergent validity of the DAS in stroke.

For the stroke group the DAS total score correlated significantly with all subscales: Emotional Apathy $r_s(51)=.71$, $p<.001$, Executive Apathy $r_s(51)=.85$, $p<.001$, and Initiation Apathy $r(51)=.86$, $p<.001$. Significant positive intercorrelations were also found between all DAS subscales: Emotional Apathy vs Initiation Apathy $r_s(51)=.39$, $p<.01$, Emotional Apathy vs. Executive Apathy $r_s(51)=.38$, $p<.01$, and Executive Apathy vs initiation Apathy $r_s(51)=.67$, $p<.001$.

Divergent Validity of the DAS

Correlations between the DAS, AES, PHQ-9 and GAD-7 are presented in Table 3. The relationship between the DAS Emotional Apathy subscale and GAD-7 was non-significant, as was the relationship between the DAS Emotional Apathy subscale and PHQ-9. As emotional apathy, depression and anxiety are considered different constructs, this supports the divergent validity of the DAS in stroke.

Table 3

Correlations between DAS, AES, PHQ-9 and GAD-7 for Stroke Survivors (N = 53.

Stroke survivors (N=53)	AES	PHQ-9	GAD-7
DAS Executive subscale	.775**	.620**	.427**
DAS Emotional subscale	.523**	.030	-.031
DAS Initiation subscale	.756**	.510**	.288*

**p<.001, *p<.05.
AES (Apathy Evaluation Scale), PHQ-9 (Patient health Questionnaire), GAD-7 (Generalised Anxiety Disorder-7)

Group Comparisons across measures

Mann-Whitney U tests were run to determine if there were group differences across questionnaires. Distributions of scores for the stroke- and non-stroke group were similar, as assessed by visual inspection (presented in Table 4). Groups differed on all scales, except for the GAD-7.

Table 4

Mann-Whitney U tests of Group Differences in DAS, AES, PHQ-9 and GAD-7 scores, with Bonferroni correction.

Scale	Stroke median (IQR)	None-stroke median (IQR)	*U*	*p*
DAS total	34 (18)	24 (29)	934.00	**<.001**
DAS Executive Apathy	12 (8)	8 (6)	1152.00	**<.001**
DAS Emotional Apathy	12 (8)	9 (4)	1165.00	**<.001**
DAS Initiation Apathy	10 (6)	6 (5)	995.00	**<.001**
AES	34 (17)	28 (8)	1197.50	**<.001**
PHQ-9	8 (9)	3 (4)	1641.50	**.018**
GAD-7	5 (6)	3 (6)	1801.00	.409

IQR = Interquartile range, p-values in bold show significant differences.

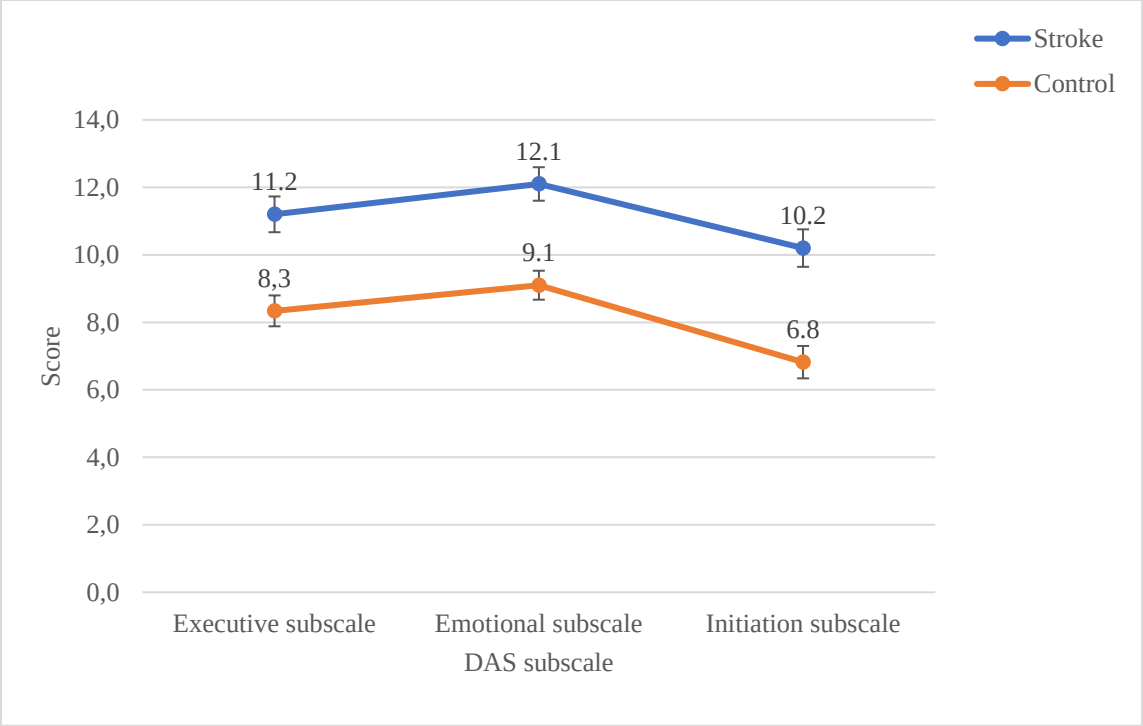
Group Comparison on the DAS

Scores on the DAS showed a significant main effect of group ($F(1,22)=33.17$, $p<.001$). As seen in Figure 1, the DAS scores of stroke survivors were higher than those of the non-stroke comparison group. There was also a significant main effect of DAS subscale

($F(2,228) = 14.82$, $p < .001$). The interaction between group and subscale was not significant ($F(2,228) = .25$, $p = 0.764$), indicating that there was no significant difference in the profile of subscales between the two groups. Figure 1 shows the means for each group across subscales.

Figure 1

DAS Apathy profiles for the Stroke and Non-stroke Groups: Means and Standard Errors



Non-parametric tests confirmed the significant main effects of groups and subscale. The results of Mann-Whitney U group comparisons per scale and subscale are presented in Table 4. A non-parametric Friedman's test found significant effect of subscale ($\chi^2(3)=103.06$, $p<.001$,W=.65), as well as significant pairwise comparison between the subscales for the non-stroke group ($\chi^2(3)=141.80$, $p<.001$, W=.67).

Group Comparison of Caseness

As seen in Figure 1, the DAS profiles of both groups followed similar patterns, although stroke survivors had higher levels of apathy across all apathy subtypes. Table 5 presents cut-off scores for the DAS in stroke, calculated as two standard deviations above our

non-stroke group means. The non-stroke group was matched to our stroke sample, with no significant differences in gender, age (U=1480.5, p=.511) or years of education (U=1185.0, p=.209) between groups.

As seen in Table 5, these calculated cut-off scores are similar to published cut-offs (Radakovic et al., 2016). We judged that published cut-off scores could therefore be applied to our stroke sample and used these to determine caseness.

Table 5

Calculation of DAS cut-off scores, based on our matched non-stroke group, and published cut-off scores.

DAS	*Mean (SD)*	Cut-off	Radakovic et al., (2016) Cut-off
Executive subscale	7.94 (3.49)	15	14
Initiation Subscale	8.96 (3.66)	16	16
Emotional subscale	7.08 (3.28)	14	15
Total score	23.98 (7.40)	39	39

As seen in Table 6, there were significant differences of caseness between groups across all measures, except for the GAD-7. Cut-offs were based on the published scores. In addition to apathy, there were significantly more stroke survivors scoring above the cut-off for depression compared with the non-stroke group.

Table 6

Frequencies of participants meeting the diagnostic cut-offs for the assessment tools. P values are corrected for multiple comparisons using Bonferroni correction.

Scale	Stroke N (%)	Non-stroke N (%)	χ^2	*p*
DAS total	17 (32.1)	3 (4.2)	17.40	**<.001**
DAS Executive apathy	18 (34.0)	7 (9.9)	10.95	**.002**
DAS Emotional subscale	9 (17.0)	0 (0)	13.00	**.001**
DAS Initiation subscale	14 (26.4)	3 (4.2)	12.63	**.001**
AES	23 (43.4)	5 (7.0)	22.94	**<.001**
PHQ-9	9 (17.0)	3 (4.2)	5.65	**.038**
GAD-7	6 (11.3)	5 (7.0)	.69	.610

DAS= The Dimensional Apathy Scale (Radakovic et al., 2016). *DAS total cut-off score ≥39, DAS Executive apathy cut-off score ≥14, DAS Emotional subscale cut-off score ≥15,DAS Initiation subscale cut-off score ≥6. AES= The Apathy Evaluation Scale (Marin et al., 1991), cut-off score ≥37. PHQ-9= The Patient Health Questionnaire (PHQ-9, Kroenke, Spitzer, & Williams, 2001), cut-off score ≥15. GAD-7 = The Generalised Anxiety Disorder (GAD-7, Spitzer, Kroenke, Williams, & Löwe, 2006), cut-off score ≥10. p-values in bold show significant differences.*

Forty-three percent of stroke survivors scored above cut-off on multiple apathy subtypes on the DAS. As seen in Table 7, these stroke survivors also had significantly higher scores for depression (PHQ-9) and anxiety (GAD-7), than stroke survivors who did not score above apathy cut-offs. The median number of apathy subtypes was two. Eight stroke survivors (15.1%) scored above cut-off for one subscale, eight (15.1%) scored above cut-off on two different subscales and six (11.3%) had elevated scores on all three subscales.

Table 7

Comparison of Stroke Survivors According to Number of Apathy Subtypes with Bonferroni correction.

	Above Published Cut-offs for ≥ 1 Apathy Subtype (N = 23)	Below Published Cut-offs for Apathy Subtypes (N = 30)	*p*
Age, median (IQR)	54.0 (17)	54.0 (11)	.986
Years of education, median (IQR)	12.0 (2)	13.0 (2)	.167
Multiple strokes median (IQR)	0.0 (0)	0.0 (0)	.767
Age at first stroke, median (IQR)	46.5 (13)	49.0 (10)	.785
PHQ-9, median (IQR)	11.5 (10)	5.0 (8)	**<.001**
GAD-7, median (IQR)	7.0 (13)	4.0 (5)	**.015**

IQR= interquartile range, p-values in bold show significant differences.

Discussion

We aimed to investigate if the DAS is a valid and reliable screening tool for apathy in stroke survivors. The DAS has been validated for degenerative diseases, but not for stroke (Radakovic & Abrahams, 2018; Radakovic, Starr, et al., 2017; Radakovic et al., 2016; Radakovic, Stephenson, et al., 2017). We found that the DAS showed good internal consistency and was strongly correlated with the AES, indicating good convergent validity. The DAS also showed good divergent validity in stroke, with significant positive correlations between Executive and Initiation apathy and depression but not Emotional apathy and depression, consistent with the distinction drawn between depression and emotional neutrality as an apathy subtype.

