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The impact of vascular comorbidities on qualitative error analysis of executive impairment in Alzheimer's disease

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Abstract

Recent evidence suggests that patients with Alzheimer's disease (AD) and vascular comorbidities (VC) perform worse across measures of verbal reasoning and abstraction when compared to patients with AD alone. We performed a qualitative error analysis of WAIS-III Similarities zero-point responses in 45 AD patients with varying numbers of VC including diabetes, hypertension and hypercholesterolemia. Errors were scored *in* set if the answer was vaguely related to the word pair (e.g., doglion: 'they can be trained') and *out of* set if the response was unrelated ('a lion can eat a dog'). AD patients with 2–3 VC did not differ on Similarities total score or qualitative errors from AD patients with 0–1 VC. When analyzing the group as a whole, we found that increasing numbers of VC were significantly associated with increasing *out of* set errors and decreasing *in* set errors in AD. Of the vascular diseases investigated, it was only the severity of diastolic blood pressure that significantly correlated with *out of* set responses. Understanding the contribution of VC to patterns of impairment in AD may provide support for directed patient and caregiver education concerning the presentation of a more severe pattern of cognitive impairment in affected individuals.

Keywords

Alzheimer's disease; vascular comorbidity; verbal reasoning; diabetes; hypertension; hypercholesterolemia

Introduction

Qualitative error analyses of neuropsychological performance was first introduced by Edith Kaplan to provide a finer grained process oriented approach to behavioral output across clinical populations (Kaplan, 1988). Expanded scores and categorization of various error types based on this 'Boston Process Approach' to neuropsychological assessment were deemed less likely than conventional quantitative approaches to result in Type 2 errors when

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assessing for alterations in performance (Kaplan, 1988). The Boston Process Approach to qualitative error analysis in dementia has been shown effective in understanding subtle group distinctions in behavior not accounted for by quantitative standardized scores (Lamar et al., 2004 for review). For example, within the context of equal numbers of intrusions and perseverations on a list learning test, Davis and colleagues (2002) applied a qualitative error analysis of these responses. Individuals with Alzheimer's disease (AD) made more semantically related intrusions and repeated these intrusions across trials as compared to individuals with vascular dementia (VaD).

While neuropsychological research has shown the effectiveness of a more qualitative approach to differentiating dementia subtypes, neuropsychological investigations in dementia have historically focused on cognitive profiles of impairment derived from quantitative analyses. Much of the work in this area highlights the striking anterograde amnesia in AD (e.g., Baillon et al., 2003) in contrast to the executive dysfunction in VaD (i.e., Traykov et al., 2002). A recent meta-analysis (Mathias & Burke, 2009) determined that quantitative scores derived from verbal memory testing resulted in a large enough effect size ($d \geq .8$), and met additional confidence interval criteria, to merit distinction as variables that would successfully discriminate between AD and VaD. In contrast, none of the quantitative measures of attention and executive function such as time to completion on the Trail Making Test met criteria for successful group differentiation (Mathias & Burke, 2009). This may be due in part to the lack of subtle distinctions afforded by a quantitative approach to executive performance.

Using a qualitative error analysis of incorrect responses on the WAIS-R Similarities subtest, we have reported conceptually based executive dysfunction in patients with AD when compared to more pervasive impairment seen in patients with VaD (Giovannetti et al., 2001). This pattern of performance was detected despite equal performance on quantitative measures of Similarities performance (i.e., total score). More specifically, when zero-point responses are coded to reflect patients' ability to attain mental set, patients with AD produce incorrect responses that are vague, but nonetheless superficially related to the given word pair (i.e., dog-lion – *they're alive*). By contrast, individuals with VaD produce errors that suggest a blatant loss of mental set (i.e., dog-lion – *a dog can eat a lion*). Thus, individuals with AD are able to establish mental set but demonstrate difficulty with higher-level response selection, i.e., trouble selecting a response with the appropriate degree of abstraction (Giovannetti et al., 2001). In contrast, individuals with VaD appear unable to operate within the parameters of the task.

