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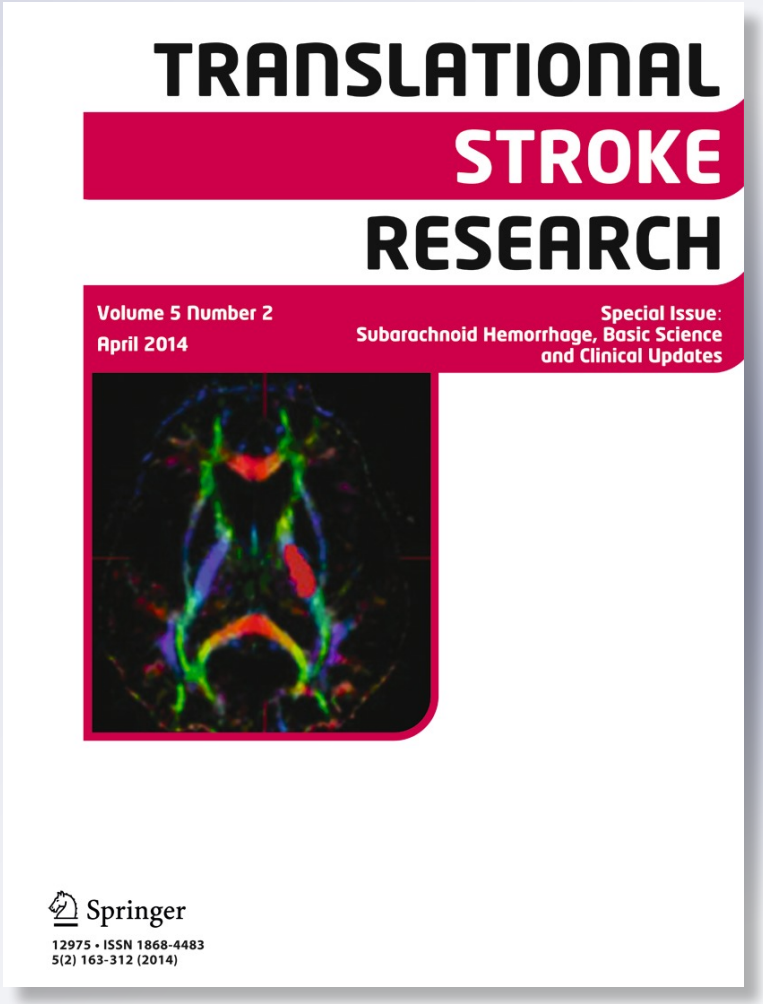
Translational Stroke Research

ISSN 1868-4483
Volume 5
Number 2

Transl. Stroke Res. (2014) 5:292-300
DOI 10.1007/s12975-013-0293-y



Springer

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ORIGINAL ARTICLE

Post-Stroke Apathy and Hypersomnia Lead to Worse Outcomes from Acute Rehabilitation

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Received: 18 June 2013 / Revised: 17 September 2013 / Accepted: 6 October 2013 / Published online: 19 October 2013

Abstract Apathy and hypersomnia occur after stroke and, by definition, reduce participation in rehabilitation, but their effect on outcome from acute rehabilitation is not known. We performed a retrospective review of 213 patients admitted to a stroke-specialized acute rehabilitation unit in the United States. All patients had ischemic or hemorrhagic stroke, and no dementia or dependence on others pre-stroke. We diagnosed apathy and hypersomnia using standardized documentation by treating therapists. We used multiple regression analysis to control for overall impairment (combination of strength, cognitive and sensory measures), age, time since stroke, and stroke type (ischemic or hemorrhagic). Forty-four (21 %) of the patients had persistent apathy, and 12 (5.6 %) had persistent hypersomnia. Both groups were more impaired in cognition, sustained attention, and more likely to be treated for depression. 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. Patients with hypersomnia were ten times more likely to go to a nursing home, and had discharge FIM scores 16 points below the mean. These findings indicate that studies to prospectively define these clinical factors and potential confounds using standardized tools are indicated, and if confirmed, justify studies to identify these patients early and develop targeted interventions.

Keywords Apathy · Hypersomnia · Stroke · Rehabilitation

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Introduction

In addition to the well-recognized motor and sensory deficits in patients with stroke, apathy and hypersomnia can reduce goal-directed behavior and therefore participation in rehabilitation. If reduction in participation due to apathy or hypersomnia affects the rehabilitation process, it could explain some of the variability in recovery [1, 2], and treatment of these conditions could improve patients' response to rehabilitation interventions, reducing disability and improving outcomes. But, as a prerequisite to initiating clinical trials of such treatments, we first need to know the prevalence of these conditions in the acute rehabilitation period, and whether they have an independent effect on outcome.

