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DOI
10.1080/13825585.2021.1967276

Publication date
2023

Document Version
Final published version

Published in
Aging, Neuropsychology, and Cognition

AGING, NEUROPSYCHOLOGY, AND COGNITION
2023, VOL. 30, NO. 1, 94–105
https://doi.org/10.1080/13825585.2021.1967276

Routledge
Taylor & Francis Group

The course of post-stroke apathy in relation to cognitive functioning: a prospective longitudinal cohort study

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ABSTRACT

Apathy is common after stroke and has been associated with cognitive impairment. However, causality between post-stroke apathy and cognitive impairment remains unclear. We assessed the course of apathy in relation to changes in cognitive functioning in stroke survivors. Using the Apathy Scale (AS) and cognitive tests on memory, processing speed and executive functioning at six- and 15 months post-stroke we tested for associations between (1) AS-scores and (change in) cognitive scores; (2) apathy course (persistent/incident/resolved) and cognitive change scores. Of 117 included participants, 29% had persistent apathy, 13% apathy resolving over time and 10% apathy emerging between 6-15 months post-stroke. Higher AS-scores were cross-sectionally and longitudinally associated with lower cognitive scores. Relations between apathy and cognitive change scores were ambiguous. These inconsistent relations between apathy and changes in cognition over time suggest that post-stroke apathy does not directly impact cognitive performance. Both these sequelae of stroke require separate attention.

ARTICLE HISTORY
Received 14 November 2020
Accepted 8 August 2021

KEYWORDS
Stroke; post-stroke apathy; cognitive impairment; cognition; longitudinal; cross-sectional; apathy scale

Main text introduction

Apathy is a frequently occurring symptom after stroke affecting around 30% of stroke patients(Van Dalen et al., 2013) and has been associated with cognitive impairments (Bickerton et al., 2015; Brodaty et al., 2013; Caeiro et al., 2013; Douven et al., 2018, 2016; Hackett et al., 2014; Kennedy et al., 2015) and poor functional and rehabilitation outcome. (Harris et al., 2014; Kennedy et al., 2015; Matsuzaki et al., 2015; Skidmore et al., 2015; Van Dalen et al., 2013) Apathy is characterized by loss of motivation, interest and emotional responses, resulting in reduced initiative, interaction with the environment and social contacts.(Ishii et al., 2009) One possible mechanism contributing to apathy is damage to

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the frontal subcortical circuit, of which the anterior cingulate is associated with goal directed behavior.(Levy & Dubois, 2006; Tekin & Cummings, 2002) Although apathy can occur in the context of depression, it often occurs independently.(Caeiro et al., 2013; Ishii et al., 2009; Levy et al., 1998; Van Dalen et al., 2013) However, apathy is not commonly evaluated as a stand-alone construct. Distinguishing apathy from depression is important. Firstly, apathy and depression may be differentially associated with cognitive impairment and poor functional outcome;(Kuzis et al., 1999; Levy et al., 1998) secondly, apathy requires different treatment than depression.(Starkstein & Leentjens, 2008)

Previous studies mainly focused on the prevalence of apathy directly after stroke occurrence, with relatively little attention for the course of apathy during follow-up. In the acute phase (defined as within 30 days post-stroke), apathy was reported to decrease steadily with one in seven patients showing resolution of symptoms.(Kennedy et al., 2015) However, longitudinal studies demonstrate that overall prevalence of apathy remains relatively stable during the first year after stroke(Mayo et al., 2009) suggesting that new cases of apathy might occur. Other studies showed that apathy prevalence increases 1 year after stroke, with persistent apathy ranging between 22% and 40%.(Caeiro et al., 2013; Harris et al., 2014)

