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Asymmetric insular function predicts positional blood pressure in non-demented elderly

DR Royall^{1,2,3}, JH Gao⁴, X Zhao⁴, MJ Polk¹, and D Kellogg²

DR Royall: royall@uthscsa.edu; JH Gao: gao@radiology.bsd.uchicago.edu; X Zhao: ZHAOX@uthscsa.edu; MJ Polk: polk@uthscsa.edu; D Kellogg: kellogg@uthscsa.edu

¹Department of Psychiatry, The University of Texas Health Sciences Center at San Antonio, and the South Texas Veterans Health Administration Geriatric Research Education and Clinical Center (GRECC), 7703 Floyd Curl Drive, San Antonio, TX 78284-7792

²Department of Medicine, The University of Texas Health Sciences Center at San Antonio, and the South Texas Veterans Health Administration Geriatric Research Education and Clinical Center (GRECC), 7703 Floyd Curl Drive, San Antonio, TX 78284-7792

³Department of Pharmacology, The University of Texas Health Sciences Center at San Antonio, and the South Texas Veterans Health Administration Geriatric Research Education and Clinical Center (GRECC), 7703 Floyd Curl Drive, San Antonio, TX 78284-7792

⁴Department of Radiology, The University of Texas Health Sciences Center at San Antonio, and the South Texas Veterans Health Administration Geriatric Research Education and Clinical Center (GRECC), 7703 Floyd Curl Drive, San Antonio, TX 78284-7792

⁵Department of Radiology. The University of Chicago

Abstract

40% of non-demented octogenarians have Braak stages consistent with insular involvement, and may be at risk for “age-related” autonomic dysfunction. We examined the association between insular resting Cerebral Blood Flow (rCBF) and cardiovascular functions in 29 non-demented elderly subjects who were highly screened to exclude comorbid cardiovascular disease. Mean insular rCBF was significantly higher on the right (R) than left (L). However, 35.4% of subjects had L dominant rCBF = a “HIGH” risk group. R insular rCBF was significantly lower in the HIGH risk group. This subset had significantly increased positional drops in systolic blood pressure. While these data cannot address AD as the specific cause, this possibility is being investigated in other cohorts.

Requests for reprints should be addressed to Dr. Donald Royall, Department of Psychiatry, The University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, Mail code:7792, San Antonio, TX 78229-3900. TEL: (210) 567-1255, FAX:(210) 567-1269, royall@uthscsa.edu.

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Keywords

autonomic function; asymmetry; aging; Alzheimer's disease; insula; orthostasis

1. Introduction

We recently proposed that right insular dysfunction due to pre-clinical Alzheimer's disease (AD) or other neuropathology may mediate fall and syncope related morbidity and mortality in non-demented elderly. {1} This is predicated on our observation of a specific association between visuospatial cognitive measures and mortality in non-demented elderly retirees. {2} Similar tests are known predict mortality in AD {3}, while right (R) hemisphere lesions are known to increase the risk of arrhythmic morbidity and mortality in stroke {4}, head injury {5} and epilepsy {6}. Strokes that affect constructional tasks often involve the R insula as well {7}. R insular stroke {8} or epileptic foci {9} often present with asystole.

We hypothesize that preclinical AD, which is known to affect the insular cortex at an early Braak stage {10}, is responsible for both our observed mortality in non-demented elderly retirees, and "age-related" autonomic dysfunction in septuagenarians and octogenarians. {11} Our preliminary studies in press elsewhere suggest that insular neurofibrillary tangle counts moderate the associations between both age, QT interval, and death. {12} 40% of non-demented octogenarians have Braak stages consistent with insular involvement, and may be at risk. {13}

In this study, we examine the association between right insular cerebral blood flow (rCBF) by perfusion magnetic resonance imaging (pMRI) and measures of cardiovascular autonomic control, in non-demented retirees [Clinical Dementia Rating Scale (CDR 1.0)] {14}, carefully screened to be free of comorbid cardiovascular disease.