Stroke survivors showed higher levels of apathy on the DAS, than did the non-stroke comparison group, for each of the three apathy subtypes in terms of symptom-rating and for caseness. Forty-three percent of stroke survivors displayed one or more apathy subtype, with the most common subtypes being Initiation and Executive apathy. The Emotional subtype was less common and reliable, and findings should be interpreted with caution. Low reporting on emotional apathy has been considered a possible indication of dysfunction in social cognition, and self-awareness (Radakovic et al., 2018; Radakovic, Starr, et al., 2017).

The DAS apathy profiles for stroke survivors and people who have not experienced stroke followed similar patterns. Our stroke sample showed a similar profile of apathy subtypes to profiles reported for people with Parkinson's (Radakovic et al., 2018) and Alzheimer's disease (Radakovic, Starr, et al., 2017). In Alzheimer's disease, no associations between the Emotional apathy subscale and depression were found, arguing that people with Alzheimer's have an awareness deficit in terms of Emotional apathy and depression (Radakovic, Starr, et al., 2017). Although no correlations were found between Emotional

apathy and depression in our sample, stroke survivors did report higher levels of both, compared with the non-stroke group.

Our findings show the importance of screening for both apathy and depression in clinical settings. Stroke survivors with more than one apathy subtype have significantly higher depression scores. This might indicate that it is useful to take apathy into account when treating depression and vice versa. Stroke survivors showed significantly higher levels of depression than the non-stroke group, but the prevalence of depression was still relatively low for this sample. This might possibly be associated with the relatively high level of motivation needed to complete the survey, as severe depression would similarly to severe apathy make the completion of the survey more challenging. Seventeen percent of our stroke survivors scored in the moderately severe to severe range for depression, which is lower than the estimated 30 % prevalence of post-stroke depression (Barker-Collo, 2007; Das & Rajanikant, 2018).

Apathy research has found associations between older age and more severe apathy scores (Brodaty, Altendorf, Withall, & Sachdev, 2010; Sagen, et al., 2010; Starkstein, Ingram, Garau & Mizrahi, 2005). For example, a longitudinal study found that apathy scores were more pronounced in heathy participants after the age of 65 years (Brodaty, et al., 2010). It was therefore potentially problematic that our groups were not matched for age. However, both the stroke sample and the control group were younger than participants in studies reporting an association between apathy and age (with a median age of 54 for stroke survivors and 45 years for controls) and showed no association between age and apathy.

There were also no significant associations between apathy and years of education, age of stroke onset, or gender. We did not include comparison based on type of stroke or stroke location, due to sample size.

Strengths, limitations and recommendations

This is the first validation of a multidimensional apathy scale in stroke. Despite being theorised to be multidimensional, research has frequently used unidimensional apathy scales such as the AES (Marin et al., 1991) and AS (Robert et al., 2002). We argue that the validation of the DAS in stroke survivor groups is a valuable contribution to PSAp research, as this scale reflects the current multidimensional conceptualisation of apathy.

A challenge faced in all apathy research is sampling the full range of apathy, as research is often based on self-selected samples. Nevertheless, we found higher levels of apathy in our stroke sample compared to our non-stroke group. It is possible however, that PSAp is even more prevalent than found in this study, given the levels of motivation required to access and complete an online survey. The dropout rate was nearly twice as high in the stroke survivor group, where over half of the participants discontinued the survey before completion. We speculate that some of these participants dropped out due to lack of motivation and this might indicate even higher prevalence of apathy for stroke than captured by our survey. The high prevalence of PSAp and implications for functional activity and recovery highlights the importance of this area of research (Hama et al., 2011; Harris et al., 2014). We were not able to obtain detailed, verified clinical information about participants in this study. Future research could usefully test associations between clinical variables (including type of stroke, stroke location and premorbid functioning) and apathy profiles by recruiting from clinical services.

Apathy research is still in its infancy and there is a need for more investigation of the assessment and treatment of apathy after stroke. We recommend validation of the carer-version of the DAS, as well as the Brief DAS, for rapid detection of apathy in the clinic (Radakovic et al., 2019). The emotional apathy subscale needs further research, perhaps this is easier assessed using informant rating. DAS also has clinical implications, as someone with

initiation apathy might need different support from others with executive apathy. Apathy is often considered secondary to other neurological or psychiatric difficulties after stroke and frequently underdiagnosed (Chase, 2011). We therefore welcome and encourage research investigating treatment options for the different DAS apathy profiles.

Conclusions

Given the high prevalence of PSAp and its implications for rehabilitation, the present study aimed to validate a multidimensional screening tool for apathy. This is important as no multidimensional measures have previously been validated for stroke. We found that DAS is a psychometrically robust method assessing multidimensional apathy in stroke and recommend using published DAS cut-off scores. Stroke survivors scored significantly higher on the Executive, Initiation and Emotional subscales of the DAS compared with the non-stroke group. Forty-three percent of stroke survivors scored above the cut-off for apathy on one of the subscales, and 63.6% of these scored above cut-off for multiple subscales. Clinical implications of these findings are that there is a need of modification in current practice in terms of assessment and interventions for PSD, PSA and PSAp.

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CHAPTER 5 – Additional Methodology

Outlining additional methodological details of the online survey

Word count: 1375

Additional Methodology and Results

The empirical study was granted ethical approval from the Faculty of Medicine and Health Sciences Research Ethics Committee FMH-REC at the University of East Anglia (reference number: 201819 – 026) and followed the Health and Care Professions Council (HCPC, 2016), British Psychological Society (BPS, 2018) and UEA Codes of Conduct (UEA, 2018).

As seen in Appendix P-U changes were made to the analysis plan to ensure the protection and integrity of anonymity using online methods for data-collection. These changes limited the time for data collection.

It is also worth mentioning that the use of online surveys is a relatively novel form of data collection in stroke. We were only able to identify a few studies using this sampling method e.g. (Rankin, Tran, Rankin, & Lees, 2014; Stein, Hillinger, Clancy, & Bishop, 2013) – we were not able to identify any validation studies using this method.

In terms of data preparation, missing data appeared to be at random counting for 0.81% on two DAS items. Two participants from the stroke group missed one question each from the DAS. In these cases, recommendations to use median imputation were followed (Acuña & Rodriguez, 2004; Tabachnick & Fidell, 2013).

Sampling distribution was visually checked using frequency graphs and Shapiro-Wilk tests used to investigate normality and linearity. Assumptions of normality were not met. Shapiro-Wilk tests showed significant departures from normality ($W(124) = .97$, $p < .01$) for the DAS total score, DAS executive apathy subscale ($W(124) = .97$, $p < .01$), and DAS emotional apathy subscale ($W(124) = .98$, $p < .05$) which were all positively skewed. Where possible non-parametric tests were used, with the exception of a 2x3 mixed measure analysis of variance (ANOVA) with a Greenhouse Gleiser correction was used testing differences between groups and subscales on the DAS and the interaction between these factors, since

ANOVA is considered robust even when assumptions of normality and equal variances are not met (Blanca, Alarcón, Arnau, Bono, & Bendayan, 2017).

In the empirical paper a 2x3 mixed model analysis of variance (ANOVA) was used to perform a between-group comparison of scores from stroke and non-stroke groups and a within-group comparison of scores on the three Dimensional Apathy Scale subscales (DAS, Radakovic & Abrahams, 2014). Mixed model analysis of variance has four main assumptions: (1) the assumption of normality, or that scores in each condition are sampled from a normally distributed population; (2) the assumption of homogeneity of variance, or that variances are the same across conditions; (3) the assumption of independence, or that samples are independent and selected at random; and (4) the assumption of sphericity, or that variances of the differences between within-subject conditions are equal (Field, 2013).

In our sample the assumption of normality was not met for the DAS total score or DAS subscales, as the distribution of these scores were significantly different to the normal distribution. All scores were positively skewed. A Shapiro-Wilk test was significant for the DAS total score ($W(124) = 947$, $p < .001$), for the executive subscale ($W(124) = 957$, $p = .001$), the initiation subscale ($W(124) = 973$, $p = .013$), and the emotional subscale ($W(124) = 976$, $p = .025$). This is however a greater problem for very small datasets (Field, 2013).

The data also violated the sphericity assumption, as the variance of all differences between all pairs in the ANOVA were significantly different. When the assumption of sphericity is not met, there is a risk that the findings on the *F* test are too liberal, finding significant differences where there are none (Haverkamp & Beauducel, 2017). The Greenhouse-Geiser correction is used to estimate the covariate matrix and is considered a robust correction when the assumption of sphericity is violated (Abdi, 2010). The ANOVA is considered robust, even when assumptions are violated, given that the sample size is over 30 (Haverkamp & Beauducel, 2017).

There is no single non-parametric equivalent of a mixed model ANOVA. To carry out the same comparisons using non-parametric tests would have required multiple Mann-Whitney U tests of between group differences and Friedman tests of within group differences. When performing repeated comparisons without correction there is a risk of a Type 1 error, or the rejection of a true null hypothesis, 'known as a false positive' (Field, 2013). The decision was to run the 2x3 ANOVA for the empirical paper, given the robustness of this method with larger sample sizes.

As seen in Table 4 in chapter 4, we calculated scores for the Apathy Evaluation Scale (Marin, Biedrzycki, & Firinciogullari, 1991).On the AES, 43.4% of the stroke survivors fell above the published cut-off for apathy (≧38), this was only 5.6% for the non-stroke group. Depression rates as measured by the PHQ-9 were lower, 17% of stroke survivors scored above the moderately severe cut-off. In the non-stroke group, 4.2% scored above this cut-off. Anxiety scores were higher, with 11.3% of the stroke sample scoring in the severe range (18.9% in the moderate range), and 5.6% of the people who have not experienced stroke (11.3% in the moderate range). The AES was found to have a strong positive correlation with the PHQ-9 in the stroke group $r_s(51) = .71$, $p < .001$ and a moderate correlation in the non-stroke group $r_s(68) = .44$, $p < .001$.

Lastly, our stroke and non-stroke samples were matched by ranking participants in the control group based on age (taking gender and years of education into account, to ensure samples still matched on these factors). Participants at the lower end were excluded from the non-stroke condition, leaving both groups with 53 participants.

In the empirical paper, we judged that published cut-off scores could therefore be applied to our stroke sample and used these to determine caseness. We did however calculate

the cut-off scores again, using cut-offs from our own sample. Findings are presented in Table 1.

Table 1

Frequencies of participants meeting the diagnostic cut-offs for the DAS, using our own cut-off scores, comparing stroke group with our matched non-stroke survivors. P values are corrected for multiple comparisons using Bonferroni correction.

