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Longer lithium exposure is associated with better white matter integrity in older adults with bipolar disorder

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Abstract

Background—Bipolar Disorder (BD) is associated with cognitive dysfunction and structural brain abnormalities. In human and non-human studies, lithium has been related to neuroprotective and neurotrophic effects. We explored whether lithium treatment is related to better brain integrity and cognitive function in older adults with BD.

Methods—We examined cognitive and neuroimaging data in 58 individuals with BD mean (SD) age 64.5 (9.8) years and 21 mentally healthy comparators (“controls”) of similar age and education. Subjects received comprehensive neurocognitive assessment and structural brain imaging, examining total gray matter volume, overall white matter integrity (fractional anisotropy), and total white matter hyperintensity (WMH) burden.

Results—In comparison to controls, subjects with BD had worse overall cognitive performance, lower total gray matter volume, and lower white matter integrity. Among BD subjects, longer duration of lithium treatment was related to higher white matter integrity after controlling for age and vascular disease burden, but not with better cognitive performance.

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Conclusions—Lithium treatment appears to be related to better brain integrity in older individuals with BD, in particular in those who take it long-term. While intriguing, these findings need to be confirmed in a larger sample.

Keywords

Lithium; Bipolar Disorder; Neuroprotection

Introduction

Bipolar disorder (BD) afflicts over 100 million individuals worldwide.(1) While BD is costly and potentially devastating, not all individuals with BD experience a profoundly debilitating course or die prematurely.(2) Some of the heterogeneity in outcome may be related to the benefits of lithium treatment.(3, 4) In particular, lithium has been shown to reduce risk for suicide.(5) Lithium has also been associated with neurogenesis in the hippocampus,(6) up-regulation of important neurotrophic factors such as B-cell lymphoma 2 (Bcl-2) and brain-derived neurotrophic factor (BDNF),(7) and inhibition of glycogen synthase kinase 3 (GSK-3), a critical regulator of amyloid precursor protein involved in the development of amyloid-β plaques as well as hyper-phosphorylation of tau involved with neurofibrillary tangle formation and Alzheimer's disease (AD).(8) GSK-3 is also involved in the regulation of brain myelination.(9) The beneficial effects of lithium are supported by molecular and cellular data,(10) mouse and human data,(11-15) and epidemiologic data suggesting that lithium may decrease incidence of dementia.(16)

There is a large literature focused on BD and cognitive dysfunction or neuroimaging abnormalities in middle-aged and younger adults.(17, 18) In brief, BD is associated with impairments in attention, working memory, information-processing speed, and executive dysfunction.(19) Neuroimaging abnormalities include enlarged ventricles, increased periventricular white matter hyperintensities (WMHs) suggestive of vascular disease burden, and lower fractional anisotropy (FA) -- a measure of white matter tract integrity.(20, 21) Few studies have integrated neurocognitive with neuroimaging findings.(17, 18) In one such study, reductions in temporal lobe gray matter were correlated with impaired cognitive function and with the number of mood episodes over four years.(22) In mentally healthy older individuals, higher WMH burden has been associated with decreased information processing speed.(23)

Long-term treatment with lithium may affect brain structure, bringing about increased total gray matter, hippocampal and amygdala volumes, and enhanced white matter tract integrity (i.e., higher FA).(24, 25) It appears that lithium's effect on gray matter volume is larger than the effect of other mood stabilizers.(26, 27) However, this requires confirmation using controlled evaluation. Further, lithium binds to cholinergic receptors and it may thus negatively affect cognition.(28) However, the literature regarding lithium's effects on cognitive function is mixed. A meta-analysis of 12 studies involving 276 subjects who had taken lithium for a mean of 3.9 years, concluded that lithium had only few and minor negative effects on cognition.(29) These studies raise the possibility that lithium may not provide cognitive enhancement, but may protect from cognitive deterioration over the long-

term. While in contrast to lithium, data suggest that atypical antipsychotics negatively affect brain structures.(30-33)

Several studies have examined cognitive dysfunction and neuroimaging abnormalities in older adults with BD.(34-38) A benefit of studying older adults with BD is the opportunity to examine the long-term effects of medications. For example, Beyer and colleagues identified gray matter volume deficits in the inferior frontal lobe in BD in subjects (n=36) with mean (SD) age 58.2 (7.8) years compared to mentally healthy control subjects (n=29) of the same age.(39) They also found that the use of lithium was associated with increased hippocampal volume.

