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Effects of Metabolic Syndrome on Language Functions in Aging

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Abstract

This study explored effects of the metabolic syndrome (MetS) on language in aging. MetS is a constellation of five vascular and metabolic risk factors associated with the development of chronic diseases and increased risk of mortality, as well as brain and cognitive impairments. We tested 281 English-speaking older adults aged 55–84, free of stroke and dementia. Presence of MetS was based on the harmonized criteria (Alberti et al., 2009). Language performance was assessed by measures of accuracy and reaction time on two tasks of lexical retrieval and two tasks of sentence processing. Regression analyses, adjusted for age, education, gender, diabetes, hypertension, and heart disease, demonstrated that participants with MetS had significantly lower accuracy on measures of lexical retrieval (action naming) and sentence processing (embedded sentences, both subject and object relative clauses). Reaction time was slightly faster on the test of embedded sentences among those with MetS. MetS adversely affects the language performance of older adults, impairing accuracy of both lexical retrieval and sentence processing. This finding reinforces and extends results of earlier research documenting the negative influence of potentially treatable medical conditions (diabetes, hypertension) on language performance in aging. The unanticipated finding that persons with MetS were faster in processing embedded sentences may represent an impairment of timing functions among older individuals with MetS. (*JINS*, 2015, *21*, 116–125)

Keywords: Health, Risk factors, Lexical retrieval, Sentence processing, Cerebrovascular, Accuracy, Reaction time

INTRODUCTION

This study presents the metabolic syndrome (MetS) as an example of a health variable that contributes to age-related changes in language performance. Theoretical accounts of such changes often appeal to the process of "aging" itself, failing to consider health status as a potential contributor to the observed decrements (Spiro & Brady, 2011). However, while health status is gradually becoming recognized as an important factor affecting cognitive capacities in aging (e.g., Morra, Zade, McGlinchey, & Milberg, 2013; van den Berg, Kloppenborg, Kessels, Kappelle, & Biessels, 2009; Waldstein, Wendell, & Katzel, 2010), few studies have examined its contribution to compromised language performance among the elderly.

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Our work is one exception, demonstrating that hypertension and diabetes mellitus impair older adults' lexical retrieval and sentence processing abilities (Albert et al., 2009; Cahana-Amitay et al., 2013). The current study extends these earlier observations by considering the impact of the metabolic syndrome—a constellation of vascular and metabolic risk factors (blood pressure, diabetes, cholesterol, body mass index) on these key aspects of language functioning in aging. It is the first study to demonstrate that the *combined* effect of cerebrovascular risk factors on language changes in the aging brain is independent of these factors individually.

Metabolic syndrome (MetS) comprises several interrelated risk factors of metabolic origin (e.g., Grundy et al., 2005). Criteria for defining MetS have evolved since the World Health Organization's (WHO; 1988) initial proposal, in terms of biomarker cutoffs, relative emphasis assigned to one or more criteria, and whether treatment for such condition(s) is a disease indicator (Ford, Li, & Zhao, 2010). Different definitions were "harmonized" by Alberti et al. (2009) (Table 1 below),

Table 1. Harmonized criteria for the metabolic syndrome (Alberti et al., 2009)

Measure	Cut-point
Elevated waist circumference	Population- and country-specific definitions[a]
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator[b])	≥150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator[b])	<40 mg/dL (1.0 mmol/L) in men; <50 mg/dL (1.3 mmol/L) in women
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥130 and/or diastolic ≥85 mm Hg
Elevated fasting glucose[c] (drug treatment of elevated glucose is an alternate indicator)	≥100 mg/dL

Note. HDL-C = high-density lipoprotein cholesterol.
[a]Cut-points for defining waist circumference vary by country, race/ethnicity, and gender. For White Americans, they are: >102 cm for men, >88 cm for women.
[b]The most commonly used drugs for elevated triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking one of these drugs can be presumed to have high triglycerides and low HDL-C. High-dose ω-3 fatty acids presumes high triglycerides.
[c]Most persons with type 2 diabetes mellitus will have elevated fasting glucose by these criteria.

such that presence of any three of the five listed criteria warrants a MetS diagnosis. This study used this "harmonized" definition.

MetS prevalence increases with age (Cornier et al., 2008), and can lead to development of cardiovascular disease and diabetes (e.g., McNeill et al., 2006), impaired brain structure and function (e.g., Yates, Sweat, Yau, Turchiano, & Convit, 2012), diminished cognitive functioning (e.g., Yaffe, Haan, Blackwell, Cherkasova, Whitmer, & West, 2007), onset of dementia (e.g., Milionis, Florentin, & Giannopoulos, 2008), and increased risk of mortality (e.g., Ford, 2005). Thus, MetS offers a useful means for exploring the combined effects of multiple risk factors and can lead to a more complete understanding of age-related language declines.