Post-stroke apathy has consistently been associated with higher rates of cognitive impairment, but the evolution of this association over time is not well defined. Most studies used a cross-sectional design and focused on global cognitive functioning. Studies that investigate the relationship between apathy and specific cognitive domains differ widely in design (diagnostic instruments, patient and stroke characteristics, time of measurement, etc.), resulting in heterogeneous results(Van Dalen et al., 2013). In one of the few prospective studies, levels of apathy increased over time in patients with relatively poor cognitive function at baseline.(Douven et al., 2016) The increase of apathy level in this study was most pronounced in patients with baseline impaired executive functioning and impaired information processing speed.(Douven et al., 2016) Most prospective studies have focused on cognition as predictor for apathy.(Douven et al., 2018) Inversely; apathy may directly impact cognitive performance by reducing goal-directed thought, effort and interest. If cognitive functioning improves when apathy symptoms wane in recovering stroke patients, this could suggest that treatment of apathy does not only alleviate the pervasive symptoms of the syndrome itself but also helps to improve cognitive functioning.

The present study aimed to provide more insight in the course of post-stroke apathy in the recovery phase, its interaction with depression and the associations with cognitive functioning over time. First, we explored the incidence and course of post-stroke apathy. Second, we hypothesized that apathy symptoms are cross-sectionally associated with cognitive functioning at both six- and 15-months post-stroke. Third, we hypothesized that baseline apathy symptoms are longitudinally associated with poorer cognitive functioning at 15 months post-stroke. Fourth, we hypothesized that baseline apathy can predict changes in cognitive functioning between six- and 15-months post-stroke. Last, we hypothesized that a change in apathy symptoms is associated with a change in cognitive functioning, indicating that there is not only an association between post-stroke apathy and cognitive functioning, but a direct influence of post-stroke apathy on cognitive functioning

Materials and methods

This study was part of the AENEAS-project (Apathy as New Outcome After Stroke). AENEAS is a prospective observational cohort study embedded as a substudy in the Preventive Antibiotics in Stroke Study (PASS).(Nederkoorn et al., 2011; Westendorp et al., 2015) In short, PASS was a large randomized controlled trial comparing preventive antibiotics in the acute phase after stroke to standard care. Patients from 30 Dutch sites were recruited for this study. The primary outcome was the modified Rankin Score (mRS) after 3 months. The overall trial results were neutral. Therefore, in the AENEAS study we analyzed grouped data of intervention and control groups.

Participants

Patients were recruited in PASS between August 2011 and August 2015. PASS inclusion criteria were age >18 years, surviving a stroke, a National Institute of Health Stroke Scale (NIHSS) score ≥1, onset of stroke symptoms <24 hours before inclusion and hospitalization. Between January 2012 and March 2014, we invited consecutive PASS patients from 12 sites with an mRS score ≤3 at 3 months post-stroke to participate in the prospective observational AENEAS study. We chose this mRS cutoff, because in patients with a higher mRS score, disability that limits mobility may preclude reliable assessment of apathy symptoms. Exclusion criteria were severe aphasia, self-reported history of major depression and dementia prior to stroke. Written informed consent was obtained from all patients. The local institutional review board approved the study.

Procedures

At the three months telephone follow-up of the PASS, patients were asked to participate in the AENEAS study. If they were interested, additional study information was sent by mail, and a researcher contacted the patient 2 weeks after. If a patient was willing to participate, visits took place in their home environment or at the research center if preferred. Baseline assessments were administered 6 months after the stroke occurred. The assessment took approximately 1–1,5 hours to complete. Follow-up assessment using the same instruments were conducted 15 months after the stroke occurred.

Assessment instruments

The NIHSS was used to asses stroke severity at the three months visit. The Academic Medical Center Linear Disability Score (ALDS)(Holman et al., 2005) was used to measure functioning. This is a generic, linear disability scale based on the Item Response Theory. Scores range from 10 to 90, with 90 being fully independent in ADL and 10 being fully dependent. Although developed for adaptive testing, it was used with 35 questions spreading the full domain from independence to severe disability. These questions can be answered with “yes,” “with effort,” “no” or “I don’t know.”