2. Methods

A convenience sample of 29 community dwelling elderly volunteers was tested with measures of cognition, autonomic function, and pMRI. Subjects were recruited from non-institutionalized levels of care in a for-profit San Antonio, TX comprehensive care retirement community (the Air Force Villages). After giving informed consent, subjects were screened for diabetes, clinical ischemic heart and cerebrovascular disease by self-report, electrocardiogram (ECG), two dimensional echocardiography (2D-ECHO), and T2 weighted MRI. Resting insular rCBF was determined by pMRI. 42 subjects were recruited. However, 13 were eventually excluded due to abnormal ECG (n = 5), a technically inadequate scan (n = 2), intolerance of the pMRI (n = 5), or on the basis of a CDR score > 0.5 (n = 1).

2.1 Neuroimaging

pMRI experiments were performed on a 1.9 T Elscint Prestige MRI scanner (Elscint Ltd., Haifa, Israel) at the Research Imaging Center of the University of Texas Health Science Center at San Antonio. Baseline images were used to rule out occult focal right hemisphere / insular cortical lesions as the cause of any constructional dyspraxia /autonomic dyscontrol.

Any cases found to have either mass lesions or focal cortical infarctions /hemorrhagic lesions were excluded.

2.2 Cerebral blood flow (CBF)

Absolute CBF was measured by dynamic contrast MRI using singular value decomposition with an adaptive threshold developed in our laboratory. {15} A single-shot multiple-slice spin echo EPI pulse sequence was used with the following parameters: TR/TE/ = 1500 ms/80 ms/90°, slice thickness = 5 mm, and an in-plane spatial resolution of 3.3 mm by 3.3 mm. For each study, multiple-slices (120 images per slice) were obtained during a total scan time of 3 minutes. All subjects received 0.2 mmol/kg of a Gadolinium (Gd) based contrast agent (Magnevist, Berlex), delivered intravenously at a rate of about 5 ml/s into the antecubital vein. Injection of the contrast agent began 1.5 minutes after the start of the scan. The duration of the injection was approximately 4 to 6 seconds.

The tissue concentration time curve was calculated using the first thirty images after injection. The average signal of the forty images prior to injection was used as the baseline signal. The arterial input function was determined in each subject from 4–6 pixels containing a large vessel, typically the middle cerebral artery. The CBF of both gray matter and white matter was determined using the procedure described in our previous publication. {15} White matter CBF does not decline with age, in contrast to gray matter CBF. {16} Cortical CBF was normalized to white matter CBF to offset intraindividual differences in absolute CBF.

The left and right insular cortices were outlined in the T1 MRI image corresponding to the first EPI image from the perfusion scan time series (because of its high contrast). Then, the outlined ROIs were registered to the regional CBF map obtained from our former calculation. The mean regional insular CBF values can be obtained by averaging the pixel values in its corresponding ROI of the rCBF map.

Because autonomic control is lateralized at the level of the insula, Left hemisphere dominant asymmetry in the ratio of L:R insular cerebral blood flow (CBF) may define a group at relatively high risk for falls, syncope or sudden death. Therefore, subjects were classified apriori into “HIGH” and “LOW” risk groups on the basis of the ratio of their R:L insular rCBF. The “HIGH” risk group included individuals with L dominant (i.e., relatively low R) insular rCBF.

2.3 Psychometric Measures

Depressive symptoms were assessed using the 15 item short Geriatric Depression Scale (GDS). {17–18} GDS scores range from zero-15. Higher scores are worse. A cut-point of 6–7 best discriminates clinically depressed from non-depressed elderly. {19}

The University of Pennsylvania Smell Identification Test (UPSIT) {20} was used to assess olfaction. The UPSIT is a standardized test of odor identification with good test-retest reliability ($r = .95$) and strong correlation with detailed olfactory threshold tests ($r = .80$). It contains 40 microencapsulated odors. The subject scratches and sniffs each test strip and chooses among multiple choices for the identity of each odor represented. The prompted

design of a multiple-choice format minimizes the likelihood that UPSIT scores will be affected by verbal memory or executive impairments. UPSIT scores ≤ 18 indicate “anosmia” (e.g. severe odor identification deficits); scores of 19–33 (men) and 19–34 (women) indicate “microsmia”. For this study, we assessed left (L) and R nostril performance separately, by asking the subject to close the contralateral nostril during UPSIT testing. The ratio of R:L UPSIT performance was then calculated.

2.4 Cognitive Measures

2.4.1 General Cognition

2.4.1.1 The Mini-Mental State Examination (MMSE) {21}: The MMSE is a well-known and widely used test for screening cognitive impairment. Scores range from 0–30. A score of 28/30 is the median for normal octogenarians of >12 years of education. {21} Scores below 24 reflect cognitive impairment.