Over the past several years, we have been following a cohort of older adults with BD, of whom a subset has been treated with lithium for 10 or more years. This cohort provides an opportunity to examine whether long-term lithium exposure is related to better brain health, including better cognitive function. We examined the relationships among long-term lithium exposure, brain integrity, and cognitive function. Our hypotheses were that in individuals with BD, longer exposure to lithium would be associated with (a) better overall cognitive function and (b) better brain integrity as indexed with higher total gray matter, higher fractional anisotropy (FA), and lower white matter hyperintensity burden. To our knowledge, this is the first examination of the relationship among lithium use, cognitive function, and brain structure in older adults with BD. If long-term use of lithium has a meaningful impact on cognitive function or brain integrity, we would expect to see these effects in older adults with BD who are more likely to experience cognitive impairment or to show brain abnormalities and who have typically been taking lithium over longer period of time. In these analyses, we examined subjects based on overall lifetime lithium exposure, regardless of whether they were currently taking lithium. In addition, we selected overall, rather than regional, measures of brain integrity to examine generalized effects of lithium treatment and to minimize the number of statistical comparisons. In our regression analyses, we controlled for factors that influence brain integrity, such as age and vascular disease burden.(40-42) Given the evidence that antipsychotics can have negative effects on brain structures, we conducted exploratory analyses examining the influence of antipsychotics on brain integrity.

Methods

Subjects

Individuals with BD I or II were recruited in the outpatient clinics and inpatient units of Western Psychiatric Institute and Clinic or referred from the community. Comparator (“control”) subjects were individuals with no psychiatric or neurologic history selected to make the groups similar in age, education, and cardiovascular disease burden; they were recruited through health fairs, advertisements in local papers, and ongoing projects studying the relationship between late-life mood disorders and cognitive function (43, 44). In addition, comparator subjects with general medical burden comparable to subjects with BD were recruited in primary care practices (45). All subjects provided written informed consent, as required by the Institutional Review Board at the University of Pittsburgh.

Inclusion criteria required

age 50 years or older; clinical euthymia for four weeks preceding neuropsychological (NP) assessment with scores of 10 or less on both the 17-item Hamilton Rating Scale for Depression (HRSD) (46) and the Young Mania Rating Scale (YMRS) (47) at the time of assessment; ability to comprehend and speak English fluently; corrected visual ability to read newspaper headlines; and hearing capacity adequate to respond to a raised conversational voice.

Exclusion criteria were

pre-existing history of dementia or neurologic disorder affecting the central nervous system (for example, Parkinson's disease, traumatic brain injury, or multiple sclerosis); electro-convulsive therapy within the past six months; and substance abuse or dependence within the past twelve months. For this report, we focused on subjects who had completed both neuroimaging and neurocognitive assessment.

Diagnosis and Treatment

Diagnosis was established by the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID-IV) administered by trained clinicians. The majority of subjects were receiving treatment in our university-based clinics. In these clinics, the goals of the pharmacotherapy intervention for BD have been to maximize the appropriate use of lithium or divalproex, either singly or in combination, to achieve remission of acute mood episodes, maintain euthymia, and limit adjunctive anti-psychotic or antidepressant medication.(48)

Recruitment

From January 1, 2010 through December 31, 2012, 209 subjects signed consent, and 166 of those who met basic eligibility requirements underwent assessment with the Structured Clinical Interview for DSM-IV-TR (SCID). One hundred subjects with BD and 38 controls met all eligibility criteria, enrolled in the study, and completed baseline testing.

Imaging was completed on 62 subjects with BD and 21 controls. Reasons for not completing the MRI included refusal (11 with BD, 8 controls), safety or physical reasons (e.g., metal fragments; 14 with BD, 3 controls), clinical reasons (e.g., claustrophobia; 9 with BD, 3 controls), and scheduling reasons (4 with BD, 3 controls). Four subjects with BD were excluded from this analysis: one had his psychiatric diagnosis revised to schizoaffective disorder following baseline testing; one because of the identification of an unknown congenital brain abnormality; one because of severe motion artifacts during FLAIR acquisition: and one because the FLAIR was not obtained due to a technical error. Thus, 58 subjects with BD and 21 controls were included in this analysis. The 58 subjects with BD who had complete MRI data did not differ significantly from the subjects with BD who did not have MRI scans on any of the demographic or clinical measures.