Apathy is a reduction of goal-directed behavior in the setting of intact consciousness, and can be due to impaired emotional reactivity, motor planning deficits, or inability to self-initiate behaviors [3]. In stroke, it is associated with damage or reduced blood flow to prefrontal cortex and basal ganglia [4–6]. Additionally, it may occur as a consequence of coexisting illnesses such as depression and neurodegenerative diseases, with potentially overlapping mechanisms [7–9].

Considering all etiologies, a recent meta-analysis of 24 studies found that apathy occurs in 29.5–40.2 % of patients after stroke, and is typically associated with worse disability and enduring cognitive deficits [10]. None of the studies in the meta-analysis were from the American acute rehabilitation population; two were performed in Japan where patients enter rehabilitation >1 month after stroke: Hama and colleagues

[11] found that 40 % of patients had apathy by patient report and 19 % by structured interview of the caregiver; Santa and colleagues [12] found 20 % of patients with apathy by patient report [12]. Studies that followed patients over time found that apathy generally remains present even up to 1 year [13, 14].

Hypersomnia is excessive total sleep and can be due to dysfunction of the brain's arousal network or nighttime sleep disruption [15]. It can occur after stroke from focal injury to basal forebrain or diencephalic structures [16], or be a feature of delirium in the setting of metabolic disturbances [17]. Three studies found that hypersomnia occurred between 4 % and 18 % of patients in the first days after stroke [18–20], and one study found it in 14 % of 44 patients in acute rehabilitation [21]. A more recent study, only reported in a review article, found that in the chronic phase (21±18 months) after stroke 27 % of patients had hypersomnia [15].

The published literature is difficult to apply to the American acute rehabilitation because none specifically looked at effect on outcome in this population. Furthermore, studies of apathy in similar time periods after stroke typically excluded patients with aphasia or severe cognitive deficits to allow for use of a patient-report measure such as the Apathy Scale [22]. To address these limitations, we conducted a preliminary study, using existing medical records, to study effects of apathy and hypersomnia on outcomes from acute rehabilitation. Instead of using a patient-report scale, we operationally defined the presence of these conditions using treating therapists' observations, ensuring that all patients could be included. We hypothesized that, independent of stroke severity and other factors, apathy and hypersomnia would have a negative impact on outcome, as judged by disposition location (nursing home vs. home) and disability.

Methods

Patient Subjects

We conducted a retrospective electronic chart review of patients treated in the Stroke Program at Burke Rehabilitation Hospital in 2011. We included 362 patients admitted from an acute care hospital with a diagnosis of ischemic or hemorrhagic stroke. We then excluded 149 patients who: completed less than 7 days of rehabilitation; had a diagnosis of a neurodegenerative disease; required assistance of another person for daily activities prior to the stroke; were transferred out of rehabilitation to a hospital for greater than 3 days; were admitted more than once within the year (we excluded the later admission); or had inadequate documentation required for analysis. This resulted in a total of 213 patients for analysis.

The study was approved by the Institutional Review Board of Burke Rehabilitation Center.

Available Documentation

Data for patient behaviors and other clinical characteristics were obtained from physician and therapist electronic clinical documentation, as well as billing, laboratory and other electronic clinical databases.

Definition of Apathy and Hypersomnia

Patients were classified as having apathy or hypersomnia based on behaviors documented by physical and speech therapists approximately three to five times per week. This observational approach allowed us to include patients with aphasia and cognitive deficits that would be unable to complete self-report scales, and ensured that the behaviors were present during therapy sessions. To limit the effect of transient disturbances of arousal (e.g., a night of inadequate sleep or infection), we required that the behaviors were documented in at least half of the daily progress notes, with a minimum of three total notes.

To define apathy and hypersomnia, we chose from a list of terms that therapists used to document patient behavior. This list included: "hypoarousal," "internally distracted," "impulsivity," "decreased initiation," "externally distracted," "flat affect," "perseveration," "restlessness," "lability," "confabulation." Our operational definition of apathy was that the therapists selected the term "decreased initiation," implying that patients did not participate in therapy unless encouraged. This was the closest term to the core of the definition of apathy — "a lack of motivation" — used by most authors [23, 24]. "Flat affect" is also a feature of apathy [23], though we only report on it here as a clinical descriptor. Our operational definition of hypersomnia was that the therapist selected the term "hypoarousal," used to describe patients who had their eyes closed and appeared sleepy during the therapy session. Note that while this definition of hypersomnia includes patients who were sleepy due to disturbed nighttime sleep, our clinical experience is that this is an uncommon cause of persistent hypersomnia and most patients identified by the operational definition had excessive total sleep. Because this study is based on a retrospective review of routine clinical records in which most patients had a single therapist for the course of their treatment, we were unable to assess inter-rater reliability.