Apathy severity was assessed using the Apathy Scale (AS),(Starkstein et al., 1992) which we used as primary outcome instrument to assess apathy. The AS is a self-rated questionnaire consisting of 14 questions about motivation, energy level, interest and emotion

of the patient. Each question has four possible answers: "not at all," "slightly," "some" or "a lot." Scores range from zero to 42, with a cutoff score of >13 indicating the presence of apathy. The AS has a Cronbach' α of .76, an interrater reliability of .81 (df = 10, P < .01) and a test-retest reliability of .90 (df = 10, P < .01). (Starkstein et al., 1992)

The presence and severity of depression were assessed using the 15-item Geriatric Depression Scale (GDS). This is a screening instrument, in which items can be answered with "yes" or "no." The maximum obtainable score is 15; a cutoff of >5 is considered indicative of depression.

The Mini-Mental State Examination (MMSE)(Folstein et al., 1975) was used to assess global cognitive functioning. Furthermore, we administered specific neuropsychological tests covering three major cognitive domains: verbal memory, measured with the immediate and delayed recall of the Dutch version of Rey's Auditory Verbal Learning test (AVLT), information processing speed, measured with the Trial-Making Test (TMT) part A and the Letter Digit Substitution Test (LDST), and executive functioning, measured with TMT part B.

Statistical analyses

We operationalized apathy as a score above the cutoff on the AS and evaluated the prevalence of apathy six- and 15-months post-stroke. We compared patients with and without apathy at six months after stroke for age, GDS and ALDS score and all cognitive test scores using t-tests and we tested whether apathy occurrence is associated with gender with a Chi square test. We also tested whether a score >5 on the GDS occurs more often among patients with apathy six months post-stroke using a Chi-square test.

To explore the incidence and course of apathy, we determined who had apathy at both time points (persistent apathy), which patients developed apathy between 6- and 15-months (incident apathy), in whom apathy was present at 6 months but not at 15 months (resolved apathy), and who had no apathy at both time points (no apathy).

We tested for cross-sectional associations between apathy symptoms with cognition at six- and 15-months post-stroke. For this, we used linear regression models with the continuous AS scores as predictor and the continuous cognitive test scores at both time points as dependent variables. We also studied associations between 6 months post-stroke apathy symptoms with the scores on cognitive tests assessed at 15 months post-stroke.

To investigate to what extent apathy at 6 months post-stroke is associated with differences over time in cognitive functioning, we calculated the difference in scores for the cognitive tests by subtracting the raw score at the 6 months assessment from the score at the 15 months assessment. We then used these change scores as dependent variables in linear regression models with the 6-month apathy score as predictor. We repeated this analysis with the raw difference in apathy score from 6- to 15-months as the predictor to study associations between change in apathy over time and change in cognition over time. We additionally conducted this analysis for patients with decreasing and increasing apathy symptoms separately to explore potential associations in opposite direction between the groups, which could be obscured when analyzed as one group (e.g., increasing apathy correlating with worsening cognition but decreasing apathy not correlating with improving cognition).

As a final step we used a four-level apathy group variable (persistent, incident, resolved and no apathy) as a predictor in regression models, in which the change scores for cognitive tests were the dependent variables.

All crude regression models were rerun with age and gender as covariates in adjusted models. In addition, we rerun the regression models with the GDS score as covariate.

Results

189 patients could be included in this sub study in PASS. For baseline measurement, visits took place in patients' home environment in 95% of the cases. Of these 189 baseline measurements, 117 (62%) were available for the assessment at 15 months post-stroke. Reasons for dropout were dementia (N = 3), mortality (N = 2), a medical condition precluding follow-up visits (N = 10), not interested in further participation (N = 9), unable to contact after repeated attempts (>5 minimum) until 1 month after the follow-up visit was originally due (N = 37) and other (N = 11). Follow-up visits took place in patients' home environments in 97% of the cases. Baseline measures in patients who did not have a follow-up assessment did not differ from those who completed both assessments with respect to age, gender and scores on the AS, GDS, ALDS and MMSE at the 6 months post-stroke visit (Supplementary Table 1). We performed the present analyses on all patients who completed both assessments. Of these, 49 (42%) had apathy according to the AS score at 6 months post-stroke. The baseline characteristics of the sample included for analysis are described in Table 1.