Scale	Stroke N (%)	Non-stroke N (%)	χ^2	*p*
DAS total	17 (32.1)	3 (4.2)	17.40	**<.001**
DAS Executive apathy	15 (28.3)	3 (5.6)	9.38	**.002**
DAS Emotional subscale	9 (17.0)	0 (0)	9.56	**.002**
DAS Initiation subscale	19 (35.85)	6 (11.32)	8.55	**.003**

DAS= The Dimensional Apathy Scale (Radakovic et al., 2014). *DAS total cut-off score ≥39, DAS Executive apathy cut-off score ≥15, DAS Emotional subscale cut-off score ≥14, DAS Initiation subscale cut-off score ≥16.*

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CHAPTER 6 – Discussion

Word count: 3084

Discussion

Thesis Aims

The overall aims of this thesis were to examine the impact of apathy on functional activity after stroke and to test if the Dimensional Apathy Scale (DAS), a multidimensional measure of apathy is reliable and valid in stroke (Radakovic & Abrahams, 2014). The systematic review, or narrative synthesis, focused on the associations between apathy and functional activity. It was followed by a validation study, aiming to investigate the psychometric properties and validity of the DAS against a gold-standard one dimensional measure of apathy, (AES, Marin, Biedrzycki, Ruth, & Firinciogullari, 1991), and its associations with depression and anxiety in stroke survivors and a non-stroke comparison group

Integrating findings from different thesis elements

Given the importance of motivation and the emphasis on goal setting in stroke rehabilitation, the systematic review hypothesised that apathy has a negative impact on functional outcome after stroke (Chapter 2). Assertiveness and goal directedness are associated with patient success in stroke rehabilitation (Dobkin, 2004; Rapolienė et al., 2018) whereas lack of motivation has been highlighted as the most important roadblock in rehabilitation, with internal and external motivation affecting rehabilitation outcome in stroke populations (Rapolienė et al., 2018). Apathy is associated with negative recovery outcomes, as well as a negative impact on family life and later social reintegration and autonomy following rehabilitation (Arnould, Rochat, Azouvi, & Van Der Linden, 2013).

The articles reviewed supported the negative impact of apathy on rehabilitation outcomes, though there were a few concerns regarding study quality. It was argued that although apathy is prevalent following stroke, research on post-stroke apathy is still in its

infancy. As highlighted in the systematic review, the lack of validated screening tools is a major limitation for PSAp research. All but one of the studies included in the systematic review used assessments based on a unidimensional conceptualisation of apathy, therefore failing to assess specific apathy subtypes.

Apathy is now often considered a multidimensional construct (Le Heron, Apps, & Husain, 2017; Levy & Dubois, 2006; Marin et al., 1991; Radakovic & Abrahams, 2014) distinct from depression (Levy et al., 1998). The only study in the systematic review that used a multidimensional measure failed to make use of the potential to characterise subtypes of apathy after stroke and examine their functional impact, as it focused on the overall severity of apathy (Skidmore et al., 2015).

Based on the multi-dimensional neurocognitive model of Levy and Dubois (2006), the DAS (Radakovic & Abrahams, 2014) is a measure developed to assess three apathy subtypes: emotional, initiation, and executive apathy. This provides more detailed data than unidimensional measures and should aid formulation and treatment of difficulties. The validation of the DAS in stroke was therefore argued to be a valuable contribution to both research as well as to clinical practice.

The findings of Chapter 4 were that stroke survivors scored significantly higher on apathy in general, as measured by the DAS and AES, than did controls. Apathy scores were high, and consistent with the PSAp research described in the introduction, 43% of stroke survivors scoring above cut-off for apathy on the AES in our sample. Just under six percent of controls scored above the same cut-off.

In terms of the dimensions of apathy, stroke survivors had significantly higher scores on all dimensions compared with the controls. Initiation and Executive Apathy were particularly prevalent in the stroke sample, and these profiles are consistent with the

validation studies of Parkinson's (Radakovic et al., 2018) and Alzheimer's disease (Radakovic, Starr, & Abrahams, 2017). Self-awareness is closely linked with meta-cognition, and the Dimensional Apathy Framework notes that self-awareness subsumes all subtypes of apathy, and therefore might be relevant in diseases such as dementia (Radakovic & Abrahams, 2018).

There was a positive correlation between depression and apathy, especially between depression on the PHQ-9 and the executive and initiation subtypes on the DAS. More stroke survivors scored above cut-off on the DAS and AES, however, compared to the PHQ-9, and apathy was found to have a higher prevalence than depression in our sample. The emotional subscale on the DAS was not significantly correlated with the GAD-7, which makes sense from a theoretical perspective, as people are unlikely to report heightened levels of anxiety at the same time as reporting flattened or neutral emotional response. There was no significant relationship between the emotional subscale and depression scores on PHQ-9.

In line with previous research (Barker-Collo, 2007; Broomfield, Quinn, Abdul-Rahim, Walters, & Evans, 2014; Schöttke & Giabbiconi, 2015), stroke survivors had significantly higher scores on both depression and anxiety compared with the controls. The effects of stroke can have devastating consequences, disrupting functional independence, daily life and autonomy (Gençer & Hocaoğlu, 2019; Rapolienė et al., 2018). Anxiety affects about one in four stroke survivors and is more frequent in younger survivors (Chun et al., 2018). Phobic anxiety is particularly common, and fear of stroke recurrence is the most commonly observed stroke related fear (Chun et al., 2018).

As seen in previous chapters, depression is common after stroke (Towfighi et al., 2017), and can be understood both as an emotional response to sudden change and disability as well as structural changes or biochemical imbalances following changes in the brain after stroke (Gençer & Hocaoğlu, 2019). The emotional impact of having a stroke can be linked

with mourning and coping with the loss and acceptance of disability, especially when individuals refuse to accept their new reality (Hama et al., 2011).

Apathy seems to be associated with even less favourable rehabilitation outcomes than depression (Hama et al., 2007). Therefore, with its devastating impact on stroke rehabilitation and outcome, apathy screening should arguably become as routine as depression screening in stroke.

The empirical study showed that the initiation and executive subscales correlated positively with depression. Apathy and depression are not the same concept. People might struggle to start and finish tasks either because of low mood or apathy. We speculate that not being able to carry out goal-directed behaviours in rehabilitation will have implications for the person regardless of origin. Further research is needed to investigate the clinical implications of this relationship and to investigate if apathy and depression should be screened for in combination.

Apathy can be mistaken for disengagement in rehabilitation, and there is a risk that apathy could be confused for lack of rehabilitation goals or wish to carry out rehabilitation and patients might not receive the rehabilitation they need and deserve. Patients benefit from inpatient stroke rehabilitation, even when experiencing apathy, (Dobkin, 2004; Langhorne, Bernhardt, & Kwakkel, 2011; Santa et al., 2008). One of the symptoms of apathy is the lack of goal directedness, which makes it harder for this group to identify the needs they have in rehabilitation (Langhorne et al., 2011; Mayo et al., 2015, 2009). It must therefore be the clinician’s responsibility to identify apathy and to be open minded and flexible in terms of treatment options based on the person’s best interests and neurological formulation.

Methodological Strengths and Limitations

We highlight that PSAp is still a novel area of research, in the shadow of post-stroke depression. This was the first systematic review directly focusing on the impact of apathy on functional recovery, which we consider a strength. The systematic review highlighted the high prevalence of PSAp, the negative association with rehabilitation outcomes, as well as the need for higher quality research, using validated, multidimensional screening tools. The empirical study was the first validation of a multidimensional apathy scale in stroke. We believe that the validation of the DAS for stroke population is relevant for use in both clinical and research settings, providing a multidimensional alternative to current practices in PSAp research, often based on older models of apathy.

The recruitment of a stroke sample covering the full range of apathy symptoms was expected to be challenging, due to the very nature of apathy itself. We did not expect the least motivated patients to want to participate in this research study, and this is also a general limitation for most apathy research (e.g. Hama et al., 2011; Kennedy, Granato, & Goldfine, 2015; Matsuzaki et al., 2015). The most severely affected patients will inevitably struggle with engagement. This is likely to be a limitation in all apathy research as participants need to at least have motivation and capacity to consent to participate. Although expecting that more stroke survivors would score in the severe range of apathy, we did however see the full range of apathy amongst our respondents.

We decided to validate the self-rated version of the DAS, as it has shown to be both valid and reliable tool for neurodegenerative disorders, which would arguably face the same challenges in terms of cognitive impairments (Radakovic, 2016; Radakovic & Abrahams, 2018; Radakovic, Stephenson, et al., 2017). Especially considering the high prevalence of apathy in the other validation studies.

The DAS is also recommended as apathy assessment tool in the updated 2018 criteria for apathy (Robert et al., 2018). Now we have evidence that the DAS is reliable and valid in stroke, research should test the properties of the informant-rated DAS in stroke. The informant version could be used even for people with severe apathy or cognitive deficits as it does not require abilities across various cognitive domains, including sustained attention, executive functioning, working memory, language processing and motor skills to name a few.

An unforeseen ethical issue regarding anonymity arose in the first stages of data collection for the empirical study. It was possible to identify individual responses and to link these with email addresses provided by participants in the online questionnaire. This was especially problematic as the PHQ-9 include a suicidality related question, and participants were informed the survey was anonymous. This issue was immediately discussed with supervisors and brought to the Faculty of Health Sciences and Medicine Research Ethics Committee at University of East Anglia (see Appendix P to R). The data collection was completely halted until this issue was resolved and amendments approved by the committee, resulting in a few changes to the methodological design of the empirical paper. Although limiting the time for data collection, the amendments also shortened the questionnaire, making it easier to access and complete by participants.

Another related limitation with the empirical paper concerned the recruitment though an online survey. It was positive that we were able to reach stroke survivors to participate in the study. Sampling though social media and stroke charities was predicted to allow access to a rich community-based sample of stroke survivors. This sampling method did not however allow for limitations in terms of who was able to participate. This was especially problematic when trying to match the stroke and control group. It was also challenging at times to sustain participation rates for the stroke survivor group. Other studies using online sampling methods

in stroke have discussed the issues with volunteering bias as well as difficulties gaining access too clinical information about participants (Franzén-Dahlin & Laska, 2012; Stein et al., 2013).

As data collection was carried out online, without face to face contact, we could not clarify by asking follow-up questions regarding lesion location or additional information about self-disclosed physical, psychological or neurological illnesses. This could potentially have resulted in a few more excluded participants than necessary when evaluating if people met inclusion or exclusion criteria. It was also considered an ethical challenge to exclude individual participant responses after they had taken the time to complete the survey.

Clinical implications

Findings have clinical implications: they show the need for thorough apathy assessment given its prevalence and association with worse rehabilitation outcomes. We hope that clinicians will become more aware and that screening for both anxiety and depression will become part of everyday practice.

Future research

Based on the findings of the systematic review, there is a general need for more high-quality research on PSAp. As addressed in the empirical study, we would recommend validation of the clinician and carer versions of the DAS, as these could allow for more objective diagnosis of apathy in stroke. A valuable contribution would also be to elaborate on the understanding of neural correlates of apathy subtypes in stroke, looking further into the Dimensional Apathy Framework. We hope that future studies will use apathy measures such as the DAS instead of unidimensional measures as they provide valuable information to the clinician not only on the severity of apathy, but also the profile of apathy.

Conclusion

The systematic review and empirical paper have made a novel contribution to the field of apathy research by validating a multi-dimensional measure of apathy which could be used to detect and characterise PSAp. We also established that apathy is associated with worse functional activity after stroke.

PSAp research is still in its infancy, and more investigation is needed. Most of the research had been conducted around the world, but little research is currently conducted in the UK on this topic. Apathy was found to have devastating effects on recovery after stroke, and we argued that apathy should be routinely screened for in clinical practice given its implication for recovery. The DAS is a valid and reliable screening tool for stroke populations, and it is suitable for use in both research and clinical practice.