We also recorded speech therapist documentation of findings in the first 48 h after admission that have been reported to co-occur with apathy, including impaired sustained attention, and impaired executive dysfunction [5, 25]. Therapists used a variety of tasks to test for these, and then documented their presence or absence based on an overall impression.

Outcome Measures

Our first outcome was discharge disposition (home vs. nursing home), as home discharge is a fundamental goal

of an acute rehabilitation stay. Our second outcome was disability, the foremost factor in determining home discharge [26]. We defined disability as the mean discharge (final 48 h of stay) FIM™ score (UB Foundation Activities, Inc.). The 18 items of the FIM are scored on an ordinal scale from 1 (dependent) to 7 (no assistance needed), so a total score ranges from 18 to 126. We calculated total FIM with the standard procedures, except that mobility was determined only by walking independence and not wheelchair independence.

We also performed two exploratory outcome measures: change in total FIM from admission (mean over first 48 h) to discharge (mean over final 48 h); and FIM at 3 months post-discharge. Change in FIM was not used as a primary outcome measure because patients had varied lengths of stay, and a recent study using Rasch analysis found that changes in the FIM are not comparable across different levels of the scale due to nonlinearities in the tool [27]. Three-month post-discharge FIM was also not used as a primary outcome measure as it was obtained by phone and was not available on approximately one-half of the patients.

We did not use change in impairment as an outcome measure, as impairment measures (e.g., Fugl-Meyer, Motricity Index) were not available at multiple time points from a sufficient number of patients.

Additional Predictors

In addition to hypersomnia and apathy, we tested the outcome measures against other patient characteristics, first with univariate statistics, and then with multiple regression analyses, including those factors with $p<0.1$ on the univariate analyses. We decided a priori to not include length of stay in the multiple regression analyses as it was typically determined within the first week of admission based on diagnosis and level of disability, and therefore primarily reflected stroke severity.

To characterize patients' impairment we created an overall measure similar to the NIH Stroke Scale (NIHSS), using available clinical data from the first 24 h of admission (Table 1). The NIHSS was not available in the medical records. Our measure, like the NIHSS, includes tests of motor function, language, sensation, vision, neglect, and overall cognition. We chose to use an overall impairment measure, rather than testing each component individually, as deficits typically co-occurred in moderate to severe strokes. The overall impairment measure also formed a unimodal distribution, which facilitated statistical testing (Fig. 1).

We did not study imaging findings of stroke location, as we did not have access to original imaging studies for most patients.

Statistical Analyses

Pearson's chi-square test was used to test association between binary variables (e.g., discharge location and presence of apathy). Student's t-test was used to compare means of continuous variables between groups (e.g., age and presence vs. absence of apathy). Simple linear regression was used to compare continuous variables with each other (e.g., age and discharge FIM score). All tests were two-tailed.

To treat multiple predictors together, we used multiple logistic regression for the outcome of discharge disposition (a binary variable), and multiple linear regression for discharge total FIM (an ordinal scale that is typically treated as continuous).

Statistical tests were run with built-in and in-house Matlab (Mathworks, MA, USA) code.

Results

Description of Patients

Of the 213 patients who met inclusion and exclusion criteria, 44 (21 %) had persistent apathy, 12 (5.6 %) had persistent

Table 1 Components of the overall impairment measure

Component	Examiner	Points towards total
Weakness (by Motricity Index[a])	Physician	0=4 points; 1–34=3 points; 35–64=2 points; 65–99=1 point; 100=0 points
Sensory loss	Physician	1 point if present
Visual field cut or visual neglect	Physician	1 point if present
Aphasia	Speech therapist	1 point if present
Spatial neglect	Occupational therapist	1 point if present
Cognitive deficit[b]	Physician (MMSE) and therapists (FIM)	1 point if MMSE<24 or admission FIM Problem Solving <4

[a] Motricity Index [36, 37] is a scale that converts a subset of the Medical Research Council (1 to 5 point) scale [38] into 0 to 100 points (0 no movement, 100 normal). It has been shown to correlate with the Rivermead Motor Assessment [39], Barthel ADLs [37], and with the Fugl-Meyer ($r=0.87$) in the 78 % of our patients who had admission Fugl-Meyer performed