Presence of MetS among older adults entails neural changes resulting from vascular and metabolic problems, often with corresponding cognitive decrements. For example, brain changes related to hypertension involve compromised white matter integrity, grey matter atrophy in frontal regions, and reduced memory and executive functions (Frisoni, Galluzzi, Pantoni, & Filippi, 2007). Some of the health conditions associated with MetS are included in well-established risk factor indices, such as the Framingham Stroke Risk Profile (FSRP) or Dementia Risk Indices (Barnes & Yaffe, 2009). These indices show that higher health risks (measured, for example, by differences between the first and fourth quartile of FSRP) are associated with decreases in brain structure (e.g., reduction in total cerebral brain volume ratio) or brain function (e.g., poor performance on cognitive tests) (Barnes et al., 2009).

Evidence describing neural changes associated with MetS when considered as a *constellation* of risk factors, however, is scarce. Neuroimaging findings indicate an association between MetS and increased risk for lacunar infarction (Bokura, Nagai, Oguro, Kobayashi, & Yamaguchi, 2010; Kwon et al., 2009; Park et al., 2008), periventricular white matter changes and subcortical white matter damage (Bokura, Yamaguchi, Iijima, Nagai, & Oguro, 2008), and microstructural changes in white matter, especially in frontal and temporal regions (Segura, Jurado, Freixenet, Falcon, Junque, & Arboix, 2009). The general observation is that the more MetS risk factors present, the greater the white matter changes observed (Bokura et al., 2008; Kwon et al., 2009).

Compromised brain structure resulting from peripheral metabolic deficiencies associated with cerebrovascular risk factors also occur in cognitively intact adults, indicating that onset of such changes might be subclinical, preceding disease manifestations and measurable behavioral declines (Leritz et al., 2010; Leritz, McGlinchey, Kellison, Rudolph, & Milberg, 2011; Salat et al., 2012). Such neural changes can affect persons as young as 55 years of age (e.g., Jeerakathil et al., 2004), suggesting that "systemic cerebrovascular health may play a role in neural tissue degeneration classically ascribed to aging" (Salat et al., 2012, p. 181).

Presence of MetS in older adults is associated with impairments in several cognitive domains, including memory, executive functioning, visuospatial abilities, and IQ (e.g., Bokura et al., 2010; Segura et al., 2009). MetS-related cognitive decrements are exacerbated in persons with high levels of inflammation, who also manifest poor performance on measures of global cognition, immediate and delayed recall, processing speed, and fluid intelligence (Yaffe et al., 2007).

Effects of MetS on language performance in aging are currently unknown. The presence of individual cerebrovascular risk factors in older adults impairs their performance on cognitive tasks involving verbal components, as in confrontation naming and verbal fluency (Waldstein et al., 2010), as well as verbal and logical memory (e.g., Awad, Gagnon, & Messier, 2004; Lamport, Lawton, Mansfield, & Dye, 2009). These findings, however, are sparse and inconsistent (van den Berg et al., 2009), likely because of methodological differences among studies in design, language measures used, and populations sampled (Cahana-Amitay et al., 2013). Nonetheless, they indicate that cerebrovascular and metabolic derangements may underlie some of the age-related decrements in language.

Only two studies have directly examined cerebrovascular and metabolic effects on language functions in aging, exploring the impact of hypertension and diabetes mellitus on lexical retrieval and sentence processing abilities. Albert et al. (2009) demonstrated that hypertension, but not diabetes, was

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associated with reductions in word-finding abilities of older adults. Cahana-Amitay et al. (2013) demonstrated adverse effects of both hypertension and diabetes on accuracy in sentence processing. In particular, diabetes impaired comprehension of syntactically complex (embedded) sentences, and hypertension impaired comprehension of sentences containing two negative markers. We related these findings to microvascular changes in white matter subserving frontal brain systems, which together with metabolic deficiency and reduced glycemic control impair neuronal function throughout the brain. This proposal can be assessed more directly by examining the effects of MetS on age-related language performance, given that this clinical syndrome combines cerebrovascular and metabolic risk factors. To our knowledge, no studies have examined the synergistic effects of the risk factors comprising MetS on language functions in aging, a gap we address here.

In this study, we asked whether MetS was associated with language performance on lexical retrieval and sentence processing tasks among older adults. Our use of MetS as an index of cerebrovascular risk is similar to use of the Framingham Stroke Risk Profile (Wolf, 2009) or indices of allostatic load (Seeman, Epel, Gruenewald, Karlamangla, & McEwen, 2010) to explore effects of health risk factors on cognition (Karlamangla et al., 2014). Namely, we considered MetS as a risk index linking clinical phenomena to language performance through its effects on the brain *via* vascular and metabolic pathways. We predicted that those with MetS (i.e., at greater risk of vascular/metabolic impairment) would demonstrate worse language performance, compared to those without MetS.

METHOD

Sample

Participants were 281 adults aged 55 to 84 years who were tested in the "Language in the Aging Brain" project (Albert et al., 2009; Cahana-Amitay et al., 2013; Goral et al., 2011). They completed a self-report questionnaire, a medical examination, and a language and cognitive testing protocol.