Clinical Measures

General medical burden was assessed with the Cumulative Illness Rating Scale-Geriatric and vascular disease burden with the Framingham Stroke Risk Profile (FSRP).(49, 50) We

obtained information on pharmacotherapy exposure from interviewing the subjects, their family members, and all available records. Information was gathered on duration of lithium exposure (years). While some information was available on mean serum lithium levels, it was insufficient to include in our analyses. Duration of antipsychotic exposure in most subjects was substantially shorter than lithium exposure with much less reliable information available on its duration. Consequently, information on exposure was limited to whether a subject had taken an antipsychotic.

Neurocognitive Assessment

As described in a previous report, NP assessment encompassed 21 well-established and validated individual tests measuring multiple cognitive domains that were organized into domain scores, based on a factor analysis.(51) Aspects of executive function were distributed throughout all domains, but they predominantly loaded with information processing speed. The domains were information processing speed/executive, memory, language, and visuospatial ability. A global score was determined based on all 21 individual tests. We normalized raw scores for all individual tests using the baseline distribution of the mentally healthy comparators (i.e., comparators' performance on any test has a mean of 0 and a standard deviation of 1).(51)

Neuroimaging

MR brain imaging was performed in the University of Pittsburgh MR Research Center using a Siemens 3 Tesla TIM Trio scanner, with a 12-channel, phased-array head coil. The following oblique-axial series oriented to the plane connecting the anterior and posterior commissures were acquired to screen subjects for unexpected pathology and evaluate for brain tissue volume loss and white matter hyperintensities: 1) T1-weighted, 2) fast spin-echo T2-weighted, 3) fast spin-echo proton density-weighted, and 4) T2-weighted interleaved fast FLuid-Attenuated Inversion Recovery (FLAIR). A volumetric Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence was performed in the coronal plane. This sequence yields 176 continuous slices, maximizes contrast among gray matter, white matter, and cerebrospinal fluid, and provides high-resolution delineation of cortical and subcortical structures. Additionally, 12-30 direction Diffusion Tensor Images were acquired using the following parameters: 3mm slice thickness, 128×128mm resolution, 256×256mm FOV, 5300ms TR, 2500ms TI, 88ms TE, and 90° flip angle in the axial plane. TR=6400 ms, TE=89 ms, slice thickness=2.5 mm, number of slices=52, b=0, and 850, s/mm2, number of averages=2, GRAPPA2, resolution 2.5×2.5×2.5mm.

MR imaging: Automated Labeling Pathway

To determine regional gray and white brain volumes, Aizenstein and colleagues at the Geriatric Psychiatry Neuroimaging (GPN) Lab (www.gpn.pitt.edu) developed a procedure referred to as the Automated Labeling Pathway (ALP), which has been previously described.(52)

MR imaging of WMHs

FLAIR images were used for WMH quantification and localization. WMH quantification was done with automated method developed in the GPN Lab, which uses a fuzzy connected algorithm to segment the WMH(53) and atlas-based segmentation to localize the WMH into the anatomical space.(54) This method enables different thresholds for different WMH clusters and avoids a single cut-off threshold for the whole brain or brain slice. This method generates total WMH volumes, as well as WMH volumes for each frontal and subcortical white matter tract defined in the Johns Hopkins White Matter Atlas.(55)

MR imaging: DTI Labeling Pathway

The processing pathway uses Tract Based Spatial Statistics (56) to generate a voxel-wise cross-registered skeletonized FA maps in MNI space, and uses ALP, and WMH quantification and localization to generate white matter tract-specific ROI summary scores for normal appearing white matter (i.e., excluding WMH on the T2-FLAIR).

Statistical Analyses

We used descriptive statistics (mean and standard deviation or count and %) to characterize the subjects with BD versus the mentally healthy comparators and antipsychotic exposure within the BD subjects. We compared two groups using a t-test or a Wilcoxon exact test for continuous measures. We used a Chi-square test or a Fisher's exact test to examine categorical variables.