At baseline, patients with apathy according to the AS had a higher score on the GDS and a lower score on the ALDS, all equating to more severe symptoms. Six patients scored above the cutoff of 5 on the GDS, which is indicative for depression. Of those, four patients had depressive symptoms in combination with apathy symptoms according to the AS, two others had isolated depressive symptoms. The Pearson correlation coefficient between apathy and depression was 0.47 (t = 5.71 l p < 0.01). At baseline, patients with apathy had lower scores on the LDST and the AVLT delayed recall and needed more time to complete TMT part B compared to patients without apathy.

Table 1. Baseline characteristics of patients with and without apathy at 6 months post-stroke.

Parameter (N = 68) (N = 49)	No Apathy Apathy p-value		
Age (mean, sd)	71.9 (10.6)	73.0 (9.9)	p = 0.57
Sex male (N, %)	43 (63.2%)	23 (46.9%)	p = 0.12
GDS (mean, sd)	1.4 (1.6)	3.1 (2.0)	p < 0.01
AS (mean, sd)	8.4 (3.4)	17.8 (3.1)	p < 0.01
ALDS (mean, sd)	84.8 (6.4)	81.0 (7.7)	p = 0.01
MMSE (mean, sd)	28.4 (1.5)	27.9 (2.2)	p = 0.13
TMT part A[1] (mean, sd)	57.7 (32.7)	63.6 (24.5)	p = 0.28
TMT part B[1] (mean, sd)	128.7 (67.5)	168.4 (73.6)	p < 0.01
LDST writing (mean, sd)	23.1 (6.8)	19.1 (8.2)	p = 0.01
AVLT direct recall (mean, sd)	39.4 (10.7)	36.7 (10.6)	p = 0.17
AVLT delayed recall (mean, sd)	8.4 (3.2)	6.9 (3.5)	p = 0.02

[1]Higher score means worse performance.

With respect to the course of post-stroke apathy, 46 (39%) patients had apathy at 15 months post-stroke. However, these were not all patients who had apathy at baseline. Thirty-four (29%) patients had persistent apathy. In 15 patients (13%) apathy resolved over time and in 12 patients (10%) apathy emerged between six- and 15-months after stroke. Fifty-six patients (48%) had no apathy at both measurements (Figure 1).

In cross-sectional analyses at six- and 15-months post-stroke (Table 2), a higher score on the AS was associated with a worse score on the MMSE, LDST and AVLT and with longer time needed to complete TMT in all unadjusted models. After adjustment for age and gender, this association was slightly attenuated and not significant for TMT part A at both six- and 15-months. Correction for GDS score did not substantially change the cross-sectional results.

In longitudinal analyses, higher baseline AS scores were associated with lower LDST and AVLT scores and with longer time needed to complete TMT part B (Supplementary Table 2) at 15 months. Correction for GDS score did not substantially change the longitudinal results.

With respect to the association between apathy and cognitive change scores, higher apathy scores at baseline were associated with a decline in scores on AVLT direct recall between six- and 15-months post-stroke. Baseline apathy score was not significantly associated with a change in scores on other cognitive tests. Additionally, changes in apathy score were not associated with any changes in cognitive function when the full sample was considered (Table 3). However, subgroup analyses showed that a decrease in AS scores was associated with increasing AVLT scores. These associations attenuated and