Procedure

Participants were recruited by flyers, mail, and newspaper and were screened for eligibility by telephone. Prospective participants were mailed a Health and Behavior Survey (HBS) which assessed demographic and health information, including health history, self-reports of physician diagnoses, medical or psychological treatment, health behaviors (alcohol and tobacco), and medication use. Eligibility criteria included being a native English speaker; no history of stroke, dementia, or loss of consciousness; no medical procedures involving general anesthesia within the past 6 months; and no radiation treatment within the past year, which could have affected cognitive/linguistic performance.

Eligible participants were then scheduled for an initial visit, during which they were administered a standardized physical exam conducted by a registered nurse, who verified the information provided in the self-report health survey. She also conducted a health and neurological examination. Blood was drawn after a 12-hr overnight fast to assay a range of biomarkers. Participants then began a battery of cognitive and language tests. The tests were given in two sessions of 2–3 hr each, scheduled within a 6-week period. This study was approved by the Institutional Review Boards of the Veterans Affairs Boston Healthcare System and the Boston University Medical Campus; all participants provided written informed consent.

Biomedical Measures

Ascertainment of MetS was based on the harmonized criteria of Alberti et al. (2009) (Table 1). Waist circumference was measured to the nearest 0.1 cm, with measurements greater than 102 cm for men and 88 cm for women indicating obesity. Abnormal biomarkers of lipids included values of triglycerides equal to or greater than 150 mg/dL, and values of high-density lipoprotein (HDL) below 40 mg/dL for men and 50 mg/dL for women. Abnormal blood pressure was defined by the mean of four readings greater than 130 mm/Hg systolic and/or 95 mm/Hg diastolic at rest. Abnormal levels of glucose were determined if fasting-glucose levels equaled or exceeded 100 mg/dL. Self-reports of physician diagnosis or use of anti-diabetic, anti-hypertensive, and cholesterol-lowering medications were also considered disease indicators.

Language Measures

We assessed two aspects of language known to decline with age: lexical retrieval and sentence processing. Measures were obtained from four tasks, two of which were administered in the first visit [Boston Naming Test (BNT), Embedded Sentences (ES)] and two in the second [Action Naming Test (ANT), Multiple Negatives (MN)]. Because some participants did not return for the second visit, we had slightly fewer cases on the second set of tasks.

All tasks were administered by computer using E-Prime software (Psychology Software Tools, Inc.). In the lexical retrieval tasks, the participant responded by verbally identifying the picture shown on the computer screen. In the sentence processing tasks, response involved a button press to indicate whether a sentence was judged as "likely" or "unlikely." Both accuracy and reaction time (RT) were assessed for each task. For the lexical retrieval tasks, correct responses were counted if they were produced unprompted or in response to a phonemic cue. The total number of correct responses was divided by the total number of properly administered items, and converted to percent correct. Response time for lexical retrieval tasks was recorded at voice onset. RTs were excluded where responses began with vocalizations unrelated to the name of the stimuli (e.g., a cough).

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Response times for the sentence processing tasks were recorded from the offset of the final word of each sentence. For each task, a participant's response time was computed as the mean RT for correct responses only, after excluding values outside the participant's mean ± 2.5SD.

Two picture-naming tests were used to assess lexical retrieval: (1) ANT (Obler & Albert, 1979) and (2) BNT (Kaplan, Goodglass, & Weintraub, 1983). In the ANT, participants named the action depicted in a picture. The stimuli consisted of 57 simple black and white line drawings that appeared one at a time on the computer screen. If the participant failed to provide a response within 20 s of picture presentation, or named an action incorrectly, the examiner provided a semantic and then, if necessary, a phonemic cue. The BNT followed the exact same procedure but for drawings of objects, and included 60 items.

Two tasks were used to assess sentence comprehension: (1) ES and (2) MN (described in Goral et al., 2011 and Cahana-Amitay et al., 2013). Both tasks comprised prerecorded sentences spoken at normal speech rate. The participant listened to the sentences through headphones and judged the likelihood of each sentence by pressing a "likely" or "unlikely" button on a response box.

In the ES task, syntactic structure and plausibility were manipulated. The participant listened to a total of 96 sentences, including 28 object-relative (OR) sentences (e.g., *The jogger identified the robber that the policeman arrested*), 28 subject-relative (SR) sentences (e.g., *The violinist listened to the conductor that directed the orchestra*), 28 control (C) sentences (e.g., *The student filed a complaint when the professor fired the assistant*), and four distractor sentences per sentence type. Sentences were equally divided between plausible (*The jogger identified the robber that the policeman arrested*) and implausible (*The neighbor complained to the landlord that the tenant evicted*). All sentences were controlled for length comprising the same number of propositions and content words (for target sentences, total number of words averaged nine; for control sentences, eleven). In the target sentences, the second half of the sentence contained the information crucial for establishing the referential link between the noun phrase and its corresponding structural position inside the relative clause (subject or object). The distractors, in contrast, contained this information in the first part of the sentence. Their administration was designed to prevent the participants from developing a tendency to focus primarily on the second part of the sentences presented.