[b] Cognitive deficit was scored as present if Mini-Mental Status Exam (MMSE) <24 *or* FIM Problem Solving <4, as the MMSE is not sensitive to executive function deficits [40]

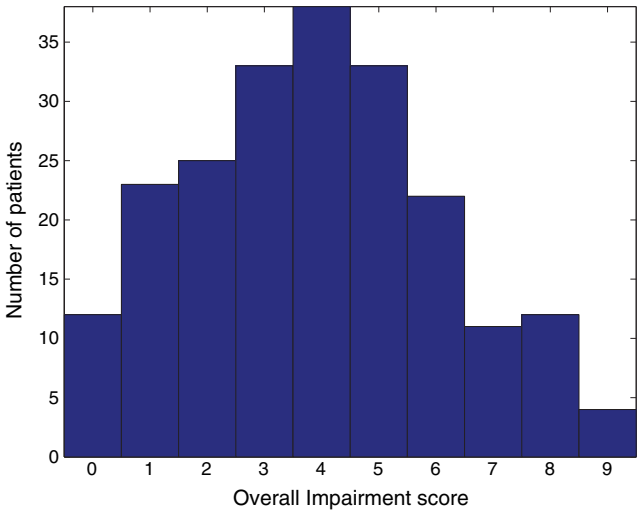

Fig. 1 Histogram of our overall impairment measure (Table 1) in all 213 subjects. Note that combining the six components into one measure produces a unimodal distribution

hypersomnia, and nine (4.2 %) had both. The remaining 148 patients (those without persistent apathy or hypersomnia) were treated as controls. We compared these groups on a range of demographics and exam findings reported by therapists and physicians from admission exams (Table 2). There were no statistically significant associations of apathy or hypersomnia with age, hemorrhagic stroke, gender, or history of previous stroke. Compared to control patients, those with apathy or hypersomnia had worse overall cognition (Mini-Mental Status Exam [MMSE] <24 or FIM problem solving <4), impaired sustained attention, and flat affect. The hypersomnia patients were significantly weaker (by Motricity Index). Both groups also had more disability at admission (by FIM), longer lengths of stay, and higher rates of nursing home discharge. Patients with apathy or hypersomnia were more likely to be placed on alerting medications (modafinil or amantadine), though only a total of six patients were on these medications.

Effect of Apathy and Hypersomnia on Outcome

On univariate analysis, the strongest correlates of nursing home disposition and discharge FIM were overall impairment (defined in Table 1), apathy and hypersomnia (all $p<0.001$; Table 3). Days between stroke and admission, age, and hemorrhagic stroke also correlated but less strongly.

On multiple regression analysis, apathy and hypersomnia remained associated with both primary outcome measures after adjusting for all other factors (Table 4). Patients with apathy were 2.4 times as likely to go to a nursing home and had discharge FIM scores 12 points lower than the mean. Patients with hypersomnia were ten times as likely to go to a nursing home and had discharge FIM scores 16 points lower than the mean. To highlight the independence from stroke severity, Fig. 2 shows that at all ranges of our overall

Table 2 Univariate comparison between patients with and without apathy/hypersomnia

	Control Patients ($n=166$)	Hypersomnia ($n=12$)	Apathy ($n=44$)
Demographics			
Age	74.9 (68.0–82.0)	78.2 (74.0–82.5)	78.1 (73.5–84.0)
Length of stay	20.2 (16.0–24.0)	*26.6* (23.0–30.5)	*23.6* (20.5–27.0)
Days since stroke	8.2 (5.0–9.0)	11.8 (6.0–15.0)	8.8 (6.0–11.5)
Female	52 % (44–60 %)	33 % (10–65 %)	59 % (43–74 %)
Hemorrhagic stroke	13 % (8–19 %)	17 % (2–48 %)	16 % (7–30 %)
Previous stroke	23 % (17–31 %)	33 % (10–65 %)	30 % (17–45 %)
Discharged to nursing home	26 % (19–33 %)	*83 %* (52–98 %)	*61 %* (45–76 %)
Exam findings from first 48 h of admission			
FIM	65.4 (57.2–76.6)	*38.0* (26.9–51.0)	*47.5* (33.1–58.9)
Impaired attention	47 % (37–52 %)	*100 %* (74–100 %)	*83 %* (65–90 %)
Flat affect	8 % (5–14 %)	*67 %* (35–90 %)	*66 %* (50–80 %)
Executive dysfunction	58 % (51–66 %)	92 % (62–100 %)	70 % (55–83 %)
Motricity Index°a	64.8 (45.0–88.0)	*42.6* (0.0–100.0)	53.9 (21.0–86.2)
Sensory abnormalitya°	47 % (39–55 %)	58 % (28–85 %)	61 % (45–76 %)
Visual field abnormality°a	55 % (48–63 %)	58 % (28–85 %)	68 % (52–81 %)
Aphasia°a	32 % (25–40 %)	25 % (5–57 %)	36 % (22–52 %)
Neglect a°	27 % (21–35 %)	50 % (21–79 %)	39 % (24–55 %)
Cognitive deficit a°	53 % (45–61 %)	*92 %* (62–100 %)	*84 %* (70–93 %)
Treatment			
Alerting Medication	1 % (0–4 %)	*33 %* (10–65 %)	*9 %* (3–22 %)