2.4.2 Memory Function

2.4.2.1 Connecticut Picture Learning Test (COPLT) {22}: The COPLT is a pictorial version of the California Verbal Learning Test. Subjects are asked to recall objects from a set of 16 line drawings of familiar objects (immediate recall), over five consecutive trials (= COPLTTOT, maximum score, 80), after distraction (= COPLT short, maximum score, 16) and after a 20 minute timed delay (= COPLT long, maximum score, 16). The difference between the short delay trial and the fifth learning trial = COPLT retention (range 0–15).

2.4.2.2 The Rey Auditory Verbal Learning Task (RAVLT) {23}: As in the COPLT, subjects are asked to recall words from a 15-word list immediately (immediate recall), over five consecutive trials (= RAVTOT, maximum score, 75), after distraction (= RAV short, maximum score, 15) and after a 20 minute timed delay (= RAV long, maximum score, 15). The difference between the short delay trial and the fifth learning trial = RAV retention (range 0–15).

2.4.3 Executive Control

2.4.3.1 CLOX: An Executive CLock-drawing Task: {24}: CLOX is a brief ECF measure based on a clock-drawing task (CDT). It is divided into two parts. CLOX1 is an unprompted task that is sensitive to executive control. CLOX2 is a copied version that is less dependent on executive skills. CLOX1 is more “executive” than several other comparable CDTs. {25} Each CLOX subtest is scored on a 15-point scale. Lower CLOX scores are impaired. Cut-points of 10/15 (CLOX1) and 12/15 (CLOX2) represent the 5th percentiles for young-adult control subjects.

2.4.3.2 The Executive Interview (EXIT25) {26}: The EXIT25 provides a standardized clinical ECF assessment. Items assess verbal fluency, design fluency, frontal release signs, motor /impulse control, imitation behavior, and other clinical signs associated with frontal system dysfunction. EXIT25 scores correlate well with other ECF measures including the Wisconsin Card Sorting Task (WCST) ($r=-.54$), Trail Making Part B ($r=.64$), Lezak’s Tinker Toy test ($r=-.57$), and the Test of Sustained Attention (Time, $r=.82$; Errors, $r=.83$). EXIT25

scores range from 0 to 50. High scores indicate impairment. A score of 10 /50 reflects the 5th percentile for young adults. Scores 15 /50 suggest clinically significant ECF dysfunction.

2.4.3.3 Trail Making Test Part B {27}: (Reitan, 1958) Trail Making is a test of conceptualization, psychomotor speed and attention. The subject draws lines to connect consecutively numbered circles on Trails A. Trails B requires the subject to connect consecutively numbered and lettered circles, alternating between the two sequences. The time in seconds to complete each task is recorded.

2.4.4 Visuospatial Function—CLOX2 and Trails A were used as foils to their more executive counterparts, CLOX1 and Trails B. In addition we used the Weschler Adult Intelligence Scale-Revised (WAIS) Digit Symbol Coding (DSS). {28} The DSS is a test of psychomotor speed and attentional control. The subject is asked to copy, as quickly as possible, nonsense symbols corresponding to specific numbers presented in a key at the top of the page.

2.5 Cardiovascular Assessment

Potential subjects with self-reported histories of diabetes, acute myocardial infarction (AMI), cerebrovascular accidents (CVA), valvular heart disease, or cardiothoracic surgery were excluded. Subjects without self-reported AMI or CVA were further tested with resting electrocardiography (ECG) and T2 weighted MRI. Five subjects were excluded because of abnormal ECG findings, including silent AMI by ECG, > first degree heart block, bundle branch blocks, or atrial fibrillation. Subjects with supraventricular arrhythmias and /or first degree heart block were allowed.

Potential subjects with any self-reported history of valvular disease or congestive heart disease were excluded. Echocardiography (2D ECHO) was obtained in a subset of cases with self-reported orthopnea /dyspnea on exertion. No subject had an abnormal left ventricular ejection fraction.

At MRI, subjects were screened for focal cortical lesions, or lacunar subcortical grey matter lesions. None were excluded on this basis. Subjects with “ischemic” periventricular white matter disease were allowed.