In the MN task, both number of negative markers and sentence plausibility were manipulated. A participant listened to a total of 50 sentences. The target stimuli consisted of 30 sentences: ten 0-negative (0N) sentences (e.g., *Tyler had been smiling, so we believe he was happy*), ten 1-negative (1N) sentences (e.g., *Because the book was long, I could not read it quickly*), and ten 2-negative (2N) sentences (e.g., *Because the ceiling light is not off, the room is not dark*). The additional 20 sentences consisted of ten 11-word and ten 12-word non-negative sentences, which we added to the stimuli to adjust for differences in sentence length among the three types of target sentences. For each group of sentences, half were plausible and half implausible (plausible: *Because the book was long, I could not read it quickly;* implausible: *Because the book was short, I could not read it quickly*).

Analyses

First, we determined whether a participant met criteria for MetS. We imputed missing data on any of the biomedical values used to define MetS (i.e., waist circumference, glucose, triglycerides, systolic and diastolic blood pressure), using the expectation-maximization (EM) algorithm (Graham, 2012). This algorithm is an iterative method for obtaining maximum likelihood (ML) estimators of means and covariances (but not standard errors) when some of the data are missing (Allison, 2001; Graham, 2009). While EM estimates are not suitable for hypothesis testing, they are valuable when used as input into other analyses (e.g., regression analysis). We included age, education, gender, MetS biomarkers and several other biomarkers [i.e., insulin, hemoglobin A1c (HbA1c), body mass index (BMI), in this estimation (75% of cases; n = 217) had all variables; 94% (n = 273) had all MetS variables]. Combining the imputed biomedical variables with information on self-report of physician diagnosis and use of medications as reported in the HBS, we determined MetS status for each participant. Specifically, we counted the number of harmonized criteria for each participant, and those who reported three or more were considered to have MetS.

Second, we compared demographics, biomarkers, and language outcomes between participants with and without MetS, using t tests for continuous and chi-squares for categorical variables. Finally, we used regression analysis to examine whether the language measures differed among those with and without MetS, adjusting for age, education, gender, and the presence of several diseases.

RESULTS

Participants were aged 55 to 84 years, with a mean age of 72 (SD = 7.4). Gender was split nearly evenly, with 51% men and 49% women. The average education was 15 years (SD = 2.0), ranging from 9 to 17+ years.

The prevalence of MetS was 41%, comparable to the 36% reported by Ford et al. (2010) for a sample of US adults aged over 20. Among those 50 and older, Ford's data suggested a prevalence of 49% in men and 52% in women; in our sample, we found that 34% of women and 46% of men met the harmonized criteria for MetS.

Table 2 presents comparisons of demographic and biomedical variables by MetS status. In addition, standardized mean differences using Hedges' g (Fritz, Morris, & Richler, 2012) are shown for continuous variables, and phi coefficients for categorical variables. With the exception of age (p = .2)

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Table 2. Demographics and biomedical variables by metabolic syndrome status

	Presence of MetS							
	No (n = 167)		Yes (n = 114)					
	Mean/%	*SD*	Mean/%	*SD*	t/x2	df	*p*	Standardized Mean difference[e]
Age	72.5	7.3	71.3	7.4	1.30	279	.2	0.16
Female	55%		41%		4.79	1	<.03	–0.13
Years educ	15.3	1.9	14.6	2.0	2.85	273	<.005	0.36
SBP[a]	125.1	17.2	131.3	13.8	3.21	279	<.002	–0.38
DBP[a]	67.6	9.1	70.0	10.8	1.95	279	.053	–0.24
Waist circ.[b]	88.6	11.7	105.5	11.6	11.91	279	<.001	–1.18
Triglycerides[c]	83.5	31.4	148.7	49.6	10.84	279	<.001	–1.11
HDL[c]	60.3	13.9	42.5	9.7	11.84	279	<.001	1.18
Glucose[c]	96.7	22.5	110.6	23.7	4.98	279	<.001	–0.58
Hb A1c (%)	5.65	0.77	5.94	1.28	2.39	279	<.02	–0.29
Insulin[d]	5.65	5.4	11.4	7.9	6.49	224	<.001	–0.81
Disease prevalence (%)								
Diabetes	4.8		29.8		33.40	1	<.001	–0.34
Hypertension	43.1		76.3		30.40	1	<.001	–0.33
Heart disease	34.7		55.3		11.65	1	<.001	–0.11

Note. HDL = high-density lipoprotein; HbA1c = hemoglobin A1c; SBP = systolic blood pressure; DBP = diastolic blood pressure
[a]Measured in cm.
[b]Measured in mm/Hg.
[c]Measured in mg/dL.
[d]Units for insulin: μIU/mL
[e]Hedges' g was used for continuous variables; the phi coefficient for categorical variables.

and diastolic blood pressure (p = .053), all other variables differed between those with and without MetS, with standardized mean differences ranging from 25% of an SD (diastolic blood pressure) to 118% [waist circumference, high-density lipoprotein (HDL)]. Those with MetS were less likely to be female and had somewhat less education. Systolic blood pressure, waist circumference, triglycerides, glucose, HbA1c, and insulin were higher, and HDL lower, in the MetS group, as expected. Those with MetS were also more likely to have diabetes, hypertension, and heart disease.