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Appendix

Appendix A: Instructions for authors: The Clinical Neuropsychologist

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Appendix N: After Care Sheet

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Appendix Q: FMH REC Ethical Approval Following Amendments

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Appendix T: Email to FMH REC Regarding Inclusion Criteria

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Appendix A: Instructions for authors: The Clinical Neuropsychologist

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From: CRD-REGISTER <irss505@york.ac.uk>
Date: 10. february 2020 kl. 15:53:05 CET
To: "Pernille Myhre (MED - Postgraduate Researcher)" <P.Myhre@uea.ac.uk>
Topic: PROSPERO Registration message [160049]

Dear Pernille,

Thank you for submitting details of your systematic review "How does apathy associate with functional activities after a stroke? A systematic review" to the PROSPERO register. We are pleased to confirm that the record will be published on our website within the next hour.

Your registration number is: CRD42020160049

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Yours sincerely,

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PROSPERO is funded by the National Institute for Health Research and produced by CRD, which is an academic department of the University of York.

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Appendix C: NICE Appraisal Checklist

Quality appraisal checklist – quantitative studies reporting correlations and associations

A correlates review (see section 3.3.4) attempts to establish the factors that are associated or correlated with positive or negative health behaviours or outcomes. Evidence for correlate reviews will come both from specifically designed correlation studies and other study designs that also report on correlations.

This checklist[15] has been developed for assessing the validity of studies reporting correlations. It is based on the appraisal step of the 'Graphical appraisal tool for epidemiological studies (GATE)', developed by Jackson et al. (2006).

This checklist enables a reviewer to appraise a study's internal and external validity after addressing the following key aspects of study design: characteristics of study participants; definition of independent variables; outcomes assessed and methods of analyses.

Like GATE, this checklist is intended to be used in an electronic (Excel) format that will facilitate both the sharing and storage of data, and through linkage with other documents, the compilation of research reports. Much of the guidance to support the completion of the critical appraisal form that is reproduced below also appears in 'pop-up' windows in the electronic version[16].

There are 5 sections of the revised GATE. Section 1 seeks to assess the key population criteria for determining the study's **external validity** – that is, the extent to which the findings of a study are generalisable beyond the confines of the study to the study's source population.

Sections 2 to 4 assess the key criteria for determining the study's **internal validity** – that is, making sure that the study has been carried out carefully, and that the identified associations are valid and are not due to some other (often unidentified) factor.

Checklist items are worded so that 1 of 5 responses is possible:

++	Indicates that for that particular aspect of study design, the study has been designed or conducted in such a way as to minimise the risk of bias.
+	Indicates that either the answer to the checklist question is not clear from the way the study is reported, or that the study may not have addressed all potential sources of bias for that particular aspect of study design.
−	Should be reserved for those aspects of the study design in which significant sources of bias may persist.
Not reported (NR)	Should be reserved for those aspects in which the study under review fails to report how they have (or might have) been considered.
Not applicable (NA)	Should be reserved for those study design aspects that are not applicable given the study design under review (for example, allocation concealment would not be applicable for case–control studies).

In addition, the reviewer is requested to complete in detail the comments section of the quality appraisal form so that the grade awarded for each study aspect is as transparent as possible.

Each study is then awarded an overall study quality grading for internal validity (IV) and a separate one for external validity (EV):

- ++ All or most of the checklist criteria have been fulfilled, where they have not been fulfilled the conclusions are very unlikely to alter.
- + Some of the checklist criteria have been fulfilled, where they have not been fulfilled, or not adequately described, the conclusions are unlikely to alter.
- – Few or no checklist criteria have been fulfilled and the conclusions are likely or very likely to alter.

Checklist

Study identification: Include full citation details		
Study design: • Refer to the glossary of study designs and the algorithm for classifying experimental and observational study designs to best describe the paper's underpinning study design		
Guidance topic:		
Assessed by:		
Section 1: Population		
1.1 Is the source population or source area well described? • Was the country (e.g. developed or non-developed, type of health care system), setting (primary schools, community centres etc), location (urban, rural), population demographics etc adequately described?	++ + – NR NA	Comments:
1.2 Is the eligible population or area representative of the source population or area? • Was the recruitment of individuals, clusters or areas well defined (e.g. advertisement, birth register)? • Was the eligible population representative of the source? Were important groups underrepresented?	++ + – NR NA	Comments:
1.3 Do the selected participants or areas represent the eligible population or area?	++ +	Comments:

• Was the method of selection of participants from the eligible population well described? • What % of selected individuals or clusters agreed to participate? Were there any sources of bias? • Were the inclusion or exclusion criteria explicit and appropriate?	– NR NA	
Section 2: Method of selection of exposure (or comparison) group		
2.1 Selection of exposure (and comparison) group. How was selection bias minimised? • How was selection bias minimised?	++ + – NR NA	Comments:
2.2 Was the selection of explanatory variables based on a sound theoretical basis? • How sound was the theoretical basis for selecting the explanatory variables?	++ + – NR NA	Comments:
2.3 Was the contamination acceptably low? • Did any in the comparison group receive the exposure? • If so, was it sufficient to cause important bias?	++ + – NR NA	Comments:
2.4 How well were likely confounding factors identified and controlled? • Were there likely to be other confounding factors not considered or appropriately adjusted for? • Was this sufficient to cause important bias?	++ + – NR NA	Comments:
2.5 Is the setting applicable to the UK?	++	Comments:

• Did the setting differ significantly from the UK?	+ – NR NA	
Section 3: Outcomes		
3.1 Were the outcome measures and procedures reliable? • Were outcome measures subjective or objective (e.g. biochemically validated nicotine levels ++ vs self-reported smoking −)? • How reliable were outcome measures (e.g. inter- or intra-rater reliability scores)? • Was there any indication that measures had been validated (e.g. validated against a gold standard measure or assessed for content validity)?	++ + – NR NA	Comments:
3.2 Were the outcome measurements complete? • Were all or most of the study participants who met the defined study outcome definitions likely to have been identified?	++ + – NR NA	Comments:
3.3 Were all the important outcomes assessed? • Were all the important benefits and harms assessed? • Was it possible to determine the overall balance of benefits and harms of the intervention versus comparison?	++ + – NR NA	Comments:
3.4 Was there a similar follow-up time in exposure and comparison groups? • If groups are followed for different lengths of time, then more events are likely to occur in the group followed-up for longer distorting the comparison. • Analyses can be adjusted to allow for differences in length of follow-up (e.g. using person-years).	++ + – NR NA	Comments:

3.5 Was follow-up time meaningful? • Was follow-up long enough to assess long-term benefits and harms? • Was it too long, e.g. participants lost to follow-up?	++ + – NR NA	Comments:
Section 4: Analyses		
4.1 Was the study sufficiently powered to detect an intervention effect (if one exists)? • A power of 0.8 (i.e. it is likely to see an effect of a given size if one exists, 80% of the time) is the conventionally accepted standard. • Is a power calculation presented? If not, what is the expected effect size? Is the sample size adequate?	++ + – NR NA	Comments:
4.2 Were multiple explanatory variables considered in the analyses? • Were there sufficient explanatory variables considered in the analysis?	++ + – NR NA	Comments:
4.3 Were the analytical methods appropriate? • Were important differences in follow-up time and likely confounders adjusted for?	++ + – NR NA	Comments:
4.6 Was the precision of association given or calculable? Is association meaningful? • Were confidence intervals or p values for effect estimates given or possible to calculate? • Were CIs wide or were they sufficiently precise to aid decision-making? If precision is lacking, is this because the study is under-powered?	++ + – NR NA	Comments:
Section 5: Summary		

5.1 Are the study results internally valid (i.e. unbiased)? • How well did the study minimise sources of bias (i.e. adjusting for potential confounders)? • Were there significant flaws in the study design?	++ + –	Comments:
5.2 Are the findings generalisable to the source population (i.e. externally valid)? • Are there sufficient details given about the study to determine if the findings are generalisable to the source population? • Consider: participants, interventions and comparisons, outcomes, resource and policy implications.	++ + –	Comments:

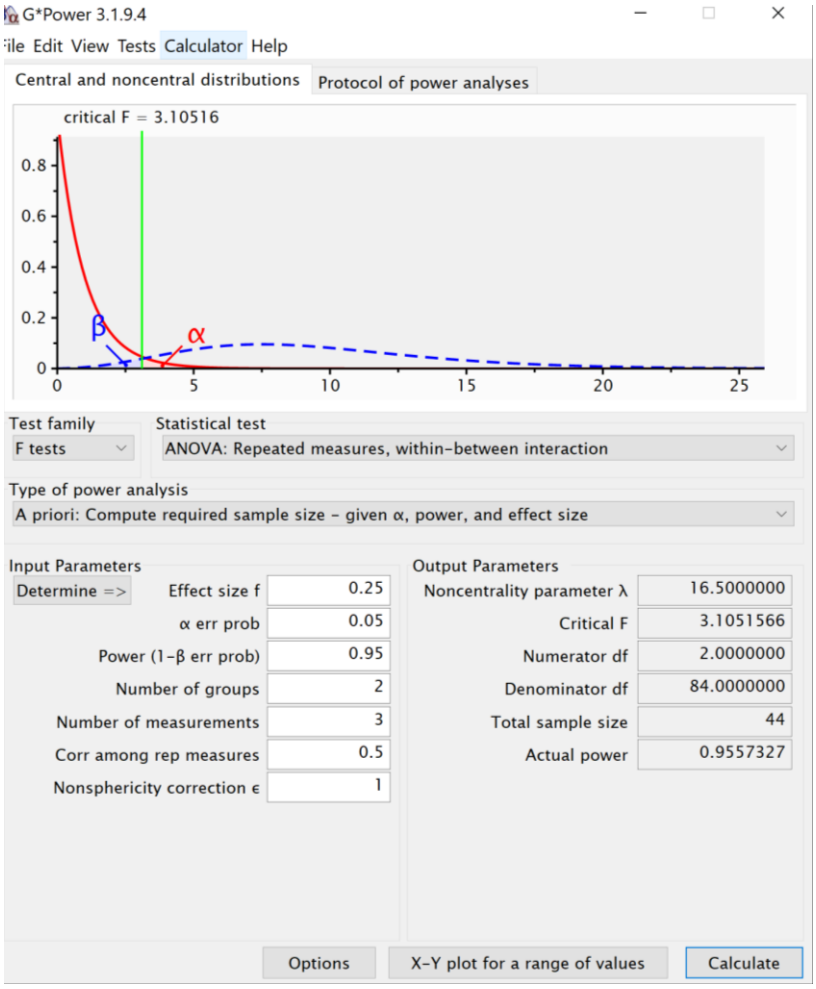
[15] Appraisal form derived from: Jackson R, Ameratunga S, Broad J et al. (2006) The GATE frame: critical appraisal with pictures. Evidence Based Medicine 11: 35–8.

[16] Available from CPHE on request.