Another possible reason for the lack of discriminatory strength of attention and executive measures in Mathias and Burke's (2009) recent meta-analysis may be due to the fact that vascular risk factors – known to negatively impact executive functioning (Robbins et al., 2005; Desmond et al., 1993; P. K. Elias et al., 2005) – are present in AD as well as VaD (Breteler, 2000; Helzner et al., 2009). The classic vascular risk factors of aging, as defined by investigators from the Rotterdam Study, include hypertension, Type 2 diabetes mellitus and hypercholesterolemia (Breteler, 2000). These vascular risk factors are often considered a hallmark of VaD and a contributing factor to small vessel disease (Fazekas et al., 1993) and executive dysfunction (Lamar et al., 2008) in this population. Vascular risk factors are also associated with AD (Breteler, 2000; Helzner et al., 2009; Luchsinger et al., 2005) and may contribute to the white matter alterations documented in this population (Gurol et al., 2006). Only recently have researchers begun to investigate whether vascular risk factors impact executive dysfunction in ADGiven that 15 to 18 million Americans 65 years and older will develop some form of dementia including AD by 2050 (Bioethics, 2005) and over 35% of this same age group will have at least one comorbid vascular risk factor (Lyketsos et al.,

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2005), it is important to understand the impact of vascular comorbidities on the clinical presentation of AD.

Emerging evidence suggests that vascular risk factors combined with AD may lead to more severe pattern of executive impairment than AD alone. For example, the presence of diabetes in conjunction with AD impairs retrieval of information (Reitz et al., 2007) and working memory (Arvanitakis et al., 2004) to a greater extent than AD alone. African Americans with AD and comorbid hypertension show significantly poorer performance on executive indices of the Mattis Dementia Rating Scale reflecting initiation/perseveration and abstract conceptualization when compared to normotensive African Americans with AD (Goldstein et al., 2005). Furthermore, an increase in the number of vascular comorbidities (e.g., hypertension and hypercholesterolemia) in patients with mild to moderate AD has been associated with impaired mental manipulation on WAIS-III Digits Backward and poorer verbal reasoning on the Similarities subtest than that seen in patients with mild to moderate AD alone (Goldstein et al., 2008). Whether individuals with AD who also have comorbid vascular risk factors show a distinct *qualitative* pattern of impairment on executive measures like the Similarities subtest has yet to be addressed in the literature.

In the current study, we examined the impact of vascular risk factors on conceptually based executive dysfunction in AD using our previously developed error analysis of incorrect responses on the Similarities subtest (Giovannetti et al., 2001). Zero-point responses were scored *in* set if the answer was vaguely related to the word pair (e.g., dog-lion: ‘they can be trained’) and *out of* set if the response was unrelated (‘a lion can eat a dog’). Individuals with VaD and associated vascular comorbidities produce more *out of* set than *in* set errors (Giovannetti et al., 2001). Furthermore, individuals with AD and increasing numbers of vascular comorbidities show a more severe pattern of executive impairment than those with AD alone (Goldstein et al., 2008; Goldstein et al., 2005). Thus, we hypothesized that individuals with AD and multiple vascular comorbidities including hypertension, diabetes and/or hypercholesterolemia would produce greater numbers of *out of* set errors during Similarities when compared to individuals with AD and few to no vascular comorbidities.

Methods

Participants

Participants were recruited from the outpatient memory assessment clinics at The Wesley Woods Center on Aging and Grady Memorial Hospital. The clinical diagnosis of probable AD was made using NINCDS-ADRDA (McKhann et al., 1984) criteria by experienced neurologists in The Emory Alzheimer’s Disease Research Center (AWA, JJL & AIL). This study was approved by the Emory University Institutional Review Board with consent obtained according to the Declaration of Helsinki.