We used *t* tests to compare mean performance (both accuracy and RT) on the language tasks between those with and without MetS, shown in Table 3. For the sentence processing tasks, performances are reported overall and by sentence type. Naming was significantly affected by presence of MetS in terms of reduced accuracy on ANT (95.2% *vs*. 96.4%, p = .012). Sentence processing was significantly affected by presence of MetS in terms of reduced accuracy on ES overall (87.9% *vs*. 90.4%; p = .002). When analyzed by sentence type, effects were observed for complex sentences (subject- and object-relatives) (SR: 87.4% *vs*. 91.2%; p < .003; OR: 83.8% *vs*. 89%; p < .001), but not for control sentences. Participants with MetS had marginally faster RTs to ES items (1.586 *vs*. 1.753 s; p = .054), observed for subject-relative (SR) sentences (1.572 *vs*. 1.770 s; p = .034). Effect size estimates ranged from 83% to 97% *SD* for accuracy, and were lower and more heterogeneous across tasks for RT, ranging from 36% to 79% of an *SD* (see Table 3).

Using multiple regression analysis, we estimated models examining the impact of MetS presence on naming tasks (ANT, BNT). We also examined the impact of MetS on each sentence type within the two sentence processing tasks ES (C, SR, OR) and MN (0N, 1N, 2N) for both accuracy and reaction time. All models were adjusted for age, gender, and years of education. The first model (Model 1) adjusts only for the effects of these demographics; in a second model, we also controlled for the presence of diabetes, hypertension, and heart disease (Model 2). Tables 4 (response accuracy) and 5 (reaction time) display the results for these two models, showing the least-squares means for those with and without MetS. Least-squares means are estimated means of the language outcomes, adjusted for the effects of the included covariates.

Table 4 compares mean accuracy on the language tasks between those with and without MetS. For Model 1 (demographics only), persons with MetS were significantly less accurate on the ANT (95.2% *vs*. 96.4%; p = .019), but did not differ from those without MetS on the BNT. Sentence processing was significantly affected by presence of MetS in terms of reduced accuracy on ES (subject- and object-relatives) (SR: 87.47% *vs*. 91.10%; p = .005; OR: 84.23% *vs*. 88.68%; p = .001), but not for control sentences. Adjusting for medical conditions in addition to demographics (Model 2), the negative effect of MetS on ANT was now marginally significant ($p \leq .10$), and the lower accuracy of those with MetS remaining significant for accuracy on two ES sentence types (SR and OR subtasks). A marginal effect

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Table 3. Language tasks by presence of metabolic syndrome

	MetS NO		MetS YES					
Accuracy	Mean	*SD*	Mean	*SD*	t	df	*p*	Standardized Mean difference[a]
ANT	96.4	3.5	95.2	4.3	2.55	257	.012	–.97
BNT	93.0	6.1	92.1	7.8	1.05	277	.3	–.94
ES	90.5	6.7	87.9	10.,6	3.18	257	.002	–.93
MN	92.9	5.8	92.0	6.6	1.11	241	.27	–.92
ES subtasks								
C	91.1	7.3	89.7	11.1	1.22	256	.23	–.92
SR	91.2	8.0	87.4	12.2	3.01	256	<.003	–.92
OR	89.0	9.1	83.8	12.9	3.77	256	<.001	–.93
MN subtasks	96.2	6.5	96.7	6.1	–0.55	239	.6	–.93
0N								
1N	93.4	9.4	91.8	10.6	1.23	239	.22	–.91
2N	82.3	14.5	80.6	15.7	0.87	239	.4	–.83
Reaction time								
ANT	1365.3	315.8	1337.0	306.3	0.71	251	.5	–.79
BNT	1297.5	280.6	1298.6	260.8	–0.03	273	.9	–.79
ES	1753.3	712.6	1586.1	632.7	1.94	256	.054	–.67
MN	955.2	498.8	972.0	530.0	–0.25	239	.8	–.46
ES subtasks								
C	1620.7	644.3	1506.1	584.1	1.45	255	.15	–.65
SR	1769.9	759.5	1571.7	678.1	2.14	255	.034	–.66
OR	1929.2	846.6	1735.0	740.5	1.90	256	.059	–.65
MN subtasks	750.6	463.2	741.9	439.6	0.15	239	.9	–.41
0N								
1N	1079.2	653.7	1095.6	749.8	–0.18	238	.9	–.36
2N	1621.4	778.6	1708.1	817.1	–0.82	233	.42	–.48

Note. ANT = Action Naming Test; BNT = Boston Naming Test; ES = Test of Embedded Sentences; MN = Test of Sentences with Multiple Negatives. C = Control Sentences; SR = Subject-Relative Sentences; OR = Object-Relative Sentences. 0N = Zero Negative Sentences; 1N = One-Negative Sentences; 2N = Two-Negative Sentences.
[a]Hedges' g was used for continuous variables; the phi coefficient for categorical variables.

was observed for MN accuracy, where the presence of MetS improved accuracy only of the zero negative control sentences (0N) (97.37% *vs*. 95.67%; $p = .089$).