Values represent mean (25th–75th percentile) or percent (95 % confidence interval by binomial). Values for patients with hypersomnia or apathy were compared to controls using *t*-tests or chi-squared as appropriate

[a] Predictors used to create the overall impairment measure (Table 1). To account for multiple comparisons in comparing clinical descriptors between patient groups, we used the False Discovery Rate (FDR) method [41, 42]. This changed the $p \leq 0.05$ threshold for statistical significance to $p \leq 0.017$ (represented by asterisk [*] here and in Table 5). See manuscript for descriptions of individual characteristics

Table 3 Univariate testing of patient descriptors against the two outcome measures

Discharge disposition				
	Nursing home discharge Odds ratio (95 % CI)	Nursing home discharge % (95 % CI) or value (25th to 75th percentiles)	Home discharge % (95 % CI) or value (25th to 75th percentiles)	*p*- value
Days Since Stroke		9.8 (5.0 - 12.5)	7.8 (5.0 - 9.0)	0.019
Age		78.4 (74.0 - 84.5)	74.2 (67.0 - 81.0)	0.002
Female	0.81 (0.46 - 1.4)	50 % (38 - 62 %)	55 % (47 - 64)	0.462
Hemorrhagic Stroke	2.6 (1.2 - 5.8)	21 % (12 - 32 %)	9 % (5 - 15)	0.018
Previous Stroke	0.63 (0.32 - 1.3)	19 % (11 - 30)	28 % (20 - 36)	0.19
Overall Impairment		5.4 (4.0 - 7.0)	3.2 (2.0 - 4.0)	<0.001
Apathy	4.4 (2.2 - 8.8)	38 % (26 - 50)	12 % (7 - 19)	<0.001
Hypersomnia	11 (2.4 - 53)	14 % (7 - 24)	1 % (0 - 5)	<0.001
Discharge Total FIM				
	FIM with predictor present or at its 75th percentile (95 % CI)	FIM with predictor absent or at its 25th percentile (95 % CI)	Estimated Effect Size	p-value
Days Since Stroke	83.4 (78.8 – 88.0)	87.0 (84.7 – 89.3)	3.6	0.002
Age	81.4 (58.6 – 104.3)	87.6 (68.4 – 106.7)	6.2	0.001
Female	83.7 (75.0 - 99.3)	85.4 (71.9 - 102.1)	N/A	0.532
Hemorrhagic Stroke	77.9 (61.0 - 93.6)	85.5 (74.9 - 101.4)	7.5	0.064
Previous Stroke	85.7 (74.4 - 100.8)	84.1 (72.0 - 101.0)	N/A	0.607
Overall Impairment	78.2 (73.4 – 83.0)	95.3 (93.4 – 97.2)	17.1	<0.001
Apathy	67.1 (51.0 - 89.6)	89.0 (79.8 - 101.9)	21.9	<0.001
Hypersomnia	54.6 (37.2 – 67.0)	86.3 (75.9 - 101.2)	31.7	<0.001

For discharge disposition: we report odds ratio only for binary predictors; p values are by chi-squared for binary predictors and *t*-test for continuous predictors. For discharge total FIM: estimated effect size is column 2 minus column 1 for those with $p<0.1$; p values are by *t*-test for binary predictors and by simple linear regression for continuous predictors