NICE. (2012). Methods for the development of NICE public health guidance (third edition). Retrieved from https://www.nice.org.uk/process/pmg4/chapter/appendix-f-quality-appraisal-checklist-quantitative-intervention-studies

Appendix D: Power Calculation

To explore how all variables of interest is associated with each other across all conditions, G*Power 3.1.9.4 (Faul, 2007) was used to calculate required sample size for the mixed design ANOVA. Power was set to 0.95, alpha was set to 0.05. A medium effect size is considered a conventional estimate, which yielded an estimated sample size of 44 participants. Following is a screenshot of the calculation window in the programme.



Faul, F., Erdfelder, E., Lang, A.-G. & Buchner, A. (2007). *G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences.* Behavior Research Methods, 39, 175-191.

Appendix E: Instruction to Authors for Publication in Neurological Sciences

Instructions for Authors

Original papers should have a structured abstract, must not exceed 3,000 words and should not include more than 4-6 illustrations and tables. Each separate part of a figure (a, b, etc.) counts as an illustration. Up to 40 references are permitted.

Submission of a manuscript implies: that the work described has not been published before; that it is not under consideration for publication anywhere else; that its publication has been approved by all co-authors, if any, as well as by the responsible authorities – tacitly or explicitly – at the institute where the work has been carried out. The publisher will not be held legally responsible should there be any claims for compensation.

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Online Submission

Please follow the hyperlink "Submit online" on the right and upload all of your manuscript files following the instructions given on the screen.

Please ensure you provide all relevant editable source files. Failing to submit these source files might cause unnecessary delays in the review and production process.

ORCID ID

This publication requires that the corresponding author provides his/her ORCiD ID before proceeding with submission.

For more information about this journal's ORCiD policy, please visit the ORCID FAQ

Title page

Title Page

Please use this **template title page** for providing the following information.

The title page should include:

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- A concise and informative title
- The affiliation(s) of the author(s), i.e. institution, (department), city, (state), country
- A clear indication and an active e-mail address of the corresponding author
- If available, the 16-digit ORCID of the author(s)

If address information is provided with the affiliation(s) it will also be published.

For authors that are (temporarily) unaffiliated we will only capture their city and country of residence, not their e-mail address unless specifically requested.

Abstract

Please provide an abstract of 150 to 250 words. The abstract should not contain any undefined abbreviations or unspecified references.

For life science journals only (when applicable)

Trial registration number and date of registration

Trial registration number, date of registration followed by “retrospectively registered”

Keywords

Please provide 4 to 6 keywords which can be used for indexing purposes.

Declarations

All manuscripts must contain the following sections under the heading 'Declarations'.

If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

Text

Text Formatting

Manuscripts should be submitted in Word.

- Use a normal, plain font (e.g., 10-point Times Roman) for text.
- Use italics for emphasis.
- Use the automatic page numbering function to number the pages.
- Do not use field functions.
- Use tab stops or other commands for indents, not the space bar.
- Use the table function, not spreadsheets, to make tables.
- Use the equation editor or MathType for equations.
- Save your file in docx format (Word 2007 or higher) or doc format (older Word versions).

Headings

Please use no more than three levels of displayed headings.

Abbreviations

Abbreviations should be defined at first mention and used consistently thereafter.

Acknowledgments

Acknowledgments of people, grants, funds, etc. should be placed in a separate section on the title page. The names of funding organizations should be written in full.

References

Citation

Reference citations in the text should be identified by numbers in square brackets. Some examples:

1. Negotiation research spans many disciplines [3].

2. This result was later contradicted by Becker and Seligman [5].

3. This effect has been widely studied [1-3, 7].

Reference list

The list of references should only include works that are cited in the text and that have been published or accepted for publication. Personal communications and unpublished works should only be mentioned in the text. Do not use footnotes or endnotes as a substitute for a reference list.

Tables

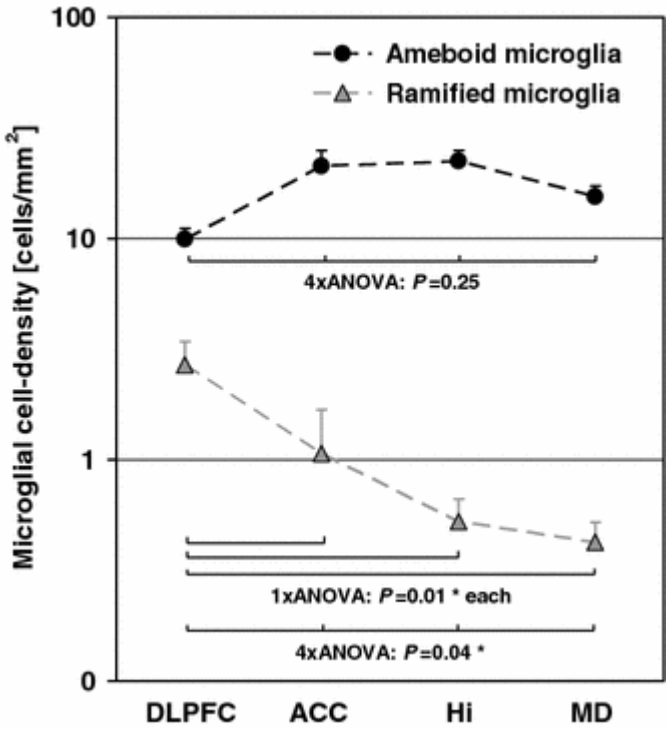
- All tables are to be numbered using Arabic numerals.
- Tables should always be cited in text in consecutive numerical order.
- For each table, please supply a table caption (title) explaining the components of the table.
- Identify any previously published material by giving the original source in the form of a reference at the end of the table caption.
- Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and included beneath the table body.

Artwork and Illustrations Guidelines

Electronic Figure Submission

- Supply all figures electronically.
- Indicate what graphics program was used to create the artwork.
- For vector graphics, the preferred format is EPS; for halftones, please use TIFF format. MSOffice files are also acceptable.
- Vector graphics containing fonts must have the fonts embedded in the files.
- Name your figure files with "Fig" and the figure number, e.g., Fig1.eps.

Line Art



- Definition: Black and white graphic with no shading.
- Do not use faint lines and/or lettering and check that all lines and lettering within the figures are legible at final size.
- All lines should be at least 0.1 mm (0.3 pt) wide.
- Scanned line drawings and line drawings in bitmap format should have a minimum resolution of 1200 dpi.
- Vector graphics containing fonts must have the fonts embedded in the files.

Figure Lettering

- To add lettering, it is best to use Helvetica or Arial (sans serif fonts).
- Keep lettering consistently sized throughout your final-sized artwork, usually about 2–3 mm (8–12 pt).
- Variance of type size within an illustration should be minimal, e.g., do not use 8-pt type on an axis and 20-pt type for the axis label.
- Avoid effects such as shading, outline letters, etc.
- Do not include titles or captions within your illustrations.

Figure Numbering

- All figures are to be numbered using Arabic numerals.
- Figures should always be cited in text in consecutive numerical order.
- Figure parts should be denoted by lowercase letters (a, b, c, etc.).
- If an appendix appears in your article and it contains one or more figures, continue the consecutive numbering of the main text. Do not number the appendix figures,"A1, A2, A3, etc." Figures in online appendices (Electronic Supplementary Material) should, however, be numbered separately.

Figure Captions

- Each figure should have a concise caption describing accurately what the figure depicts. Include the captions in the text file of the manuscript, not in the figure file.
- Figure captions begin with the term Fig. in bold type, followed by the figure number, also in bold type.
- No punctuation is to be included after the number, nor is any punctuation to be placed at the end of the caption.
- Identify all elements found in the figure in the figure caption; and use boxes, circles, etc., as coordinate points in graphs.
- Identify previously published material by giving the original source in the form of a reference citation at the end of the figure caption.

Figure Placement and Size

- Figures should be submitted separately from the text, if possible.
- When preparing your figures, size figures to fit in the column width.
- For large-sized journals the figures should be 84 mm (for double-column text areas), or 174 mm (for single-column text areas) wide and not higher than 234 mm.
- For small-sized journals, the figures should be 119 mm wide and not higher than 195 mm.

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Accessibility

In order to give people of all abilities and disabilities access to the content of your figures, please make sure that

- All figures have descriptive captions (blind users could then use a text-to-speech software or a text-to-Braille hardware)
- Patterns are used instead of or in addition to colors for conveying information (colorblind users would then be able to distinguish the visual elements)
- Any figure lettering has a contrast ratio of at least 4.5:1

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  - an erratum/correction may be placed with the article

  - an expression of concern may be placed with the article

  - or in severe cases retraction of the article may occur.

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All authors whose names appear on the submission

1) made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work;

2) drafted the work or revised it critically for important intellectual content;

3) approved the version to be published; and

4) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

* Based on/adapted from:

ICMJE, Defining the Role of Authors and Contributors,

Transparency in authors' contributions and responsibilities to promote integrity in scientific publication, McNutt at all, PNAS February 27, 2018

Disclosures and declarations

All authors are requested to include information regarding sources of funding, financial or non-financial interests, study-specific approval by the appropriate ethics committee for research involving humans and/or animals, informed consent if the research involved human participants, and a statement on welfare of animals if the research involved animals (as appropriate).

The decision whether such information should be included is not only dependent on the scope of the journal, but also the scope of the article. Work submitted for publication may have implications for public health or general welfare and in those cases it is the responsibility of all authors to include the appropriate disclosures and declarations.

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One author is assigned as Corresponding Author and acts on behalf of all co-authors and ensures that questions related to the accuracy or integrity of any part of the work are appropriately addressed.

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- managing all communication between the Journal and all co-authors, before and after publication;*
- providing transparency on re-use of material and mention any unpublished material (for example manuscripts in press) included in the manuscript in a cover letter to the Editor;
- making sure disclosures, declarations and transparency on data statements from all authors are included in the manuscript as appropriate (see above).

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Please check the Instructions for Authors of the Journal that you are submitting to for specific instructions regarding contribution statements.

In absence of specific instructions and in research fields where it is possible to describe discrete efforts, the Publisher recommends authors to include contribution statements in the work that specifies the contribution of every author in order to promote transparency. These contributions should be listed at the separate title page.

Examples of such statement(s) are shown below:

• Free text:

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [full name], [full name] and [full name]. The first draft of the manuscript was written by [full name] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Example: CRediT taxonomy:

• Conceptualization: [full name], …; Methodology: [full name], …; Formal analysis and investigation: [full name], …; Writing - original draft preparation: [full name, …]; Writing - review and editing: [full name], …; Funding acquisition: [full name], …; Resources: [full name], …; Supervision: [full name],….

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A Graduate Student's Guide to Determining Authorship Credit and Authorship Order, APA Science Student Council 2006

Affiliation

The primary affiliation for each author should be the institution where the majority of their work was done. If an author has subsequently moved, the current address may additionally be stated. Addresses will not be updated or changed after publication of the article.

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Please make sure that the names of all authors are present and correctly spelled, and that addresses and affiliations are current.