Table 5 shows that, adjusting for demographics, participants with MetS had faster RTs observed for subject-relative (SR) sentences on the ES task (1.573 *vs*. 1.773 s; $p = .031$).

Table 4. Results of regression models for effect of metabolic syndrome (MetS) on language tasks – accuracy

	Model 1 - adjusted for demographics						Model 2 - adjusted for demographics & disease					
	Mets-Yes		Mets-No				Mets-Yes		Mets-No			
Task	*Mean Accuracy (%)*	*SE*	*Mean Accuracy (%)*	*SE*	t	prob(t)	*Mean Accuracy (%)*	*SE*	*Mean Accuracy (%)*	*SE*	t	prob(t)
Lexical Retrieval												
ANT	95.22	0.39	96.40	0.31	–2.35	**0.0195**	95.36	0.41	96.30	0.32	–1.69	**0.0917**
BNT	92.16	0.63	92.86	0.50	–0.86	0.391	92.37	0.66	92.72	0.522	–0.40	0.69
Sentence Processing												
ES	87.23	0.82	90.24	0.67	–2.79	0.006	87.06	0.89	90.36	0.72	–2.70	0.08
C	89.79	0.91	90.99	0.74	–1.01	0.310	89.80	0.98	90.98	0.79	–0.87	0.385
SR	87.47	–2.82	91.10	0.80	–2.82	**0.005**	87.54	1.63	91.06	0.85	–2.40	**0.017**
OR	84.23	1.03	88.68	0.84	–3.28	**0.001**	83.49	1.11	89.18	0.89	–3.71	**0.0003**
MN	92.24	0.63	92.87	0.50	–0.78	0.47	93.05	0.67	92.34	0.52	0.77	0.44
0N	96.79	0.66	96.05	0.53	0.86	0.390	97.36	0.72	95.67	0.57	1.71	0.089
1N	92.01	1.01	93.35	0.92	–1.02	0.311	92.37	1.10	93.11	0.87	–0.49	0.63
2N	81.21	1.54	82.13	1.24	–0.46	0.645	83.31	1.64	80.74	1.29	1.15	0.25

Note. ANT = Actions Naming Test; BNT = Boston Naming Test; ES = Test of Embedded Sentences; MN = Test of Sentences with Multiple Negatives. C = Control Sentences; SR = Subject-Relative Sentences; OR = Object-Relative Sentences. 0N = Zero Negative Sentences; 1N = One-Negative Sentences; 2N = Two-Negative Sentences.

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Table 5. Results of regression models for effect of metabolic syndrome (MetS) on language tasks– reaction time

	Model 1 - adjusted for demographics						Model 2 - adjusted for demographics & disease					
	MetS - Yes		MetS - No				Mets - Yes		Mets - No			
Task	*Mean* RT (ms)	*SE*	*Mean RT (ms)*	*SE*	t	prob(t)	*Mean RT (ms)*	*SE*	*Mean RT (ms)*	*SE*	t	prob(t)
Lexical retrieval												
ANT	1329.43	31.96	1366.87	25.58	–0.90	0.368	1303.74	34.19	1383.54	26.70	–1.72	0.086
BNT	1282.73	26.10	1303.28	21.40	–0.60	0.550	1275.35	27.85	1308.30	22.39	–0.87	0.387
Sentence processing												
ES	1597.32	65.09	1756.28	53.38	–1.86	0.065	1610.32	70.78	1747.41	56.71	–1.41	0.16
C	1533.39	59.81	1618.36	48.82	–1.08	0.282	1530.88	64.98	1620.06	51.78	–1.00	0.318
SR	1573.78	70.22	1773.63	57.31	–2.17	**0.031**	1599.56	76.28	1756.21	60.80	–1.50	0.136
OR	1745.68	77.69	1932.06	63.71	–1.82	0.070	1763.44	84.55	1919.94	67.75	–1.34	0.180
MN	950.87	51.68	965.87	41.85	–0.22	0.82	954.84	56.47	963.23	44.57	–0.11	0.92
0N	726.89	45.60	759.16	36.13	–0.54	0.589	732.99	49.87	755.11	39.36	–0.32	0.75
1N	1068.41	71.21	1095.69	57.32	–0.29	0.769	1059.67	77.77	1101.44	60.98	–0.39	0.69
2N	1685.29	82.64	1630.01	67.12	0.51	0.610	1707.81	89.84	1614.94	71.15	0.75	0.45

Note. ANT = Actions Naming Test; BNT = Boston Naming Test; ES = Test of Embedded Sentences; MN = Test of Sentences with Multiple Negatives. C = Control Sentences; SR = Subject-Relative Sentences; OR = Object-Relative Sentences. 0N = Zero Negative Sentences; 1N = One-Negative Sentences; 2N = Two-Negative Sentences.