We used Pearson correlations to examine the association of global cognitive function with other measures in the subjects with BD. We entered variables that were correlated ($p \leq 0.10$) with global cognitive function in a regression model, using both backward and forward stepwise regression to obtain a stable parsimonious model predicting global cognition in subjects with BD. We used the same process to obtain a stable model for whole brain FA and WMH in subjects with BD.

Results

Subjects with BD and mentally healthy comparators had similar age and education. Subjects with BD had higher medical comorbidity (CIRS-G), but comparable cardiovascular disease burden and Framingham (FSRP) scores (see Table 1). Subjects with BD performed below mentally healthy comparators when looking at overall cognitive function (global score) and within specific domains with language ability being least affected and information processing speed/executive (speed/executive) function most affected (Table 1). Subjects with BD had lower total gray matter volume, lower white matter integrity (FA), but comparable amounts of WMH burden (Table 1).

Of the 58 subjects with BD, 33 had taken lithium and 25 had minimal ($\ll$ 1 year) or no exposure. The 33 subjects with lithium exposure had mean (SD) lithium treatment of 13.8 (12.4) years (median=11, min=1, max=43). There were no statistically significant differences between the 33 BD subjects with lithium exposure versus minimal exposure in age, gender, race, education, mood, and medical burden, including vascular burden (FSRP).

Age, education, race (Caucasian versus non-Caucasian), FSRP, total gray matter, white matter integrity (FA), and WMH were all correlated with global cognitive function ($p \leq 0.10$; Table 2). Duration of lithium treatment was not significantly associated with global cognitive function. In the stepwise regression, higher white matter integrity (FA) and more years of education were significantly associated with better global cognition (Table 3).

Age and FSRP, but not duration of lithium treatment, were correlated with total gray matter volume (Table 2).

Duration of lithium treatment, age, education, FSRP, race (Caucasian versus non-Caucasian), and CIRS-G were significantly associated with white matter integrity (FA) (Table 2). In the stepwise regression, longer duration of lithium treatment and younger age were significantly associated with higher FA (Table 3).

Lithium duration, age, education, FSRP, and CIRS-G were also significantly associated with WMH burden (Table 2). In the stepwise regression, only younger age was significantly associated with lower WMH burden (Table 3).

Subjects with antipsychotic exposure are presented in supplementary information (Table S1). Note that duration of antipsychotic exposure in most subjects was substantially shorter than lithium exposure with much less reliable information available on its duration. Information on exposure was limited to whether a subject had taken an antipsychotic. There were 26 subjects who had both lithium and antipsychotic exposure, 19 subjects with antipsychotic exposure and no lithium exposure, 7 with lithium and no antipsychotic exposure, and 6 with neither lithium nor antipsychotic exposure. Exploratory analyses of antipsychotic exposure revealed no differences in cognitive function and brain integrity between those with antipsychotic exposure versus not (see supplementary Table S2). The only significant difference between subjects with antipsychotic exposure versus not was age ($t[56]=3.0$; $p=0.05$). Those who were treated with at least one antipsychotic were younger than those never treated with an antipsychotic.

Discussion

We found that long-term lithium exposure is related to indices of better brain integrity. While our findings are intriguing, they need to be confirmed in a larger sample given various limitations. Foremost, our N is small and our examination is cross-sectional with lithium exposure determined retrospectively. Quantifying long-term lithium exposure in older adults can be imprecise. If it were available, more accurate quantification of lithium exposure, including adherence, dosage, stoppage, etc., would enhance the power to detect differences associated with it. Further, quantification of antipsychotic exposure using chlorpromazine equivalents would help account for antipsychotic effect on cognition and measures of brain integrity. Additional limitations include concerns about the generalizability of findings derived from patients treated in an academic medical center that prioritizes lithium as a first-line agent as well as survivorship bias.