We excluded participants who had neuroradiologic evidence of current or previous large-vessel strokes or a neurologic examination consistent with current or previous strokes. Participants were excluded if there was any history of psychiatric (Axis I) disorders (APA, 1994), alcohol or substance abuse or neurologic conditions which could affect cognition such as seizures or significant head injury resulting in hospitalization.

When using the Boston Process Approach on Similarities zero-point responses in past research (Giovannetti et al., 2001), we employed a cut-off for overall dementia severity using the Mini-Mental State Examination (MMSE≥17; Folstein et al., 1974) and a cut-off for depressive symptomatology using the Geriatric Depression Scale (GDS≤10; Yesavage, 1988). We employed these cut-offs in the current sample as well. As a result 45 participants averaging 75 years of age contributed data to the final analyses.

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Vascular Comorbidities

The following vascular comorbidities were chosen based on research indicating their impact on executive functioning in aging (e.g., M. F. Elias et al., 2005; P. K. Elias et al., 2005; Kilander et al., 1998; Robbins et al., 2005) and dementia (e.g., Arvanitakis et al., 2004; Goldstein et al., 2008; Goldstein et al., 2005). We determined cut-off points for each vascular comorbidity using published guidelines of expert panels (Chobanian et al., 2003; The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003; The National Cholesterol Education Program Expert Panel, 2001). In addition to objective measurements, we conducted a comprehensive review of study participants' medical records, including all available hospital and primary care physician documents – both recent and remote – where available, and we obtained a detailed medical history from significant others.

Hypertension—Two blood pressure readings separated by two minutes were averaged, with additional readings obtained if the first two readings differed by more than 5 mm Hg. Hypertension was defined as systolic blood pressure (BP) 140 mm Hg or higher, diastolic BP 90 mm Hg or higher or taking antihypertensive medication (Chobanian et al., 2003).

Type 2 Diabetes Mellitus—Blood draws were obtained following at least an eight hour fasting period. Diabetes was defined as a fasting plasma glucose level of 126 mg/dl or higher (7.0 mmol/L), or taking insulin or oral hypoglycemic agents (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003).

Hypercholesterolemia—A fasting (no caloric intake for at least eight hours) serum lipid profile was obtained for each participant. Hypercholesterolemia was established by a serum total cholesterol level of 240 mg/dl (6.2 mmol/L) or greater, or taking medications for the expressed purpose of lowering cholesterol levels (The National Cholesterol Education Program Expert Panel, 2001).

Issues of under diagnosis- that is, missing the presence of a vascular risk factor based on normal results- were addressed in several ways. The above criteria defined a vascular risk factor as being present if the individual took medication specifically for its treatment; this was expected to mitigate under diagnosis. We also, however, conducted a review of patients' medical records (including those from outside physicians) and obtained a detailed medical history from the patient and a reliable informant.

Alternatively, over diagnosis or diagnosing a vascular risk factor that was not present was also addressed through several means. In the example of HTN, blood pressure readings were obtained after a minimum of 30 minutes interaction with the research nurse to mitigate against elevations due to anxiety. Furthermore, in cases where elevations occurred in the absence of a documented history of HTN or antihypertensive medication use, we reviewed previous medial records and notes of follow-up neurologic assessments.

Each participant received a binary score for the presence (1) or absence (0) of individual vascular comorbidities. The three categories were summed to create a composite index of vascular comorbidity (maximum=3). Patients with AD and 0 to 1 vascular comorbidities (VC) comprised a Low VC group (n=22) while patients with AD and 2 to 3 vascular comorbidities made up a High VC group (n=23). A breakdown of demographic and vascular comorbidity information as it relates to the current study participants is found in Table 1.