Table 4 Multiple regression analyses

Logistic regression for nursing home disposition			
	Odds ratio (95 % CI)	Odds ratio of 75th vs. 25th percentile or present vs. absent (95 % CI)	*p*- value
Age	1.06 (1.02 to 1.10)	2.17 (1.26 to 3.72)	0.005
Overall Impairment	1.76 (1.44 to 2.14)	5.41 (2.97 to 9.86)	<0.001
Days since stroke	1.04 (0.98 to 1.10)	1.21 (0.90 to 1.63	0.203
Hemorrhagic stroke	1.86 (0.69 to 5.01)	1.86 (0.69 to 5.01)	0.218
Apathy	2.41 (1.01 to 5.74)	2.41 (1.01 to 5.74)	0.046
Hypersomnia	10.06 (1.33 to 75.83)	10.06 (1.33 to 75.83)	0.025
Linear regression for total FIM at discharge			
	Beta (95 % CI)	Difference in discharge FIM, 75th vs. 25th percentile or present vs. absent (95 % CI)	p-value
Age	−0.33 (−0.5 to −0.1)	−4.4 (−6.9 to −1.8)	<0.001
Overall impairment	−4.82 (−5.7 to −4.0)	−14.0 (−17.0 to −12.0)	<0.001
Days since stroke	−0.36 (−0.7 to −0.04)	−1.8 (−3.4 to −0.18)	0.031
Hemorrhagic stroke	−1.42 (−6.8 to 4.0)	−1.4 (−6.8 to 4.0)	0.609
Apathy	−12.4 (−17.2 to −7.6)	−12.4 (−17.2 to −7.6)	<0.001
Hypersomnia	−16.2 (−24.6 to −7.9)	−16.2 (−24.6 to −7.9)	<0.001

In the first data column, we report the odds ratio and beta, both in units of change in outcome per unit change of the predictor. In the second data column we report the continuous predictors (e.g., age) as difference in outcome at its 75th percentile vs. its 25th percentile for easier comparison with the binary predictors (e.g., presence of apathy). Values for binary predictors represent effect on outcome when present vs. absent

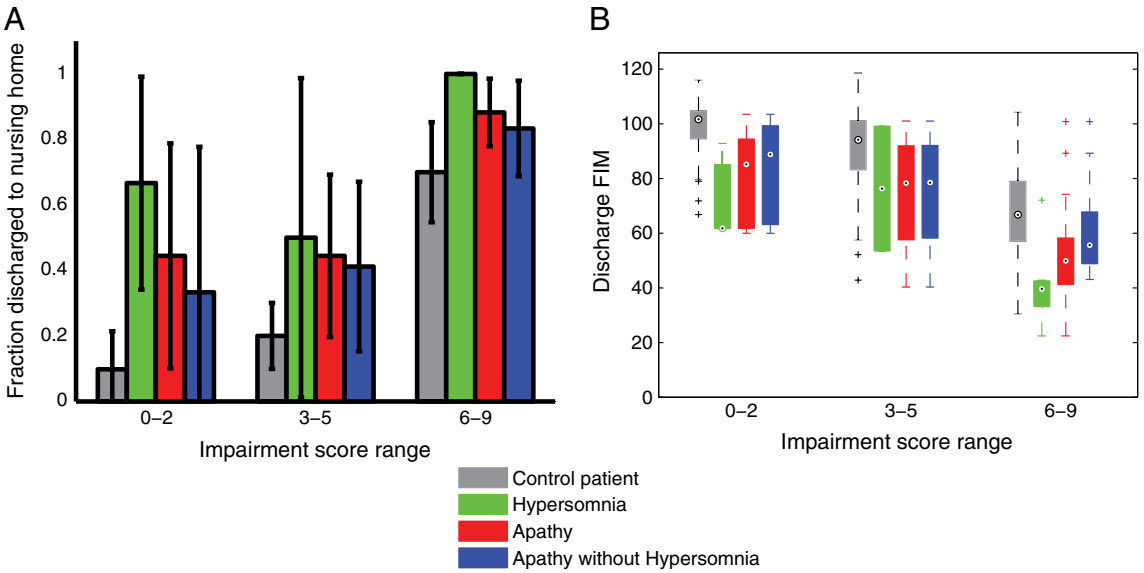

Fig. 2 Presence of apathy and hypersomnia are associated with higher nursing home discharge rates (**a**) and lower discharge FIM scores (**b**), after controlling for our overall impairment measure (Table 1). Error bars in **a** are 95 % confidence limits by binomial statistics. **b** *Encircled dots* are medians; *bars* represent 25th–75th percentiles; *whiskers* extend to extreme data points not considered outliers

impairment measure, patients with apathy or hypersomnia were more likely to go to a nursing home and had lower discharge FIM.