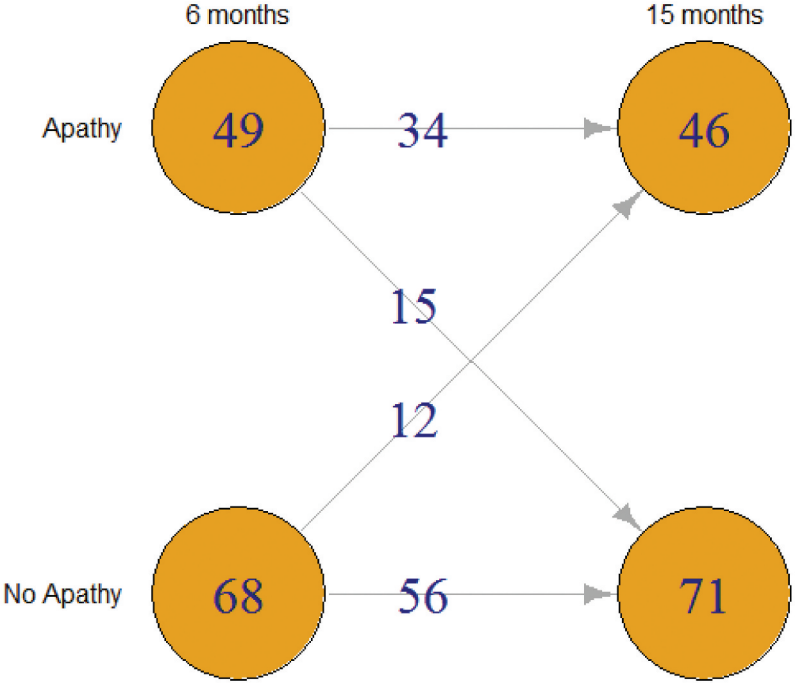

Figure 1. Numbers of participants that had apathy at 6 and 15 months post-stroke and numbers of those who had no apathy, resolved apathy, incident apathy and persistent apathy.

Table 2. Regression models. Cross-sectional analyses. Predictor is AS score at six or 15 months post-stroke. Outcomes are cognitive scores at 6 months and 15 months post-stroke. N = 117.

Cognitive test	6 months post-stroke scores Beta (95% CI) - Unadjusted model Beta (95% CI) - Adjusted model[2]	15 months post-stroke scores Beta (95% CI) - Unadjusted model Beta (95% CI) - Adjusted model[2]		
MMSE	−0.07 (−0.13 to −0.01, p = 0.02)	−0.06 (−0.12 to −0.01, p = 0.03)	−0.11 (−0.18 to −0.04, p < 0.01)	−0.10 (−0.16 to −0.03, p = 0.01)
TMT part A[a]	1.06 (0.08 to 2.04, p = 0.03)	0.86 (−0.10 to 1.83, p = 0.08)	1.21 (0.16 to 2.27, p = 0.02)	0.99 (−0.01 to 1.99, p = 0.05)
TMT part B[a]	3.59 (1.23 to 5.94, p < 0.01)	2.70 (0.59 to 4.82, p = 0.01)	5.02 (2.67 to 7.36, p < 0.01)	4.37 (2.32 to 6.41, p < 0.01)
LDST	−0.35 (−0.60 to −0.10, p = 0.01)	−0.37 (−0.61 to −0.13, p < 0.01)	−0.45 (−0.70 to −0.19, p < 0.01)	−0.40 (−0.62 to −0.17, p < 0.01)
AVLT direct recall	−0.36 (−0.71 to −0.02, p = 0.04)	−0.37 (−0.72 to −0.02, p = 0.04)	−0.76 (−1.13 to −0.38, p < 0.01)	−0.73 (−1.09 to −0.37, p < 0.01)
AVLT delayed recall	−0.19 (−0.29 to −0.08, p < 0.01)	−0.19 (−0.29 to −0.08, p < 0.01)	−0.21 (−0.33 to −0.09, p < 0.01)	−0.20 (−0.31 to −0.09, p < 0.01)

Bèta represents unit increase in cognitive score per point increase in AS. Higher scores mean worse performance except for TMT A and B.
[a]Higher score means worse performance. [2] Adjusted for age and gender.

were not significant after adjusting for age and gender. Furthermore, decreasing AS scores were associated with decreasing MMSE scores, also when adjusting for covariates (Supplementary Table 3). Increasing AS scores over time were associated with lower LDST and AVLT direct recall scores, also after adjusting for age and gender (Supplementary Table 4). Correction for GDS score did not substantial change the association between apathy and cognitive change scores.

When categorizing patients in "persistent apathy," "incident apathy," "resolved apathy" or "no apathy," patients with persistent apathy showed a significantly higher increase of the time they needed to complete the TMT B compared to patients with no apathy. AS scores at 6- and 15-months for patient with resolved apathy are shown in supplementary table 5 and for those with incident apathy in supplementary table 6. The difference scores on the other cognitive tests of patient with resolved, incident or persistent apathy did not significantly differ from those with no apathy (Table 4).