Notwithstanding these limitations, our results are congruent with several human studies that have reported a neuroprotective effect of lithium in older persons (15, 57-60). Terao and

colleagues examined the clinical records of 1,423 outpatients, comparing older patients (n =30; mean (SD) age: 68.4 (5.2) years) with a history of taking lithium and matched controls (n=20; 70.3 (6.4) years). The patients treated with lithium had significantly higher Mini Mental State Exam scores.(61) Nunes and colleagues compared the prevalence of Alzheimer's disease (AD) in 66 older patients with BD treated with lithium chronically and 48 similar patients with BD without recent treatment with lithium. The mean (SD) age was 67.4 (4.7) years and AD was diagnosed in 3 (5%) of the patients on lithium versus 16 (33%) of those who were not on lithium, which was significantly lower.(60) When lithium was given to 71 patients with mild AD (mean (SD) age: 68.6 (7.8) years) in a single-blind, placebo-controlled, multi-center, no treatment effect on GSK-3 activity or CSF-based biomarker concentrations was observed over 10 weeks.(59)

Lithium was not associated with either a worsening or an improvement in global cognitive performance as measured by the ADAS-Cog subscale. However, in a subset of 27 subjects, lithium was associated with increased serum levels of BDNF and there was an improvement in ADAS-Cog subscale in those with increased BDNF(15, 62). Similarly, in a one-year placebo-controlled trial in 45 patients with amnestic mild cognitive impairment age 60 years and older, lithium reduced cognitive decline and CSF concentration of phosph-tau.(58)

Taken together, the human studies summarized above and our data suggest that lithium may enhance brain integrity positively when it is taken long-term and possibly early on. In particular, lithium might improve myelination by acting on neuroglial signaling pathways, such as GSK-3.(9) Given our intriguing findings and the findings of others summarized above, we suggest as a possible next step in the evaluation of the benefits of lithium treatment on brain health, a short-term (one-year) prospective randomized controlled trial of add-on lithium versus placebo in older adults with BD who have had minimal recent lithium exposure, evaluating both cognitive and brain imaging outcomes as well as measuring biomarkers (e.g., BDNF, GSK-3 activity, and inflammatory markers). Depending on the outcome of a short-term study, a larger, longer-term study may then be undertaken. If such future studies confirm the neuroprotective effect of lithium in BD, this may alter long-term treatment options in favor of lithium. Additionally, these studies may also suggest a role for lithium treatment for neuroprotection in individuals without BD who are at high risk for neurodegeneration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Baseline comparison between of subjects with BD and mentally healthy comparators

	Subjects with BD Mean (SD) or %(N) [n if reduced sample]	Controls Mean(SD) or %(N) [n if reduced sample]	Statistical test comparing BD subjects with BD and controls
N	58	21	
Age	64.5 (9.8)	65.6 (7.5)	t(77)=-0.48, p=0.63
%Female	70.7 (N=41)	52.4 (N=11)	Chi-sq(1)=2.3, p=0.13
%White	87.9 (N=51)	90.5 (N=19)	Fisher's Exact p=0.99
Education (years)	14.9 (3.2)	15.6 (2.9)	Wilcoxon Test p=0.49
YMRS score	2.40 (2.0)	0.381 (0.67)	Wilcoxon Test p<0.0001
HDRS 17-item score	4.05 (2.7)	1.38 (1.4)	Wilcoxon Test p<0.0001
Framingham Stroke Risk Profile*	0.109 (0.11)	0.075 (0.06)	t(77)=1.1, p=0.28
Cumulative Illness Rating Scale: Total	8.09 (3.2)	5.52 (3.6)	t(77)=3.0, p=0.003
Count	5.31 (2.0)	3.71 (2.3)	t(77)=3.0, p=0.003
Cognitive Domains: Global	-0.823 (1.2)	0.132 (0.44)	Wilcoxon Test p<0.0001
Visual	-0.758 (0.94)	0.088 (0.51)	t(64.9†)=-5.1, p<0.0001
Memory	-0.677 (0.90)	0.024 (0.60)	t(53.9†)=-4.0, p=0.0002
Language	-0.454 (0.94) [n=57]	0.198 (0.66)	t(76)=-2.9, p=0.005
Speed/Executive	-1.16 (2.6)	0.176 (0.48)	Wilcoxon Test p<0.0001
Imaging: Total Gray Matter Volume (normalized)	32.2 (4.1)	34.2 (3.1)	t(77)=-2.1, p=0.04
Overall White Matter Integrity (Fractional Anisotropy)	0.369 (0.02)	0.383 (0.01)	t(60.4†)=-3.5, p=0.0009
White Matter Hyperintensity Burden*	0.002 (0.003)	0.0007 (0.0009)	t(69.2†)=1.5, p= 0.14