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WAIS-III Similarities Administration and Scoring

Individuals received the WAIS-III Similarities subtest as part of a comprehensive neuropsychological evaluation. The Similarities subtest was administered and scored according to the WAIS-III manual (Wechsler, 1997) by individuals blind to participants' vascular comorbidities. All responses given a score of zero as outlined by the WAIS-III manual were then coded using previously established criteria (Giovannetti et al., 2001) for the following qualitative errors:

I. In set responses

- **a.** *Vague responses*. A superficial albeit superordinate categorical response (e.g., dog & lion: 'they eat')
- **b.** *Subordinate responses*. A shared concrete attribute (e.g., coat & suit: 'they both have sleeves') or highly specific property about the Similarities pair that may not be correct in all instances (e.g., boat & automobile: 'they both have motors').

II. Out of set responses

- **a.** *One Object responses*. A response to only one member of the word pair (e.g., coat & suit: 'one is minus a pair of pants').
- **b.** *Juxtapositions*. A description of how one member of the word pair might interact with the other member (e.g., fly & tree: 'the fly has a place to land').
- **c.** *Different responses*. An accurate description of how the two items of the word pair are different (e.g., eye & ear: 'you see with your eyes and hear with your ears').

Intra-rater (ML) reliability for a subset of participants (n=32) was high (*in* set: r=0.97, *out of* set: r=0.99; both p-levels <0.001) as was inter-rater (ML & DJL) reliability (*in* set: r=0.71, *out of* set: r=0.91; both p-levels <0.001).

Results

Neither qualitative error variable, *in* set nor *out of* set (Table 1), violated assumptions of normality when tested in the overall sample and within individual groups using the Kolmogrov-Smirnov statistic (all p-values >0.05). Thus, parametric tests were used for all analyses.

Between-Group Analyses

Separate analyses of variance (ANOVA) investigating group differences across measures of age, overall cognitive status, years of education and depressive symptomatology revealed a significant difference in age only [High>Low VC; $F(1, 43)=5.2$, $p<0.05$; Table 1]. The sex frequency distribution between groups was also significantly different, $x^2(1, N=45)=5.1$, $p<0.05$, with the Low group containing more men than the High group. Thus, we used age and sex as covariates in all analyses.

Quantitative & Qualitative Similarities Performance—An analysis of variance controlling for age and sex (ANCOVA) investigated between-group differences on WAIS-III Similarities total raw score. No significant between-group differences were found, $F(1,41)=0.14$, $p=0.71$. A 2×2 ANCOVA controlling for age and sex investigated between-group differences for *in* set and *out of* set error production. Neither the 2-way interaction,

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F(1,41)=0.85, p=0.36, nor the main effects [group: F(1,41)=0.25, p=0.62; error: F(1,41)=0.13, p=0.72] were significant.

Post-hoc Analyses

A closer inspection of our group divisions, reliant on the presence of either 0–1 or 2–3 vascular comorbidities, revealed very little difference between the numbers of individuals with one versus two vascular risk factors. Approximately 42% of our AD sample had one vascular risk factor and 40% had two (Table 1). In light of this, we collapsed our binary group divisions and investigated the impact of increasing vascular comorbidities on qualitative error production in the entire AD sample.

Presence of Vascular Risk Factors—Separate Pearson product moment correlations between the number of vascular comorbidities and the number of *in* set and *out of* set errors controlling for age and sex revealed a significant dissociation. The presence of increasing numbers of vascular comorbidities was associated with *decreasing in* set errors ($r = -0.31$, $p=0.02$). In contrast, the presence of increasing numbers of vascular comorbidities was associated with *increasing out of* set errors ($r = +0.27$, $p=0.03$). A partial correlation between Similarities total raw score and number of vascular comorbidities was not significant (Table 2).

Severity of Vascular Risk Factors—We performed a more in-depth assessment of the relationship between the severity of individual vascular risk factors and performance on the WAIS-III Similarities subtest by looking at actual values (i.e., systolic and diastolic blood pressure, glucose and cholesterol levels) as opposed to categorical presence. Pearson product moment correlations controlling for age and sex did not reveal any significant associations between *in* set or *out of* set errors and glucose or cholesterol levels (Table 2). There was a significant association between increased *out of* set errors and elevated diastolic blood pressure ($r = +0.28$, $p=0.03$). Only cholesterol levels were significantly associated with Similarities total raw score ($r = -0.31$, $p=0.02$).