Autonomic function in the remaining cases was assessed by ECG and 24 hour Holter monitoring. Mean p-r (PR) intervals and rate corrected Q-T intervals (QTc) were calculated from Holter records. Systolic blood pressures (SBP) were assessed lying, sitting and standing, by mercury sphygmomanography, using a size appropriate cuff in the right upper extremity. Positional blood pressure changes (SBP) were assessed by the difference between sitting and standing SBP.

2.6 Statistical Analyses

Cross-group differences were tested by Student's t test, and Analysis of Variance (ANOVA). Associations between continuous variables were tested by parametric correlations. Significant univariate correlations were adjusted in multiple regression models. Because of the small sample size, regression models were limited to one covariate.

3. Results

Left (L) and R insular rCBF were highly intercorrelated ($r = 0.97$, $p < 0.001$). Each was also strongly correlated with both total white matter and frontal cortical rCBF ($r = 0.80$ – 0.83 , all $p < 0.001$).

Mean resting insular rCBF was significantly higher on the R (t-test for dependent samples: $t = 2.5$; $p = 0.02$) and the ratio of R:L insular rCBF was skewed in favor of R insular dominance. On the other hand, 10/29 subjects (34.5%) had L dominant rCBF and were assigned to the theoretically "HIGH" risk group, defined by relatively low R insular rCBF.

Clinical data, stratified by "risk" group, are presented in Table 1. There were no differences in L insular, frontal or white matter rCBF across HIGH /LOW risk groups. In contrast, R insular rCBF was significantly lower in HIGH risk group (by ANOVA: $df\ 1,28\ F = 6.5$; $p = 0.01$). The ratio of R insular to frontal rCBF was significantly lower in the HIGH risk group [$t = -2.54\ (27)$, $p = 0.017$]. There was no difference in the ratio of L insular to frontal rCBF. Similarly, the ratio of R insular to total white matter rCBF was significantly lower in the HIGH risk group [$t = -2.86\ (27)$, $p < 0.01$]. There was no difference in the ratio of L insular to total white matter rCBF. These findings suggest an absolute reduction in R insular rCBF in HIGH risk cases.

The HIGH risk group also had a greater positional drop in blood pressure [by ANOVA: $df\ (1,27)\ F = 4.9$, $p = 0.04$] (Figure 1). There were no cross group differences with regard to resting heart rate, mean 24 hour P-R interval, or mean 24 hour rate corrected QT interval.

The HIGH risk group was significantly younger [$t = -2.39\ (27)\ p = 0.02$], and had fewer depressive symptoms on the GDS [$t = -2.24\ (26)\ p = 0.03$]. Neither group approached the threshold for clinically significant GDS scores. HIGH risk subjects performed significantly better on the COPLT [Short: $t = 2.95\ (22)$, $P = 0.01$]; Long: $t = 2.44\ (22)$, $p = 0.02$], but not the RAVLT. The HIGH risk group also performed less well on the Trails A [$t = -2.15\ (27)$, $p = 0.04$]. There were no cross-group differences on measures of general cognition (MMSE) or executive function (CLOX1, EXIT25, Trails B) and the mean scores were in the normal range on all of these measures.

Positional blood pressure change was significantly associated with memory, as measured by the COPLT [TOTAL: $r = -0.44$, $p < 0.05$; Short: $r = -0.49$, $p < 0.05$; Long: $r = -0.44$, $p < 0.05$]. However, these associations were all inverse, suggesting that positional drops in blood pressure were associated with better memory performance. These associations resisted adjustment for age. However, no memory measure predicted positional blood pressure change after adjusting for R:L insular rCBF (all $p = ns$), suggesting that asymmetric insular function mediates their association. Positional blood pressure change was not significantly correlated with RAVLT scores, CLOX1, CLOX2, DSS, EXIT25, MMSE, Trails A /B, or UPSIT scores.

The ratio of R:L insular rCBF was also significantly associated with COPLT and not RAVLT performance, (COPLT /Total: $r = -0.46$, $p < 0.01$; COPLT /Short: $r = -0.68$, $p < 0.01$; COPLT /Long: $r = -0.70$, $p = 0.005$). These associations were again inverse,

suggesting that asymmetric reductions in R insular rCBF predicted better memory performance. Conversely, asymmetric reductions in L insular rCBF would be associated with worsened memory performance. The associations between R:L insular rCBF and COPLT /Short, and COPLT /Long resisted adjustment for age.