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Authors should include the following statements (if applicable) in a separate section entitled "Compliance with Ethical Standards" when submitting a paper:

- Disclosure of potential conflicts of interest
- Research involving Human Participants and/or Animals
- Informed consent

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The corresponding author should be prepared to collect documentation of compliance with ethical standards and send if requested during peer review or after publication.

The Editors reserve the right to reject manuscripts that do not comply with the above-mentioned guidelines. The author will be held responsible for false statements or failure to fulfill the above-mentioned guidelines.

Disclosure of potential conflicts of interest

Authors must disclose all relationships or interests that could influence or bias the work. Although an author may not feel there are conflicts, disclosure of relationships and interests affords a more transparent process, leading to an accurate and objective assessment of the work. Awareness of real or perceived conflicts of interests is a perspective to which the readers are entitled and is not meant to imply that a financial relationship with an organization that sponsored the research or compensation for consultancy work is inappropriate. Examples of potential conflicts of interests **that are directly or indirectly related to the research** may include but are not limited to the following:

- Research grants from funding agencies (please give the research funder and the grant number)
- Honoraria for speaking at symposia

- Financial support for attending symposia
- Financial support for educational programs
- Employment or consultation
- Support from a project sponsor
- Position on advisory board or board of directors or other type of management relationships
- Multiple affiliations
- Financial relationships, for example equity ownership or investment interest
- Intellectual property rights (e.g. patients, copyrights and royalties from such rights)
- Holdings of spouse and/or children that may have financial interest in the work

In addition, interests that go beyond financial interests and compensation (non-financial interests) that may be important to readers should be disclosed. These may include but are not limited to personal relationships or competing interests directly or indirectly tied to this research, or professional interests or personal beliefs that may influence your research.

The corresponding author collects the conflict of interest disclosure forms from all authors. In author collaborations where formal agreements for representation allow it, it is sufficient for the corresponding author to sign the disclosure form on behalf of all authors. Examples of forms can be found

here:

The corresponding author will include a summary statement **on the title page that is separate from their manuscript,** that reflects what is recorded in the potential conflict of interest disclosure form(s).

See below examples of disclosures:

Funding: This study was funded by X (grant number X).

Conflict of Interest: Author A has received research grants from Company A. Author B has received a speaker honorarium from Company X and owns stock in Company Y. Author C is a member of committee Z.

If no conflict exists, the authors should state:

Conflict of Interest: The authors declare that they have no conflict of interest.

Research involving human participants, their data or biological material

Ethics approval

When reporting a study that involved human participants, their data or biological material, authors should include a statement that confirms that the study was approved (or granted exemption) by the appropriate institutional and/or national research ethics committee (including the name of the ethics committee) and certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. If doubt exists whether the research was conducted in accordance with the 1964 Helsinki Declaration or comparable standards, the

authors must explain the reasons for their approach, and demonstrate that an independent ethics committee or institutional review board explicitly approved the doubtful aspects of the study. If a study was granted exemption from requiring ethics approval, this should also be detailed in the manuscript (including the reasons for the exemption).

Summary of requirements

The above should be summarized in a statement and included on **a title page that is separate from the manuscript** with a section entitled **"Declarations"** when submitting a paper. Having all statements in one place allows for a consistent and unified review of the information by the Editor-in-Chief and/or peer reviewers and may speed up the handling of the paper. Declarations include Funding, Conflicts of interest/competing interests, Ethics approval, Consent, Data and/or Code availability and Authors' contribution statements. **Please use the following template title page for providing the statements.**

Once and if the paper is accepted for publication, the production department will put the respective statements in a distinctly identified section clearly visible for readers.

Appendix F: Poster for Recruitment

Understanding Motivation after Stroke

We are looking for stroke survivors to take part in an internet survey about motivation, mood and abilities after stroke. Anyone who is 18 or over and has ever been admitted to hospital following a stroke is very welcome to take part.

Stroke can cause a loss of motivation, interest and concern known as apathy, thought to affect as many as a quarter of stroke survivors. Apathy can be a barrier to their stroke rehabilitation, as it can make it harder for them to find the motivation to take part in treatment. It also affects everyday life, making it harder for them to look after themselves or do everyday tasks. Despite this, apathy is not always assessed after stroke and it is unclear what is the best way to understand and assess apathy after stroke.

Our research will help decide if a particular apathy questionnaire would be a useful assessment for stroke survivors, to detect and make sense of difficulties with motivation. You can decide if you want to take part in the survey or not – the research is completely voluntary and will not affect your care. All your answers will be confidential and stored in compliance with the General Data Protection Regulation.

If you would like to take part, please follow the link. You do not need to have problems with motivation to take part. You can also email stroke.psyresearch@uea.ac.uk for more information.

If you choose to take part in the study, you can chose to be entered in to a prize draw where you could win one of five £25 Amazon Vouchers.

University of East Anglia

Members of the study team:

Pernille Myhre, Trainee Clinical Psychologist[1]

Supervisors: Dr Catherine Ford, Clinical Lecturer in Psychology [1]
Dr Ratko Radakovic, Neuropsychology researcher[1]

Research Panel: Dr Fergus Gracey, Senior Research Fellow[1]

Collaborators: Dr Andrew Bateman, Reader and Director NIHR Research Design Service [2] & Dr Sara Simblett, Postdoctoral Research Associate[3]

[1]Dept of Clinical and Applied Psychology, UEA, [2]School of Health and Social Care, University of Essex, [3]Institute of Psychiatry, Psychology and Neuroscience, London

Appendix G: Participant Information Sheet

Participant Information Sheet for Stroke Survivors

Please take time to read the following information so that you may understand why this research is being done.

What is the purpose of the study?
Apathy is a lack of motivation, where people can have problems in starting things, problems with finishing things or can be emotionally neutral to things. Demotivation in the form of apathy is quite common following a stroke and is observed in about 20 – 40% of patients. Apathy can be an obstacle to stroke rehabilitation, as it causes difficulties in finding the motivation to participate in rehabilitation and treatment after stroke. Evidence has suggested that there may be different types of apathy and there is currently no effective method for measuring these different types of apathy after stroke. This study will validate an apathy questionnaire for stroke survivors and test if it is a suitable assessment tool for identifying and profiling post-stroke apathy.

Why have I been chosen?
We will be recruiting about one hundred stroke survivors for this study. We would like to ask you to complete some questionnaires in relation to your motivation, mood and everyday activities.

Do I have to take part?
No, it is your choice whether to take part or not. If you decide to do so, please tick the box to continue. If you do not wish to participate, close this window. Please keep in mind that your participation in this study is voluntary so you may withdraw from the study at any time without explanation up until you click "submit" at the end of the questionnaire.

What do I have to do?
Participation in this study involves completing the questions in this online survey. Please read the instructions at the beginning of each questionnaire carefully before completing them. The questionnaire should take approximately 20 minutes in total to complete. Once you have completed please press "submit". There is no further participation in the study.

What are the possible disadvantages and risks of taking part?
There will be no direct benefit to you for participating in this study. Your individual results will not be revealed to you but any future publications of the findings from this research will be made available to you. The hope for this research is that it will improve knowledge about demotivational symptoms related to stroke.

What if I experience discomfort while completing the questionnaires?
While it is not anticipated that you will be uncomfortable in completing the questionnaires, you may contact:

Pernille Myhre
Email: stroke.psyresearch@uea.ac.uk

Will my taking part in this study be kept confidential?
All information collected for the duration of this study will be kept strictly confidential. None of the information you provide will be directly associated with your personal information.

What will happen to the results of the research study?
The results of this study will be published in suitable peer-reviewed scientific journals. Talks and presentations may be made at meetings and conferences. Your personal details will not be revealed in every one of these cases.

Who is organising the research?
This study is being organised by Pernille Myhre, Dr. Catherine Ford and Dr. Ratko Radakovic from the University of East Anglia (UEA).

Who has reviewed this study?
This study has been granted approval by the FMH Ethics committee at UEA.

Prize draw
If you choose to take part in the study, you may be entered in to a prize draw where you could win one of five £25 Amazon Vouchers. You enter by adding your email address on the next page, but this is completely voluntary.

Contact for Further information
If you have any further questions about the study at any time or, at a later date, the outcome of the study:

Pernille Myhre
Email: stroke.psyresearch@uea.ac.uk

Members of the study team:
Pernille Myhre, Trainee Clinical Psychologist[1]
Supervisors: Dr Catherine Ford, Clinical Lecturer in Psychology [1]
Dr Ratko Radakovic, Neuropsychology researcher[1]
Research Panel: Dr Fergus Gracey, Senior Research Fellow[1]
Collaborators: Dr Andrew Bateman, Reader and Director NIHR Research Design Service[2] &
Dr Sara Simblett, Postdoctoral Research Associate[3]

[1]Dept of Clinical and Applied Psychology, UEA, [2]School of Health and Social Care, University of Essex, [3]Institute of Psychiatry, Psychology and Neuroscience, London

Participant Information Sheet for Control group

Study title: Profiling Apathy After Stroke

Please take time to read the following information so that you may understand why this research is being done.

What is the purpose of the study?
Apathy is a lack of motivation, where people can have problems in starting things, problems with finishing things or can be emotionally neutral to things. Demotivation in the form of apathy is quite common following a stroke and is observed in about 20 – 40% of patients. Apathy can be an obstacle to stroke rehabilitation, as it causes difficulties in finding the motivation to participate in rehabilitation and treatment after stroke. Evidence has suggested that there may be different types of apathy and there is currently no effective method for measuring different types of apathy after stroke. This study will validate an apathy questionnaire for stroke survivors and test if it is a suitable assessment tool for identifying and profiling post-stroke apathy.

Why have I been chosen?
We will be recruiting about one hundred healthy participants who have not experienced a stroke.

Do I have to take part?
No, it is your choice whether to take part or not. If you decide to do so, please tick "next" to continue. If you do not wish to participate, close this window. Please keep in mind that your participation in this study is voluntary so you may withdraw from the study at any time without explanation up until you click submit.

What do I have to do?
Participation in this study involves completing the questions in this online survey. Please read the instructions at the beginning of each questionnaire carefully before completing them. The questionnaire should take up to 15 minutes in total to complete. Once you have completed please press "submit". There is no further participation in the study.

What are the possible disadvantages and risks of taking part?
There will be no direct benefit to you in taking part. Your individual results will not be revealed to you but any future publications of the findings from this research will be made available to you. The hope for this research is that it will improve knowledge about demotivational symptoms related with stroke.

What if I experience discomfort while completing the questionnaires?
While it is not anticipated that you will be uncomfortable in completing the questionnaires, you may contact:

Pernille Myhre
Email: stroke.psyresearch@uea.ac.uk

Will my taking part in this study be kept confidential?
All information collected for the duration of this study will be kept strictly confidential. You

will be given an identification code to keep your details anonymous throughout the study and any future publications.

What will happen to the results of the research study?
The results of this study will be published in suitable peer-reviewed scientific journals. Talks and presentations may be made at meetings and conferences. Your personal details will not be revealed in any one of these cases.

Who is organising the research?
This study is being organised by Pernille Myhre, Dr. Catherine Ford and Dr. Ratko Radakovic from the University of East Anglia (UEA).