Discussion

We found that the number of vascular risk factors in mild AD did not contribute to impairment in overall performance on the WAIS-III Similarities subtest. Using the Boston Process Approach to qualitative error analysis, however, we found that as the number of vascular comorbidities increased in our AD sample the production of *out of* set errors also increased whereas *in* set errors decreased. Thus, the type of errors produced by patients with AD and increasing vascular comorbidities became more indicative of executive dysfunction akin to that seen in VaD (Giovannetti et al., 2001) – a neurodegenerative disorder traditionally associated with vascular comorbidities. These relationships may be due, in part, to the role of hypertension, particularly elevated diastolic blood pressure, on executive functioning in AD.

Of the vascular diseases investigated, it was the severity of diastolic blood pressure that showed a significant association to *out of* set error production in mild AD. The majority of our sample (34 out of 45 or 75%) met The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure criteria (Chobanian et al., 2003) for hypertension. Upon closer inspection, two-thirds of these patients were uncontrolled on their antihypertensive medications based on onsite blood pressure evaluations the day of testing. This suggests that uncontrolled hypertension in AD may lead to subtle alterations in executive functioning.

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In contrast to the qualitative effects of vascular comorbidities on differential error production during Similarities performance, we did not observe a significant relationship between increased number of vascular comorbidities and poorer quantitative (i.e., standardized) performance. We previously found that AD patients with both hypertension and hypercholesterolemia obtained lower total Similarities subtest scores than patients with only one or no vascular comorbidities (Goldstein et al., 2008). A certain degree of support exists in the current study, however, when considering the severity of hypercholesterolemia on Similarities performance. An increas in cholesterol levels was significantly associated with a decrease in total Similarities subtest scores in our AD sample. Participant and methodological differences across studies may explain the variation in results. Unlike the previous study, the current investigation included patients who were milder in cognitive severity on the MMSE and fasting at the time of measurement of their vascular comorbidities. Future research is necessary to fully examine the relationship between dementia severity and specific vascular comorbidities on verbal reasoning and abstraction in AD.

In the absence of dementia, there is evidence that vascular risk factors negatively impact verbal reasoning and abstraction. For example, elevations in blood pressure (Robbins et al., 2005), the presence of diabetes (Desmond et al., 1993), and high cholesterol levels (P. K. Elias et al., 2005) are all independent vascular risk factors that negatively impact verbal reasoning and abstraction in non-demented older adults. When they occur together, the degree of executive impairment is significantly increased (Brady et al., 2001; P. K. Elias et al., 1997; Knopman et al., 2001). The majority of work investigating these vascular risk factors in AD has focused on overall measures of cognition (Bhargava et al., 2006) or composite scores encompassing multiple cognitive domains (Helzner et al., 2009). Our preliminary results combined with our previous work (Goldstein et al., 2008; Goldstein et al., 2005) are, to our knowledge, some of the first exploring the impact of vascular comorbidities on a specific cognitive domain. The findings point toward subtle alterations within verbal reasoning and abstraction in the presence of increasing vascular comorbidities and AD. However, in order to gain a better sense of the clinical significance of these results a larger study of multiple executive measures incorporating standardized and qualitative error analysis methods is warranted.

We acknowledge that we lacked information pertaining to mid-life development and/or presence of each vascular risk factor. While this information has proven useful in understanding later development of cognitive dysfunction and dementia in an aging population (Breteler, 2000; M. F. Elias et al., 2004; Launer, 2005), we were interested in understanding how the current presence of specific vascular risk factors impacted an established profile of executive impairment in AD (Giovannetti et al., 2001) at the time of evaluation. Furthermore, we did not delineate between AD patients with vascular comorbidities controlled by medication from those not controlled by medication or the duration of this medical (in-)stability across the lifespan. Future large-scale studies incorporating these methodological variations are therefore necessary to confirm and extend our preliminary findings.