4. Discussion

We have demonstrated a significant association between the ratio of R:L insular rCBF and 1) positional blood pressure changes, and 2) cognitive test performance, especially on memory measures, in a small sample of elderly persons, free of comorbid diabetes mellitus or cardiovascular disease.

Moreover, these associations can be demonstrated in the absence of clinically significant cognitive impairment. These data support our hypothesis that a subset of non-demented elderly persons (35% of this sample) exhibit relatively reduced R insular rCBF. This asymmetry appears to be related to absolute reductions in R insular rCBF, rather than relative increases in L insular rCBF.

Since autonomic control is lateralized in humans at the level of the insula this may have implications for autonomic related morbidity and mortality in the elderly. Hilz et al. {6} have demonstrated positional drops in systolic blood pressure and augmentation of “high frequency” (HF) spectral power density in inter-beat R-R heart rate variability (HRV) among epileptic subjects undergoing R hemisphere cortical functional inactivation as part their perioperative assessments. As in this study, asymmetric R hemisphere dysfunction was associated with a drop in positional blood pressure, but not resting heart rate, and the absolute value of the positional changes was somewhat less than that which is felt to be clinically “meaningful”. Nonetheless, HF spectral power has been previously associated with parasympathetic modulation {29} and is a significant predictor of mortality. {30}

The cause(s) for an absolute reduction in R insular rCBF among the HIGH risk group cannot be determined from these data. However, it is not likely to be due to ischemic lesions, as these subjects were carefully screened for ischemic cardiovascular disease, and did not exhibit gross ischemic cerebrovascular disease in their T2 weighted MRI scans. On the other hand both AD and Lewy Body Disease (LBD) are associated with insular lesions {31} and LBD is associated with greater visuospatial cognitive impairment {32}, accelerated mortality {33} and greater fall risk {34} than AD.

We are currently testing the hypothesis that insular neurodegenerative changes are associated with autonomic dysfunction among decedents from the Honolulu-Asia Aging Study (HAAS). Our preliminary data suggests that the associations between age, QTc intervals and survival are moderated by insular NFT counts. {12} Insular involvement by the AD process would require a Braak stage of at least II-III. {13} These Braak stages are consistent with normal cognition /MCI {35} and thus with the range of test scores we observed in this sample.

However, we have unexpectedly found the HIGH risk group to be younger and generally less memory impaired than those in the LOW risk group. Similarly, memory impairment,

even on the COPLT, was inversely related to the observed asymmetric reduction in R insular rCBF and positional changes in blood pressure.

There might be several reasons for this. First, this finding may be spurious. Our sample size is small and multiple comparisons favor spurious associations. On the other hand, we previously observed a specific association between Trails A and survival {2}. This association did not extend to Trails B or comparable executive measures (e.g., CLOX1 or the EXIT25). Similarly, the HIGH risk group in this study performed significantly worse on Trails A, but neither Trials B, CLOX1, or the EXIT25, consistent with our previous results.

Second, the insular mediated positional changes we observed might be due to medication effects not considered here. However, this does not seem likely. First, medications would be expected to affect the insula bilaterally, as has been shown for antidepressants {36} and antipsychotics. {37} Second, certain medications that might be expected to affect both memory and autonomic control (e.g., anticholinergics and antidepressants), would be expected to favor a positive association between memory impairment and positional changes in systolic blood pressure. The use of acetylcholinesterase inhibitors among memory impaired subjects might explain an inverse association between the severity of memory impairments and orthostasis, as the latter is a known side-effect of this class.

Finally, it may be that memory tasks, even visual memory tasks such as the COPLT, depend on left mesiotemporal regions of interest. In fact, surprisingly little is known about the CNS correlates of many cognitive measures, and even clock-drawing tasks can be associated with left hemisphere ROI. {38–39} Lye et al. {40} report significant associations between L, not R hippocampal atrophy and a visuospatial memory task in a large non-demented elderly sample of similar age and MMSE performance to our own. Similarly, Stern et al. {41} report L anterior insular activation during a verbal memory task. Thus, poor memory performance in our subjects may reflect asymmetric AD pathology involving the left hemisphere, favoring a low risk presentation. This would explain our failure to associate memory measures with mortality in elderly retirees. {2}

In summary, a substantial fraction of well elderly persons free of clinically significant cardiovascular disease can be demonstrated to have asymmetric resting insular rCBF by pMRI. This has implications for autonomic related morbidity and mortality in the elderly. A greater positional drop in blood pressure can be demonstrated in association with L>R insular rCBF, and absolute reductions in R insular rCBF. These changes can be demonstrated in the absence of dementia. Although these data cannot address the cause of these asymmetries in insular rCBF, preclinical AD pathology is endemic in the non-demented elderly, involves the insula, and is likely to be unilateral in its earlier stages.