*Log(X) transformation used for analyses. Means and standard deviations reported in original units

†Satterwaithe method for unequal variances

YMRS: Young Mania rating Scale; HDRS: Hamilton Depression Rating Scale

Table 2

Correlations among demographic and clinical variables with measures of cognition and brain integrity

Pearson Correlation Coefficients Prob > |r| under H0: Rho=0 Number of Observations				
	Global Cognitive Function	**Total Gray Matter Volume**	**Whole Brain Mean FA**	**nWMH***
Li Duration (years)*	0.165, p=0.22	-0.033, p=0.80	0.363, p=0.005	-0.342, p=0.009
Age	-0.501, p<0.0001	-0.381, p=0.003	-0.518, p<0.0001	0.541, p<0.0001
Education	0.564, p<0.0001	0.136, p=0.31	0.227, p=0.09	-0.335, p=0.01
Gender (Female)	-0.121, p=0.37	0.118, p=0.38	-0.077, p=0.56	0.127, p=0.34
Race (Caucasian)	0.253, p=0.06	0.048, p=0.72	0.217, p=0.10	0.086, p=0.52
YMRS score	-0.004, p=0.98	0.111, p=0.41	0.050, p=0.71	0.004, p=0.98
HDRS 17-item score	0.209, p=0.11	0.156, p=0.24	0.109, p=0.42	0.078, p=0.56
Framingham Stroke Risk Profile	-0.482, p=0.0001	-0.266, p=0.04	-0.420, p=0.001	0.381, p=0.003
Cumulative Illness Rating Scale: Total	-0.058, p=0.67	-0.120, p=0.37	-0.224, p=0.09	0.240, p=0.07
Count	-0.068, p=0.61	-0.061, p=0.65	-0.160, p=0.23	0.240, p=0.07
Cognitive Domains: Global	------	0.299, p=0.02	0.533, p<0.0001	-0.466, p=0.0002
Visual	0.873, p<0.0001	0.141, p=0.29	0.489, p<0.0001	-0.421, p=0.001
Memory	0.774, p<0.0001	0.207, p=0.12	0.382, p=0.003	-0.486, p=0.0001
Language	0.694, p<0.0001 [N=57]	0.199, p=0.14 [N=57]	0.323, p=0.01 [N=57]	-0.166, p=0.22 [N=57]
Speed/Executive	0.893, p<0.0001	0.378, p=0.003	0.532, p<0.0001	-0.384, p=0.003
Total Gray Matter Volume (normalized)	0.299, p=0.02	-----	0.340, p=0.009	-0.102, p=0.44
Overall White Matter Integrity (Fractional Anisotropy)	0.533, p<0.0001	0.340, p=0.009	------	-0.382, p=0.003
White Matter Hyperintensity Burden*	-0.466, p=0.0002	-0.102, p=0.44	-0.382, p=0.003	------

*Log(X) transformation used for analyses

YMRS: Young Mania rating Scale; HDRS: Hamilton Depression Rating Scale

Table 3
Multivariate regressions in BD subjects

Model	Beta (standard error), p-value; standardized beta
Outcome:	Global Cognition
	F(2, 55)=26.6, p<0.0001, R^2=0.49
Intercept	-12.5 (2.0), p<0.0001
Overall White Matter Integrity (Fractional Anisotropy)	24.5 (5.7), p<0.0001; stb=0.43
Education	0.180 (0.04), p<0.0001; stb=0.47
Outcome:	Overall White Matter Integrity (Fractional Anisotropy)
	F(2, 55)=16.4, p<0.0001 R^2=0.37
Intercept	0.433 (0.02), p<0.0001
Lithium Duration (years)	0.0006 (0.0002), p=0.004; stb=0.33
Age	-0.001 (0.0002), p<0.0001; stb=-0.49
Outcome:	White Matter Hyperintensity Burden
	F(1, 56)=23.1, p<0.0001, R^2=0.29
Intercept	-12.8 (1.2), p<0.0001
Age	0.088 (0.02), p<0.0001; stb=0.54

* Log(X) transformation used for analyses