As seen in Table 4, hypersomnia was more strongly associated with the outcome measures than apathy. Since 20 % of the patients with apathy also had hypersomnia, we wondered whether the effect of apathy was merely due to the subset with hypersomnia. To address this, we calculated the same multiple regression analyses with hypersomnia patients removed. We found that apathy remained correlated with fraction discharged to nursing home, but was no longer statistically significant (odds ratio 2.19, 95 % confidence interval [CI] 0.91 to 5.29, $p=0.082$). Apathy remained significantly correlated with lower discharge FIM (10.73 points lower, 95 % CI −15.71 to −5.75, $p<0.001$). We also illustrate this with separate bars in Fig. 2a and b. Thus, apathy by itself had a significant association with outcome, though not nearly as large as hypersomnia. We did not do the converse and test the effect of hypersomnia with apathy patients removed, as only three of 12 hypersomnia patients did not have apathy.

Exploratory Outcome Measures

Regarding change in total FIM from admission to discharge, in the whole sample, the mean change was 23.2 points (25th percentile 15.7; 75th percentile 30.3). On univariate analysis, only apathy (4.4 fewer points, $p=0.013$) and hypersomnia (7.0 fewer points, $p=0.024$), correlated significantly with change in FIM. Admission FIM, overall impairment, previous stroke, length of stay, age, and days between stroke and admission did not correlate with change in FIM (all $p>0.2$). On multiple regression analysis using apathy and hypersomnia only, neither remained significant predictors of change in FIM ($p=0.062$ for apathy and $p=0.13$ for hypersomnia). Interpretation of the change in FIM is problematic because, as mentioned above, the scale is not a uniform reflection of function: the same change in score at the lower end of the scale may represent a different functional improvement than at the upper end of the scale.

Regarding FIM at 3 months after discharge, we had data on 52 % of patients (110 out of the 213 patients). Seventeen (15 %) of this subgroup of patients had apathy, and two (2 %) had hypersomnia during their admission. Patients were followed up at a mean of 120 days after discharge (no statistically significant difference in number of days for patients with versus without apathy, t-test $p=0.3$). In multiple regression analysis, using the same predictors as discharge FIM above, we found that age, overall impairment and apathy remained significant predictors of 3-month FIM scores, with apathy predicting 13 points lower FIM ($p<0.01$). While consistent with discharge FIM scores (Table 4), these results are less reliable due to the low number of participants and because the data were obtained by telephone.

Other Potential Causes of Apathy and Hypersomnia

Apathy and hypersomnia can occur in patients with stroke due to causes other than the stroke. As this was a retrospective study, we were unable to determine the specific cause in a given patient, but we were able to test for the prevalence of three potential causes: infection, depression and sedating medications (Table 5).

Table 5 Univariate testing of other factors that can cause apathy or hypersomnia

	Control Patients		
	(n=166)	Hypersomnia (n=12)	Apathy (n=44)
Infection during stay			
By Billing Code	22 % (16–29 %)	42 % (15–72 %)	32 % (19–48 %)
By Antibiotic Initiation	34 % (27–42 %)	50 % (21–79 %)	*59 %* (43–74 %)
By Antibiotic Initiation WBC	20 % (15–27 %)	33 % (10–65 %)	*39 %* (24–55 %)
New diagnosis of depression			
By Billing Code	39 % (31–46 %)	*92 %* (62–100 %)	57 % (41–72 %)
By Antidepressant Initiation	25 % (18–32 %)	*75 %* (43–95 %)	*50 %* (35–65 %)
Sedating Medication	8 % (4–13 %)	8 % (0–38 %)	14 % (5–27 %)

See Table 2 for methodology and interpretation of symbols

We tested for infection using billing codes, initiation of antibiotics, and presence of a single elevated white blood cell count (WBC). Apathy was associated with infection as defined by initiation of antibiotic and an elevated WBC, though there was no association between hypersomnia and infection. We tested for depression by billing code and initiation of treatment with an antidepressant. Both apathy and hypersomnia were associated with both criteria for depression (the association of apathy and depression by billing code was close to statistical significance). We found no association of either condition with use of sedating medications (antipsychotics, benzodiazepines, meclizine, tizanidine and cyclobenzaprine).

Discussion

We found that 21 percent of the patients admitted to an acute rehabilitation hospital for ischemic or hemorrhagic stroke had apathy, and six percent had hypersomnia. Both apathy and hypersomnia were associated with higher rates of nursing home discharges and higher disability (by FIM score) at discharge, even after controlling for stroke severity at admission by a multi-system impairment measure, age, stroke type (hemorrhagic vs. ischemic), and time since stroke. To our knowledge, this is the first study to assess the effect of apathy and hypersomnia on outcome from the American acute rehabilitation population, and confirms the relevance of these disorders in this population.