Who has reviewed this study?
This study has been granted approval by the FMH Ethics committee at UEA

Prize draw
If you choose to take part in the study, you may be entered into a prize draw where you could win one of five £25 Amazon Vouchers. You enter by adding your email address on the next page, but this is completely voluntary.

Contact for Further information
If you have any further questions about the study at any time or, at a later date, the outcome of the study:

Pernille Myhre
Email: stroke.psyresearch@uea.ac.uk

Members of the study team:
Pernille Myhre, Trainee Clinical Psychologist[1]
Supervisors: Dr Catherine Ford, Clinical Lecturer in Psychology [1]
Dr Ratko Radakovic, Neuropsychology researcher[1]
Research Panel: Dr Fergus Gracey, Senior Research Fellow[1]
Collaborators: Dr Andrew Bateman, Reader and Director NIHR Research Design Service [2] & Dr Sara Simblett, Postdoctoral Research Associate[3]

[1]Dept of Clinical and Applied Psychology, UEA, [2]School of Health and Social Care, University of Essex, [3]Institute of Psychiatry, Psychology and Neuroscience, London

Please tick if you agree with the following statements: * *Required*

Please don't select more than 1 answer(s) per row.

Please select at least 5 answer(s).

	I agree
I confirm that I have read the above information about this study,	☐
I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, by closing the browser window.	☐
I understand that the information collected about me will be used to support other research in the future and may be shared anonymously with other researchers	☐
I understand that my responses will not be identifiable once I have submitted the form, and that I will not be contacted based on the information I provide in this form	☐
By ticking this box, I agree to take part in the above study	☐

Appendix H: Demographic Information

1. What is your gender? – Male/Female/Other
2. What is your age?
3. Have you ever been admitted to hospital following a stroke? Yes/No
4. If known, what type of stroke did you get hospitalised for?
5. What was your age when first admitted to hospital following a stroke?
6. Have you experienced multiple strokes? If you selected Yes, please write number of times:
7. What is your marital status? – Single, never married/ Married or domestic partnership/ Widowed/ Divorced/ Separated
8. What is the highest degree or level of school you have completed?
9. At what age did you start school?
10. At what age did you leave school?
11. What is your current employment status? – Employed full time/ Employed part time/ Unemployed and currently looking for work/ Unemployed and not currently looking for work/ Student/ Retired/ Homemaker/ Self-employed/ Unable to work
12. Do you have any physical illness?
13. Do you have any mental health conditions or alcohol/substance related disorders?
14. Have you ever had any other neurological issues (including severe diabetes, epilepsy, traumatic brain injury, and subarachnoid haemorrhage)?

Appendix I: Dimensional Apathy Scale (DAS) – Self-Rated Version

DAS **Dimensional Apathy Scale (Self)** PN:

Age..... Sex..... Marital Status.....

Years of Education.....

Choose the answer on how you have **felt, behaved or thought**, based on the rate of occurrence in the last month: (Circle the statement that applies)

1. I need a bit of encouragement to get things started
   - ◊ Almost always
   - ◊ Often
   - ◊ Occasionally
   - ◊ Hardly Ever

2. I contact my friends
   - ◊ Almost always
   - ◊ Often
   - ◊ Occasionally
   - ◊ Hardly Ever

3. I express my emotions
   - ◊ Almost always
   - ◊ Often
   - ◊ Occasionally
   - ◊ Hardly Ever

4. I think of new things to do during the day
   - ◊ Almost always
   - ◊ Often
   - ◊ Occasionally
   - ◊ Hardly Ever

5. I am concerned about how my family feel
   - ◊ Almost always
   - ◊ Often
   - ◊ Occasionally
   - ◊ Hardly Ever

6. I find myself staring in to space
   - ◊ Almost always
   - ◊ Often
   - ◊ Occasionally
   - ◊ Hardly Ever

7. Before I do something I think about how others would feel about it
   - ◊ Almost always
   - ◊ Often
   - ◊ Occasionally
   - ◊ Hardly Ever

8. I plan my days activities in advance
   - ◊ Almost always
   - ◊ Often
   - ◊ Occasionally
   - ◊ Hardly Ever

9. When I receive bad news I feel bad about it
   - ◊ Almost always
   - ◊ Often
   - ◊ Occasionally
   - ◊ Hardly Ever

10. I am able to focus on a task until it is finished
    - ◊ Almost always
    - ◊ Often
    - ◊ Occasionally
    - ◊ Hardly Ever

11. I lack motivation
    - ◊ Almost always
    - ◊ Often
    - ◊ Occasionally
    - ◊ Hardly Ever

12. I struggle to empathise with other people
    - ◊ Almost always
    - ◊ Often
    - ◊ Occasionally
    - ◊ Hardly Ever

DAS **Dimensional Apathy Scale (Self)** PN:

13. I set goals for myself
    - ◊ Almost always
    - ◊ Often
    - ◊ Occasionally
    - ◊ Hardly Ever

14. I try new things
    - ◊ Almost always
    - ◊ Often
    - ◊ Occasionally
    - ◊ Hardly Ever

15. I am unconcerned about how others feel about my behaviour
    - ◊ Almost always
    - ◊ Often
    - ◊ Occasionally
    - ◊ Hardly Ever

16. I act on things I have thought about during the day
    - ◊ Almost always
    - ◊ Often
    - ◊ Occasionally
    - ◊ Hardly Ever

17. When doing a demanding task, I have difficulty working out what I have to do
    - ◊ Almost always
    - ◊ Often
    - ◊ Occasionally
    - ◊ Hardly Ever

18. I keep myself busy
    - ◊ Almost always
    - ◊ Often
    - ◊ Occasionally
    - ◊ Hardly Ever

19. I get easily confused when doing several things at once
    - ◊ Almost always
    - ◊ Often
    - ◊ Occasionally
    - ◊ Hardly Ever

20. I become emotional easily when watching something happy or sad on TV
    - ◊ Almost always
    - ◊ Often
    - ◊ Occasionally
    - ◊ Hardly Ever

21. I find it difficult to keep my mind on things
    - ◊ Almost always
    - ◊ Often
    - ◊ Occasionally
    - ◊ Hardly Ever

22. I am spontaneous
    - ◊ Almost always
    - ◊ Often
    - ◊ Occasionally
    - ◊ Hardly Ever

23. I am easily distracted
    - ◊ Almost always
    - ◊ Often
    - ◊ Occasionally
    - ◊ Hardly Ever

24. I feel indifferent to what is going on around me
    - ◊ Almost always
    - ◊ Often
    - ◊ Occasionally
    - ◊ Hardly Ever

DAS (DIMENSIONAL APATHY SCALE)

Scoring Instructions

Using the scoring instructions below, sum the total scores for each subscale.

Scoring Instructions

Positive Item Scoring +		Negative Item Scoring	
◊ Almost always	**0**	◊ Almost always	**3**
◊ Often	**1**	◊ Often	**2**
◊ Occasionally	**2**	◊ Occasionally	**1**
◊ Hardly Ever	**3**	◊ Hardly Ever	**0**

Scoring Sheet

Executive Subscale

Item	Score
1	
6	
10+	
11	
17	
19	
21	
23	

Total:

Emotional Subscale

Item	Score
3+	
5+	
7+	
9+	
12	
15	
20+	
24	

Total:

Behaviour/Cognitive Initiation Subscale

Item	Score
2+	
4+	
8+	
13+	
14+	
16+	
18+	
22+	

Total:

Appendix J: Apathy Evaluation Scale – Self (AES-S)

PN:____

Apathy Evaluation Scale (Self)

Date: ___/___/___

For each statement, circle the answer that best describes your thoughts, feelings, and activity in the past 4 weeks.

1. I am interested in things.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

2. I get things done during the day.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

3. Getting things started on my own is important to me.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

4. I am interested in having new experiences.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

5. I am interested in learning new things.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

6. I put little effort into anything.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

7. I approach life with intensity.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

8. Seeing a job through to the end is important to me.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

9. I spend time doing things that interest me.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

P.T.O.

PN:____

10. Someone has to tell me what to do each day.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

11. I am less concerned about my problems than I should be.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

12. I have friends.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

13. Getting together with friends is important to me.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

14. When something good happens, I get excited.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

15. I have an accurate understanding of my problems.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

16. Getting things done during the day is important to me.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

17. I have initiative.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

18. I have motivation.

NOT AT ALL SLIGHTLY SOMEWHAT A LOT

The Apathy Evaluation Scale was developed by Robert S. Marin, M.D. Development and validation studies are described in RS Marin, RC Biedrzycki, S Firinciogullari: "Reliability and Validity of the Apathy Evaluation Scale," *Psychiatry Research*, 38:143-162, 1991.

Appendix K: Patient Health Questionnaire (PHQ-9)

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

Appendix L: Generalised Anxiety Disorder Questionnaire (GAD-7)

Generalized Anxiety Disorder 7-item (GAD-7) scale

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all sure	Several days	Over half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
Add the score for each column	+	+	+	
Total Score *(add your column scores)* =				

If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all _____
Somewhat difficult _____
Very difficult _____
Extremely difficult _____

Source: Spitzer RL, Kroenke K, Williams JBW, Lowe B. A brief measure for assessing generalized anxiety disorder. *Arch Inern Med.* 2006;166:1092-1097.

Appendix M: Consent Form

CONSENT FORM

Title of Project: Profiling Apathy after Stroke

Name of Researcher: Pernille Myhre, Catherine Ford and Ratko Radakovic

Please tick if you agree with the following statements:

- ☐ I confirm that I have read the above information about this study,
- ☐ I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, by closing the browser window.
- ☐ I understand that the information collected about me will be used to support other research in the future and may be shared anonymously with other researchers.
- ☐ I understand that my responses will not be identifiable once I have submitted the form, and that I will not be contacted based on the information I provide in this form.
- ☐ By ticking this box, I agree to take part in the above study

If you choose to take part in the study, you may be entered into a prize drawer where you could win one of five £25 Amazon Vouchers. If you would like to enter the price draw, please enter your email address: _____

Appendix N: After Care Sheet

Thank you for your participation in this research!

The aim of the current study is to investigate the validity of a relatively new questionnaire, the Dimensional Apathy scale (Radakovic & Abrahams, 2014), to see if it can be used to assess apathy in stroke survivors.

The results of this study will not include your name or any identifiable characteristics.

If you have any questions related to the study, please contact the research team via the email address below. You might request a summary of the research findings of this project. If you would like a summary, please contact us via the email address below.

(email address)

If you need to talk to someone about any distress that might have resulted from participating in this study, please follow the guidelines in the After-Care Information sheet, such as talking to your GP.

You can also call one of the following helplines:

- The Stroke Association Helpline on **0303 3033 100** or email **helpline@stroke.org.uk**. This is
- Silver Helpline on **0800 4 70 80 90.** This is a free and confidential helpline "providing friendship, information and advice for older people, open every day for 24 hours

Appendix O: Thesis Budget Form

THESIS FUNDING REQUEST FORM

Trainee: Pernille Spillum Myhre

Title of Project: Profiling Apathy After Stroke

Item description	Unit cost (£)	Quantity	Overall Cost
Amazon voucher	£25	10	£250
Integral INFD16GCRYPTO197 Crypto 16 GB AES 256-bit Encrypted USB Flash Drive, FIPS 197 Certified From Amazon	£28.30	1	£28.30
		TOTAL:	£278.30

Joint budget?: No If yes, name of collaborator:

Trainee signature: **Date:** 09/07/2018

I confirm that I have been consulted on this trainee's budget and support the claim for the proposed costings.