Discussion

In this prospective cohort of stroke patients, we found that apathy appears in approximately one third of the stroke survivors, which is in line with previous studies.(Brodaty et al., 2013; Caeiro et al., 2013; Van Dalen et al., 2013) In our study, most cases had persistent apathy over time (29%). Importantly, a considerable proportion of participants had apathy at 6 months that resolved over time (13%), while 10% developed apathy >6 months post-stroke. Apathy often occurred in the absence of depression and was a more frequent neuropsychiatric symptom than depression. Second, we found that higher apathy

Table 3. Results from regression analysis with Apathy score 6 months after stroke and change score on Apathy Scale as predictors and change scores on cognitive tests between 6 and 15 months after stroke as outcomes. N = 117.

Cognitive test	Predictor	Beta (95% CI, p) – Unadjusted model	Beta (95% CI, p) – Adjusted model[2]
MMSE	AS score at 6 months post-stroke*	0.01 (−0.04 to 0.05, p = 0.81)	0.01 (−0.04 to 0.06, p = 0.67)
TMT part A[a]	AS score at 6 months post-stroke	−0.35 (−1.03 to 0.34, p = 0.32)	−0.50 (−1.23 to 0.22, p = 0.17)
TMT part B[a]	AS score at 6 months post-stroke	1.19 (−0.20 to 2.58, p = 0.09)	1.11 (−0.36 to 2.59, p = 0.14)
LDST	AS score at 6 months post-stroke	0.12 (−0.08 to 0.32, p = 0.25)	0.15 (−0.05 to 0.36, p = 0.14)
WLT direct recall	AS score at 6 months post-stroke	−0.31 (−0.53 to −0.08, p = 0.01)	−0.33 (−0.55 to −0.10, p = 0.01)
MMSE	Change score on AS between 6 and 15 months post-stroke[#]	−0.04 (−0.10 to 0.01, p = 0.12)	−0.05 (−0.11 to 0.01, p = 0.12)
TMT part A[a]	Change score on AS between 6 and 15 months post-stroke	0.25 (−0.55 to 1.04, p = 0.54)	0.04 (−0.88 to 0.96, p = 0.93)
TMT part B[a]	Change score on AS between 6 and 15 months post-stroke	−0.31 (−1.90 to 1.28, p = 0.70)	0.37 (−1.45 to 2.20, p = 0.69)
LDST	Change score on AS between 6 and 15 months post-stroke	−0.23 (−0.46 to 0.00, p = 0.05)	−0.19 (−0.45 to 0.07, p = 0.16)
WLT direct recall	Change score on AS between 6 and 15 months post-stroke	0.13 (−0.14 to 0.40, p = 0.34)	−0.05 (−0.35 to 0.24, p = 0.72)
WLT delayed recall	Change score on AS between 6 and 15 months post-stroke	−0.01 (−0.10 to 0.08, p = 0.81)	−0.01 (−0.11 to 0.09, p = 0.88)

*Bèta represents unit increase in cognitive score per point increase in AS. [#]Bèta represents unit increase in change score per point increase in AS change score.
[a]Higher score means worse performance. [2] Adjusted for age and gender.

symptoms were cross-sectionally and longitudinally associated with worse cognitive functioning at both six- and 15-months post-stroke. Longitudinal analyses on associations between cognitive tests scores and apathy yielded ambiguous but mostly neutral results.

Baseline apathy was associated with a decline in delayed recall over time. We did not find any association between the course of apathy and the course of cognitive functioning when the full sample was considered. However, subgroup analyses showed that decreasing apathy symptoms over time were associated with an improvement of both direct and delayed recall over time, while increasing apathy symptoms were associated with a worse score on one out of two information processing speed tasks. Possibly, associations between the course of apathy symptoms and change in cognition over time were only found in the subgroup analyses, since increasing and decreasing AS scores may have masked each other when the sample was analyzed as a single group. When we separated our study sample into groups of patients with no apathy, resolved apathy, incident apathy and persistent apathy, we did not find any association between apathy and difference scores on the cognitive tests.