Our study had a relatively small sample size limited to patients who were followed in Memory Disorders Clinics. Recruitment through this clinic may have restricted the range of resulting vascular comorbidities, thereby making our group divisions reliant on the presence of either one or two vascular diseases. These factors, combined with our use of a binary presence/absence outcome measure for each vascular risk factor, may have negatively impacted the magnitude of our correlations.

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In summary, this is the first study to our knowledge attempting to identify the impact of vascular comorbidities on a specific profile of impairment derived from a qualitative error analysis in AD. Our results suggest an interplay of vascular comorbidities and mild AD on the shift from conceptually based errors (i.e., dog-lion – *they're alive*) to a more blatant loss of mental set (i.e., dog-lion – *a dog can eat a lion*) during the Similarities subtest. This may be due, in part, to the additional impact of hypertension, specifically elevated diastolic blood pressure, in AD. It is important to expand the Boston Process Approach of qualitative error analysis across other executive test measures and cognitive domains in order to fully understand the contribution of vascular risk factors to patterns of cognitive impairment in mild AD. In addition, future research should examine the effects of additional vascular risk factors such as smoking and cardiac disease including atrial fibrillation and myocardial infarction. Such directed study may ultimately provide support for more focused patient and caregiver education concerning the presentation of cognitive dysfunction and the aggressive management of vascular risk factors in affected individuals.

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Table 1

Group Data

		Low VC (n=22)	High VC (n=23)
Demographic Information			
Age (years)*		70.5 (11.5)	77.7 (9.4)
MMSE		22.3 (3.4)	21.6 (2.8)
Education (years)		13.2 (2.0)	13.1 (3.0)
GDS		3.6 (2.9)	3.4 (3.1)
Sex (M:F)*		12:10	5:18
Vascular Comorbidity Information			
Total number present (n)	0	3 (6.7%)	-
	1	19 (42.2%)	-
	2	-	18 (40.0%)
	3	-	5 (11.1%)
Prevalence of disease (n)	HTN	11 (50%)	23 (100%)
	DM	1 (5%)	5 (22%)
	CHOL	7 (32%)	23 (100%)
WAIS-III Similarities subtest Information			
Total raw score		13.6 (7.3)	11.6 (6.4)
in set errors		2.0 (1.8)	2.0 (1.2)
out of set errors		1.9 (1.7)	2.2 (1.7)

* $p<0.05$;

** $p<0.001$

NOTE: All values depict *means (standard deviations)* unless otherwise stated in table.

VC=Vascular comorbidities; MMSE=Mini-Mental State Examination; GDS=Geriatric Depression Scale; HTN=hypertension; DM=Type 2 diabetes mellitus; CHOL=hypercholesterolemia; WAIS-III=Wechsler Adult Intelligence Scale-III.

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Table 2

Correlations between *in* set and *out of* set errors and vascular comorbidities

	***in* set**	***out of* set**	**total raw score**
PRESENCE	**−0.31 (0.02)**	**+0.27 (0.03)**	−0.18 (0.11)
SEVERITY			
Glucose Level	−0.11 (0.24)	+0.15 (0.16)	−0.22 (0.07)
Cholesterol Level	+0.01 (0.47)	+0.06 (0.36)	**−0.31 (0.02)**
Systolic Blood Pressure	+0.20 (0.10)	+0.02 (0.44)	−0.10 (0.26)
Diastolic Blood Pressure	−0.10 (0.25)	**+0.28 (0.03)**	+0.07 (0.31)

NOTE: All numbers represent r-values (p-level) with degrees of freedom (1,41). Bolded values signify significant associations based on one-tailed p≤ 0.05.