When diabetes, hypertension, and CHD were included (Model 2), the effect of MetS on ES RT (SR subtask) was no longer significant. No other effect of MetS on reaction time was significant in either Model 1 or Model 2.

In summary, the results of the regression analyses largely confirm those reported in Table 3 (the unadjusted mean comparisons), but revealed two additional, marginal findings. Model 2 (demographics plus disease) showed that performance on accuracy for 0N and reaction time for ANT differed by MetS status, such that those with MetS had better 0N accuracy and faster ANT RT.

DISCUSSION

In this study, presence of the metabolic syndrome was linked to impaired language performance of older adults, adversely affecting accuracy on tasks of both lexical retrieval and sentence processing. These findings continued to hold even after age was controlled, lending support to Spiro and Brady's (2011) argument that adverse changes in cardiovascular and metabolic health, rather than age *per se*, are a crucial factor accounting for observed cognitive decrements in aging.

Because MetS is a syndrome consisting of multiple cerebrovascular risk factors, united perhaps by shared biological mechanisms (e.g., insulin resistance), it offers a conceptually appealing, clinically-driven approach to characterizing the combined impact of cerebrovascular and metabolic risk factors on language. Although other health risk factor indices exist, such as the Framingham Stroke Risk Profile (e.g., Wolf, 2009), the Dementia Risk Indices (e.g., Barnes & Yaffe, 2009), or measures of allostatic load (e.g., Seeman et al., 2010), MetS offers several advantages. First, it is widely recognized as a clinically meaningful syndrome; second, it is easy to assess in an epidemiologic study as it is based on commonly measured biomarkers. Thus, we advocate its use as a clinically useful biomarker that may have effects on language in aging.

Why MetS impaired performance on only two of our four language tasks—Action Naming Test (ANT) and Embedded Sentences (ES) is not clear. We speculate that the selective effects of MetS on ANT may reflect functional-neuroanatomical distinctions between action and object words found in lesion, neuroimaging, and electrophysiological studies of verb and noun processing. These neural correlates likely capture the linguistic differences between nouns and verbs, in terms of their abstract lexical representations and their syntactic roles in sentences [e.g., that verbs encode information about transitivity, while nouns denote count/mass, animacy, and other features (e.g., Levelt, 1989)]. Indeed, evidence converges on the observation that the semantic-pragmatic-syntactic knowledge underlying action words is mediated by frontal networks, while the linguistic knowledge associated with object words is subserved by temporal networks (e.g., Vigliocco, Vinson, Druks, Barber, & Cappa, 2011). This neural organization places action but not object words at greater risk of being affected by impairments in cerebrovascular biomarkers that compromise the integrity of frontal brain systems, such as those associated with MetS.

Similarly, we propose that the differential effects of MetS on ES but not on MN are associated with the distinct neural patterns that support the processing of these two distinct sentence types (for related comments see also Cahana-Amitay et al., 2013). For the ES stimuli, syntactic parsing determines whether a given noun phrase is correctly linked to its trace within the relative clause. For MN stimuli, however, semantic computations determine whether the presence of a

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negative marker reverses the truth value of a sentence. The processing of syntactically complex sentences is subserved by a network implicating the left inferior frontal gyrus (e.g., Caplan, Stanczak, & Waters, 2008); sentential negation networks, however, also engage the left inferior parietal lobule to support aspects of semantic processing (Bahlmann, Mueller, Makuuchi, & Friderici, 2011). Under this scenario, neural networks involved in complex syntactic processing, but not in simple syntactic and semantic processing, are particularly vulnerable to presence of MetS, providing a possible explanation for why MetS selectively spared affirmative control sentences (0N). Why MetS improved 0N accuracy (as opposed to simply not affecting it), however, remains unresolved.

The specific MetS-related language decrements we found are consistent with our previous observations regarding the relationship between poor cardiovascular/metabolic health and impaired language in aging (Albert et al., 2009; Cahana-Amitay et al., 2013). Results from these earlier studies, reinforced by the present findings, support our hypothesis that the neurobiological effects of hypertension, diabetes, and the metabolic syndrome on language functions among older adults involve, at least two separate, biologically modifiable, pathogenetic mechanisms, acting on the brain simultaneously. One implicates microvascular changes in brain systems mediated primarily by frontal white matter. The other consists of metabolic neuronal dysfunction related to insulin resistance and reduced glycemic control influencing neuronal networks underlying language and cognition in widely distributed fields affecting the brain in a multifocal manner.