Our findings on the prevalence of apathy and hypersomnia are generally in accord with previous studies, and reported differences are likely due to differences in patient population and methodology [10, 21]. Other studies of patients in similar time periods after stroke also found more disability in patients with apathy [12, 13, 25, 28] and hypersomnia [21]. We were unable to find other studies correlating apathy or hypersomnia with disposition location from acute rehabilitation.

We found that patients with both apathy and hypersomnia had more impaired overall cognition (abnormal MMSE or FIM problem solving) and were more likely to have deficits of sustained attention as reported by treating therapists (Table 2). Multiple other studies also found correlation of apathy with low MMSE [13, 25, 28], though [12] did not. Hypersomnia also correlated with motor impairment. These associations could reflect proximity of lesions underlying these conditions to those causing other impairments, or that the patients did not perform at their peak ability on impairment measures (i.e., inadequate effort devoted to task performance).

Limitations

The primary limitation of this study is that the data were collected retrospectively using a clinical database, rather than prospectively using formal research scales, and multiple raters to check reliability. Nevertheless, clinical records of individual therapists can be a meaningful and valid measure, as previous work on depression has shown that clinician impression can be as good as formal scales [29]. Clinician impression also offers the ability to assess patients with aphasia or cognitive deficits who cannot respond to the typical questionnaires used for apathy.

Other limitations include the role of possibly confounding factors such as infection and depression. Infections can modify the linkage between stroke and hypersomnia or apathy, as more severe strokes lead to infections (e.g., by dysphagia or urinary retention), which can lead to delirium, a disorder of arousal and attention [17]. We found no association of infections and hypersomnia. We found an unclear association of infection with apathy, as these patients were more likely to have an elevated WBC and be started on an antibiotic, but were no more likely to have a billing code reflecting an infection (Table 5). One interpretation that could be tested in a prospective study is that apathetic patients were more likely to be tested and treated for presumed infections that turned out to not be actual infections.

Depression is a potential confounder, as it is associated with worse stroke outcomes [30, 31], and can present with apathy [7]. Our database did not include formal testing of depression, but both groups were more likely to have billing codes consistent with depression (trend for apathy, significant for hypersomnia), and more than twice as likely to be treated with antidepressants (Table 5). Multiple previous studies found no association between depression and apathy after stroke [11, 12, 28, 32], suggesting that many of these patients were not actually depressed, but were treated as if they were. More studies are needed to disambiguate depression from apathy and hypersomnia in stroke patients, especially as there are reports of some antidepressants worsening apathy [33, 34].

Implications

While we have shown that apathy and hypersomnia are strongly associated with outcome from acute rehabilitation, we do not address the mechanism of this effect. There are several possibilities, not mutually exclusive. One possibility is that the behavioral abnormalities of these conditions result in more dependence on others, and therefore need for institutional care. This is supported by our finding of lower FIM score after controlling for overall impairment (Fig. 2b and Table 4). A second possibility is that patients with these conditions have slower rates of recovery due to decreased participation in therapy. This could be formally evaluated in a prospective study with serial measurements of impairment as well as participation. A third possibility is that both apathy and hypersomnia are signs of under-aroused brains, which are not performing as well as they could (as proposed in [35]).

Our findings demonstrate that apathy and hypersomnia are common in patients undergoing acute rehabilitation after stroke. Both conditions contributed to explaining the range of outcomes of patients in acute rehabilitation, and should be added as covariates in prospective observational and interventional studies. Both can be measured by purely observational means, allowing inclusion of patients with language and cognitive disorders [21, 32], and should use validated and blinded measures to the extent possible. If prospective trials confirm their relevance, targeted treatments should be developed based on studies of underlying mechanism. Adequate treatment at an early stage could potentially improve patient response to acute rehabilitation, thereby lowering costs of care by increasing the fraction of patients discharged home.

Acknowledgments We thank Cathy Dwyer, Janet Herbold and Michael Reding from the Burke Rehabilitation Hospital for assistance with acquiring and interpreting the original data. We gratefully acknowledge funding support from the Burke Medical Research Institute.

Conflict of Interest Ari Harris declares that he has no conflict of interest. Jessica Elder declares that she has no conflict of interest. Nicholas Schiff declares that he has no conflict of interest. Jonathan Victor declares that he has no conflict of interest. Andrew Goldfine declares that he has no conflict of interest.

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