The course of apathy over time as well as apathy measured 6 months post-stroke, do not predict subsequent cognitive decline overall, but may be related to changes in the memory domain. This holds that, although symptoms of apathy and cognitive decline often occur simultaneously, they are not dependent on each other. Successful treatment of apathy would thus not necessarily lead to an improvement of cognition nor do improvements in cognition necessarily translate into reduced apathy. Therefore, it is important that both constructs are taken into account separately in health care programs

Table 4. Results from regression analysis with apathy group as predictor and change scores on cognitive tests between 6 and 15 months after stroke as outcomes. N = 117.

Cognitive test	Mean (sd)	Beta (95% CI, p) –	
	Unadjusted model	Adjusted model[2]	
	Beta (95% CI, p) –		
MMSE			
No apathy (ref) (N = 56)	−0.4 (1.3)	1	1
Resolved apathy (N = 15)	−0.1 (1.2)	0.31 (−0.51 to 1.13, p = 0.46)	0.24 (−0.62 to 1.09, p = 0.59)
Incident apathy (N = 12)	−1.0 (1.7)	−0.63 (−1.55 to 0.30, p = 0.19)	−0.70 (−1.65 to 0.25, p = 0.15)
Persistent apathy (N = 34)	−0.5 (1.6)	−0.12 (−0.74 to 0.49, p = 0.69)	−0.09 (−0.72 to 0.55, p = 0.79)
TMT part A[a]			
No apathy (ref) (N = 56)	3.0 (19.1)	1	1
Resolved apathy (N = 15)	0.9 (16.3)	−2.05 (−13.91 to 9.82, p = 0.73)	−1.88 (−14.35 to 10.59, p = 0.77)
Incident apathy (N = 12)	2.9 (22.7)	−0.11 (−15.49 to 15.28, p = 0.99)	0.96 (−14.86 to 16.77, p = 0.90)
Persistent apathy (N = 34)	5.2 (23.7)	2.18 (−6.99 to 11.35, p = 0.64)	0.52 (−9.20 to 10.25, p = 0.92)
TMT part B[a]			
No apathy (ref) (N = 56)	−0.2 (28.9)	1	1
Resolved apathy (N = 15)	−6.9 (42.2)	−6.67 (−29.58 to 16.24, p = 0.56)	−7.79 (−32.03 to 16.45, p = 0.52)
Incident apathy (N = 12)	2.6 (62.8)	2.82 (−26.84 to 32.48, p = 0.85)	4.44 (−26.25 to 35.14, p = 0.77)
Persistent apathy (N = 34)	18.6 (45.8)	18.78 (0.64 to 36.92, p = 0.04)	17.62 (−1.74 to 36.98, p = 0.07)
LDST			
No apathy (ref) (N = 56)	−0.7 (6.1)	1	1
Resolved apathy (N = 15)	2.7 (7.6)	3.39 (−0.07 to 6.84, p = 0.05)	3.08 (−0.45 to 6.61, p = 0.09)
Incident apathy (N = 12)	−2.9 (6.9)	−2.23 (−6.50 to 2.03, p = 0.30)	−2.54 (−6.80 to 1.72, p = 0.24)
Persistent apathy (N = 34)	−0.1 (4.5)	0.53 (−2.11 to 3.17, p = 0.69)	1.06 (−1.61 to 3.72, p = 0.43)
AVLT direct recall			
No apathy (ref) (N = 56)	2.8 (6.3)	1	1
Resolved apathy (N = 15)	−1.2 (6.8)	−4.01 (−8.06 to 0.03, p = 0.05)	−4.06 (−8.15 to 0.04, p = 0.05)
Incident apathy (N = 12)	0.0 (10.8)	−2.81 (−7.39 to 1.76, p = 0.23)	−3.75 (−8.29 to 0.79, p = 0.10)
Persistent apathy (N = 34)	1.2 (6.7)	−1.62 (−4.74 to 1.50, p = 0.31)	−1.90 (−5.04 to 1.24, p = 0.23)
AVLT delayed recall			
No apathy (ref) (N = 56)	0.5 (2.1)	1	1
Resolved apathy (N = 15)	−0.1 (2.5)	−0.61 (−1.96 to 0.75, p = 0.38)	−1.04 (−2.39 to 0.32, p = 0.13)
Incident apathy (N = 12)	0.6 (2.2)	0.16 (−1.37 to 1.70, p = 0.83)	−0.11 (−1.61 to 1.40, p = 0.89)
Persistent apathy (N = 34)	0.5 (2.7)	0.01 (−1.03 to 1.05, p = 0.98)	0.01 (−1.03 to 1.05, p = 0.98)