Signed: Catherine Ford. **Date:** 09/07/2018
(Primary Supervisor)

Office use only

Approved? YES / NO Amount approved (if different to above):

If no, please detail:

Signed: ……. **Date:** …../…../…..
(Academic Director)

Appendix P: FMH REC approval of Thesis Proposal with Amendments

Faculty of Medicine and Health Sciences Research Ethics Committee

University of East Anglia

Pernille Myhre
MED

Research & Innovation Services
Floor 1, The Registry
University of East Anglia
Norwich Research Park
Norwich, NR4 7TJ

Email: fmh.ethics@uea.ac.uk

Web: www.uea.ac.uk/researchandenterprise

08 December 2018

Dear Pernille

Title: Profiling Apathy After Stroke.

Reference: 201819 - 026

The submission of your research proposal was discussed at the Faculty Research Ethics Committee meeting on Thursday 29 November.

The Committee were happy to approve your application in principle but have the following concerns which they would like you to address and amend accordingly:

- On the PIS for stroke survivors the title refers to them as patients, please substitute participants.
- There are variations in word order throughout of carers/family/close friends… carers/relatives/friends… partners/relatives/friends/carers… partner/relative/friend/patient… - it is important to be consistent.
- An explanation as to exactly what apathy is on the PIS would be helpful for participants.
- More detail about the study team on recruitment posters and participant information sheets would also be helpful for participants.
- As a general point, please remember that your application needs to be readable by the lay-person so any jargon should be avoided.

Please write to me once you have resolved/clarified the above issues. I require documentation confirming that you have complied with the Committee's requirements. The Committee have requested that you detail the changes below the relevant point on the text in this letter and also include your amendments as a tracked change within your application/proposal. The revisions to your application can be considered by Chair's action rather than go to a committee meeting, which means that the above documentation can be resubmitted at any time. Please could you send your revisions to me as an attachment in an email as this will speed up the decision making process.

As your project does not have ethics approval until the above issues have been resolved, I want to remind you that you should not be undertaking your research project until you have ethical approval by the Faculty Research Ethics Committee. Planning on the project or literature based elements can still take place but not the research involving the above ethical issues. This is to ensure that you and your research are insured by the University and that your research is undertaken within the University's 'Guidelines on Good Practice in Research' approved by Senate in July 2015.

Yours sincerely

Professor M J Wilkinson
Chair, FMH Research Ethics Committee

Appendix Q: FMH REC Ethical Approval Following Amendments

Faculty of Medicine and Health Sciences Research Ethics Committee

University of East Anglia

Pernille Myhre
MED

Research & Innovation Services
Floor 1, The Registry
University of East Anglia
Norwich Research Park
Norwich, NR4 7TJ

Email: fmh.ethics@uea.ac.uk

Web: www.uea.ac.uk/researchandenterprise

14 January 2019

Dear Pernille

Title: Profiling Apathy After Stroke.

Reference: 201819 - 026

Your submission (above) was considered by the Faculty Research Ethics Committee at their meeting on 29 November 2018, and following subsequent review of some minor amendments, I confirm that your proposal has been approved.

Please could you ensure that any further amendments to either the protocol or documents submitted are notified to us in advance and also that any adverse events which occur during your project are reported to the Committee. Please could you also arrange to send us a report once your project is completed.

Approval by the FMH Research Committee should not be taken as evidence that your study is compliant with GDPR and the Data Protection Act 2018. If you need guidance on how to make your study GDPR compliant, please contact your institution's Data Protection Officer.

Yours sincerely

Professor M J Wilkinson
Chair, FMH Research Ethics Committee

Appendix R: Email to FMH REC Regarding Ethical Issue

Dear Chair of FMH Ethics Board,

I am writing to you regarding FMH REC approval for thesis project 'Profiling Apathy after Stroke' (FMH REC ref 201819 – 026),

This study is based on an online survey for stroke survivors and their carers. The survey uses measures of apathy (the Dimensional Apathy Scale, DAS and the Apathy Evaluation Scale, AES), mood (the PHQ9 measure of depression and the GAD7 measure of anxiety) and executive functions (the Dysexecutive Syndrome scale, DEX) to provide an initial validation of the DAS in stroke, to aid detection and characterization of post-stroke apathy syndromes.

The measure of executive functions (the DEX) is copyrighted, but we did not anticipate this being problematic, as we received permission from the company involved to include it in the online survey, provided survey access were controlled via individual access codes obtained by emailing the study email address. Initially this appeared a good way to incorporate the DEX questionnaire, which also allowed us to link data from stroke participants and family carers to provide a paired control group and informant ratings of motivation/apathy.

Since starting the study however, we – Dr Catherine Ford (primary supervisor), Dr Ratko Radakovic (Secondary supervisor) and Pernille Myhre (trainee) – have become aware of difficulties with the use of access codes and have therefore halted recruitment, as there are currently issues with the following:

1) The need for access codes raises difficulties preserving participant anonymity, as people may provide personal details in emails when requesting a code (e.g. name and stroke survivor status) and we have found that the online survey software records the code provided, so responses could potentially be linked back to emails.

2) The PHQ9 measure of depression includes a question about suicidal thoughts and if participants are not fully anonymous, this raises questions about how to respond should a participant disclose suicidality.

3) Recruitment has been very slow (N = 8) and it has been suggested this may reflect the requirement to email for an access code, as opposed to simply following a link online.

We have halted study recruitment while seeking your advice and guidance on these issues. We have made some amendments to the study design to accommodate these issues, hoping this will ease recruitment as well as overcoming these ethical issues.

As you can see in the tracked changes, we have removed elements of the study affecting anonymity, namely, the DEX measure and collection of paired data from stroke and stroke carer participants. We have included a control group of people that have not experienced a stroke as comparison. This would enable the link to the survey to be published online without need for access codes. Inclusion of the DEX is not critical to the primary aim of validating the Dimensional Apathy Scale and we could recruit an independent healthy controls group instead of a paired family carer group.

Hoping in anticipation that this change will be accepted by the chair.

Kind regards,

Pernille Myhre
Trainee Clinical Psychologist

Appendix S: FMH REC Ethical Approval of Amendment

Faculty of Medicine and Health Sciences Research Ethics Committee

University of East Anglia

Pernille Myhre
MED

Research & Innovation Services
Floor 1, The Registry
University of East Anglia
Norwich Research Park
Norwich, NR4 7TJ

Email: fmh.ethics@uea.ac.uk

Web: www.uea.ac.uk/researchandenterprise

23 July 2019

Dear Pernille

Title: Profiling Apathy After Stroke

Reference: 201819 - 026

Thank you for your e-mail of 23 July notifying us of the amendments you would like to make to your above proposal.

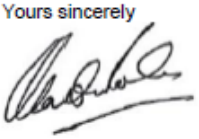
Your research group have reacted in a positive and responsible way to an unexpected but clearly important ethical challenge. I agree that we could no longer be supportive of the original plan now that we know that anonymity could be threatened so easily and with such major implications. The amendments suggested seem to comply with the original aims and intentions and appear also to eliminate the newfound problems. On this basis I am happy to approve your amendments.

Please can you ensure that any further amendments to either the protocol or documents submitted are notified to us in advance, and also that any adverse events which occur during your project are reported to the Committee.

Approval by the FMH Research Committee should not be taken as evidence that your study is compliant with GDPR and the Data Protection Act 2018. If you need guidance on how to make your study GDPR compliant, please contact your institution's Data Protection Officer.

Please can you also arrange to send us a report once your project is completed.

Yours sincerely



Prof Alastair Forbes
Chair, FMH Research Ethics Committee

Appendix T: Email to FMH REC Regarding Inclusion Criteria

From: Pernille Myhre (MED - Postgraduate Researcher) <P.Myhre@uea.ac.uk>
Sent: 15 November 2019 16:52
To: FMH Ethics <fmh.ethics@uea.ac.uk>
Cc: Catherine Ford (MED - Staff) <Catherine.Ford@uea.ac.uk>; Ratko Radakovic (HSC - Staff) <R.Radakovic@uea.ac.uk>
Subject: Study: Profiling Apathy After Stroke 201819 - 026

Dear FMH REC Committee,

Study: Profiling Apathy After Stroke 201819 - 026

We are delighted to inform you that we were able to recruit 62 stroke survivors and 80 controls to this study and have closed data collection.

It has come to our attention, however, that a number of participants responded to our online survey despite meeting our exclusion criteria ("patients who have a major co-morbid medical, neurological or psychiatric history, including severe diabetes, epilepsy, traumatic brain injury, alcohol/substance related disorders, and subarachnoid haemorrhage).

I have discussed this with my primary and secondary research supervisors at UEA (Dr Catherine Ford and Dr Ratko Radakovic) and have consulted the literature on multimorbidity in the context of stroke. Many of the medical and psychiatric conditions that have been listed by participants are known risk factors for stroke or potential consequences of strokes, therefore it does not seem ethical to exclude their data. We would instead prefer to include all participants' data as far as possible, except when a major, stroke-unrelated, neurological condition has been disclosed.

This would entail the following change to our exclusion criteria: no major, medical, neurological or psychiatric co-morbidities unrelated to stroke (e.g. neither a potential risk factor or consequence of stroke).

Please see amendment on **page 37** of the protocol (attached).

I would be grateful if you could advise on whether you would consider taking Chair's action to approve this change to the protocol.

Kind regards,

Pernille Spillum Myhre

Trainee Clinical Psychologist
Department of Clinical Psychology
Norwich Medical School
University of East Anglia

Appendix U: FMH REC Ethical Approval of Change to Inclusion Criteria

Faculty of Medicine and Health Sciences Research Ethics Committee

University of East Anglia

Pernille Myhre
MED

NORWICH MEDICAL SCHOOL
Bob Champion Research & Educational Building
James Watson Road
University of East Anglia
Norwich Research Park
Norwich NR4 7UQ

Email: fmh.ethics@uea.ac.uk
www.med.uea.ac.uk

5th December 2019

Dear Pernille

Project title: Profiling apathy after stroke

Reference: 2018/19-026

Thank you for your email of 15th November 2019 notifying us of the amendment you would like to make to your above proposal. This has been considered and I can confirm that your amendment has been approved.

Please can you ensure that any further amendments to either the protocol or documents submitted are notified to us in advance, and that any adverse events which occur during your project are reported to the Committee.

Approval by the FMH Research Committee should not be taken as evidence that your study is compliant with GDPR and the Data Protection Act 2018. If you need guidance on how to make your study GDPR compliant, please contact your institution's Data Protection Officer.

Please can you arrange to send us a report once your project is completed.

Yours sincerely

Prof Alastair Forbes
Chair
FMH Research Ethics Committee