Indeed, glucose abnormalities impair cognitive skills involving verbal components (e.g., Awad et al., 2004; Lamport et al., 2009), suggesting that long-term effects of poor glycemic control implicate neural changes (reduced regional cerebral blood flow) in frontal, temporal, and parietal regions later in life (Thambisetty et al., 2013). Because the involvement of these cortical regions in lexical and syntactic processes has been well-documented in neuroimaging studies described elsewhere (e.g., Price, 2012), and because insulin resistance is a key mechanism underlying MetS (e.g., Yates et al., 2012), our findings that both lexical retrieval and sentence processing abilities were negatively affected by MetS should come as no surprise.

Our speculations about the effects of glucose intolerance and insulin resistance on language performance in aging are consistent with a model proposed by Yates et al. (2012), in which neural damage resulting from insulin resistance and MetS leads to changes in vascular reactivity in the brain, disrupting the neuronal environment for optimal neural activation. In this model, insulin resistance impairs the brain's ability to increase synaptic activity through vasodilatation and clearing of metabolic waste, which is necessary for cognitive performance, and so reduces cerebral vascular reactivity (capillary recruitment) in vulnerable brain areas such as the frontal cortex. This reduced cerebral vascular reactivity is also associated with obesity-related inflammation, which leads to cognitive decline over time.

Such a mechanism might help explain our unanticipated finding that persons with MetS were slightly faster than their healthy counterparts in the processing of embedded sentences (ES). One possible interpretation is that persons with MetS show greater speed-accuracy tradeoff, compared to those without the syndrome, affecting the processing speed of cognitively challenging sentence types, such as those in ES. The neural underpinnings of speed-accuracy tradeoff are assumed to implicate anterior cortices, such as the supplementary motor area and the dorsolateral prefrontal cortex, when speed-emphasized responses are called for (Bogacz, Wagenmakers, Forstmann, & Nieuwenhuis, 2009). The demand for speedy responses is assumed to alter the baseline activation rate of the neurons integrating inputs in service of the expected response. Thus, structural changes to frontal brain regions mediating speed-accuracy tradeoffs can presumably result in changes in the ability to produce fast *versus* correct responses among people with MetS. However, the reaction times for ES reported here were only measured for correct responses, leaving open this possibility for future research.

Moreover, the observed change in reaction time involved a counter-intuitive *reduction* in processing speed of ES, which are syntactically complex sentences and pose comprehension problems for older adults (e.g., Goral et al., 2011). To account for this surprising pattern, we propose that MetS components adversely affect frontal networks supporting executive function systems, altering their vascular reactivity, leading to a disorder of timing functions and causing a greater degree of impulsivity and reduced capacity for response inhibition (Rubia, Halari, Christakou, & Taylor, 2009). Although impulsivity is clearly a multidimensional construct (see Bari & Robbins, 2013), which may interact with MetS at emotional and psychosocial levels (e.g., Sutin et al., 2010) that extend well beyond the scope of this study, we use the operational definition of impulsivity as a disorder of timing by Rubia et al. (2009). Thus, regarding the effect of metabolic syndrome on language in aging, we see the impairment of impulse control as a neurocognitive deficit resulting from dysfunction of the frontal executive system.

According to this analysis, participants with MetS would respond impulsively, that is, produce faster responses, to the ES task. This suggestion predicts faster reaction time in both correct and incorrect responses. These speeded responses should not be as pronounced during sentential negation, which also implicates networks in the parietal cortices to support semantic processing (Bahlmann et al., 2011). This idea is consistent with findings from neurophysiological studies of sentence comprehension among healthy adults exploring time-linked features of syntactic and semantic processing, demonstrating that syntactic processing precedes syntactic-semantic integration (e.g., Friederici, Gunter, Hahne, & Mauth, 2003). Independent evidence suggests that timing deficits, such as premature motor responses, reduced patience to temporal delays, or poor temporal planning, are related to the dysexecutive problems of impulsivity (Rubia et al., 2009). A future study exploring the relationship among

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MetS, executive functions, and speed of processing could address this question more directly.

To fully understand the impact of MetS on language functions among older adults, additional biomarkers should be examined. These include biomarkers of inflammation, which are reciprocally linked to the development of insulin resistance (Yates et al., 2012) and closely interact with mechanisms of glucose abnormalities and heart disease *via* pathophysiology of stress responses (e.g., Yudkin, Kumari, Humphries, & Vidya, 2000). Thus, age-related changes in language functions, including those manifested among older adults with MetS, are likely associated with stress-induced pathophysiology. Future research exploring interdependencies among biomarkers of physiologic dysregulation, measures of chronic stress, and measures of language functions in aging is thus a next logical step.

In summary, this study clearly demonstrates that the presence of MetS impairs action naming and processing of syntactically complex sentences in elderly individuals beyond the effects expected by the individual components of this syndrome. We speculate that changes in cerebral vascular reactivity play a role in the neural dysfunction underlying these language decrements.

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