Bèta represents unit increase in cognitive score per point increase in AS. Higher scores mean worse performance except for TMT A and B.

[a]Higher score means worse performance. [2] Adjusted for age and gender.

for stroke survivors. Although cognitive disorders are often more easily recognized, apathy deserves attention, as it is a severely debilitating condition that places a great burden on both patients and caregivers.(Brodaty et al., 2013; Caeiro et al., 2013; Van Dalen et al., 2013) Whether our finding of an association between a decrease in apathy symptoms and an improvement of verbal short-term memory may be generalized to other aspects of memory, such as working memory and visual memory, or to cognitive domains that were not investigated in the present study, needs to be addressed in future studies.

Our study has provided more insight in the association between apathy and cognition. However, there were some limitations. At first, the sample size was relatively small, although comparable to most other observational studies that investigated associations between apathy and cognition.(Brodaty et al., 2005; Caeiro et al., 2012; Onoda et al., 2011; Withall et al., 2011) However, the longitudinal sample size of 117 individuals would have given us 80% power to detect relatively weak correlations (r-coefficient ≥0.26) with a p-value <0.05, (Schober et al., 2018) suggesting small sample size does not play a major role in the lack of a correlation between apathy and cognitive measures.

Secondly, this study suffered from a high number of patients who were lost to follow-up. Reasons for our inability to contact these individuals at follow-up may include refusal of contact, address change, admission to a nursing home and mortality. We were unable to retrieve these data due to privacy legislation. It may be suggested that patients who were lost to follow-up could have had more disability or worse cognitive functioning, although at baseline those lost to follow-up did not differ from those who completed the study and no participant had severe disability at baseline due to the exclusion criterion of an mRS >3. Although the inclusion criteria of mRS score ≤3 may have limited the generalizability of our results to the full stroke population, it diminishes the risk that positive answers on questions aiming to assess apathy were in fact due to disability. Finally, this is an exploratory study, and our findings should be confirmed in other, preferably larger samples of stroke survivors. Strength of our study was to use the AS cutoff of 14 to separate patients into those with and without apathy, a cutoff that has been validated repeatedly. Still, since we also used continuous baseline AS scores and AS difference scores as predictors in regression models, we went beyond using only this dichotomization to study our hypotheses, and results were consistent using these different approaches. Future studies should focus more on the longitudinal relationship between apathy and depression. We have found that apathy and depression are correlated to each other, but also that they are clearly separate constructs after stroke, with apathy often occurring in isolation without depressive symptoms. More longitudinal data would give us more insight in how these constructs relate to each other.

To conclude, in this exploratory study we found no clear relation between change in apathy and change in cognition, which suggests both these sequelae of stroke warrant separate attention. Our results suggest that post-stroke apathy after 6 months is amenable to substantial improvement in the long term, which is less evident for cognitive decline.(Pendlebury & Rothwell, 2019; Tang et al., 2018)

Acknowledgments

This work was supported by The Netherlands Organization for Health Research and Development [grant number 171002302, grant no 016116358]; The Netherlands Heart Foundation [grant number 2009B095]; European Research Council (ERC) Starting Grant [grant number 281156]; and European Research Council (ERC) Advanced Grant [grant number 339374]. There are no disclosures to report.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by the European Research Council (ERC) Starting Grant [281156]; The Netherlands Heart Foundation [2009B095]; European Research Council (ERC) Advanced Grant [339374]; The Netherlands Organization for Health Research and Development [016116358,171002302].

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Appendices

- Supplemental Online Material Content 1: docx
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