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Figure 1.
Positional Change in Systolic Blood Pressure

Table 1

Clinical Characteristics by Risk Group

	HIGH RISK Mean (SD) N = 10	LOW RISK Mean (SD) N = 19	t-value	df	p
AGE	76.60 (4.1)	80.68 (4.5)	-2.39	27	0.02
%Female	37.4	30.8	0.34	27	0.74
R/L	0.90 (0.06)	1.15 (0.09)	- 8.37	27	<0.001
L/W	1.70 (0.37)	1.77 (0.42)	-0.46	27	0.65
R/W	1.52 (0.33)	2.05 (0.53)	- 2.86	27	<0.01
L/G	0.99 (0.35)	1.05 (0.30)	- 0.52	27	0.61
R/G	0.89 (0.32)	1.21(0.33)	- 2.54	27	0.017
ECGHR	63.50 (8.62)	66.32 (8.83)	- 0.82	27	0.42
PR	180.40 (25.45)	177.79 (28.94)	0.24	27	0.81
QTc	426.10 (30.60)	419.63 (16.20)	0.75	27	0.46
SBP	-8.00 (12.68)	1.22 (8.90)	- 2.26	26	0.033
GDS	0.44 (0.73)	1.63 (1.50)	- 2.24	26	0.03
LUPSIT	9.25 (0.89)	8.11(2.58)	1.21	25	0.24
RUPSIT	8.75 (2.12)	7.58 (2.04)	1.35	25	0.19
R/LUPSIT	0.95 (0.24)	1.01 (0.35)	-0.43	25	0.67
MMSE	29.30 (1.06)	28.4 (1.17)	1.98	27	0.06
EXIT25	8.70 (2.31)	11.74 (5.21)	-1.75	27	0.09
CLOX1	12.20 (2.20)	10.00 (3.71)	1.71	27	0.10
CLOX2	13.90 (0.88)	13.21 (1.62)	1.25	27	0.22
DSS	44.00 (16.14)	37.689(62)	1.35	28	ns
TRAILS A	37.60 (8.14)	51.53 (19.47)	-2.15	27	0.04
TRAILS B	96.90 (27.59)	108.22 (35.88)	-0.86	26	0.40
RAV /TOT A1-5	38.50 (7.68)	36.26 (8.88)	0.67	27	0.51
RAV Retention	15.70 (2.41)	15.1667 5.33854	0.30	26	0.77
RAV /Short	7.80 (3.19)	6.05 (3.41)	1.34	27	0.19
RAV /Long	6.80 (2.39)	5.53 (3.41)	1.05	27	0.30

	HIGH RISK Mean (SD) N = 10	LOW RISK Mean (SD) N = 19	t-value	df	p
COPLT /TOT A1 A5	52.57 (7.21)	43.71 (13.71)	1.61	22	0.12
COPLT /Retention	15.71 (0.49)	15.77(0.75)	-0.16	22	0.87
COPLT /Short	12.86 (2.80)	7.82 (4.11)	2.95	22	0.01
COPLT /Long	13.43 (1.27)	8.88 (4.81)	2.44	22	0.02

COPLT /Long = Connecticut Picture Learning Test (COPLT) recall after 20 minute delay; COPLT /Retention = Immediate recall after distraction – the fifth learning trial on the COPLT; COPLT /Short = COPLT recall after distraction; COPLT /TOT A1–5 = Sum of learning trials 1 –5 from the COPLT; DSS = Digit Symbol Substitution; ECGHR = resting heart rate by electrocardiography; EXIT25 = Executive Interview; GDS = Geriatric Depression Scale (15 item short form); L/G = ratio of left insular / total grey matter rCBF by perfusion magnetic resonance imaging (pMRD); LUPSIT = left nostril University of Pennsylvania Smell Identification Test (UPSIT); L/W = ratio of left insular / frontal white matter rCBF by pMRI; MMSE = Mini-Mental State Exam; PR = mean p – r interval by 24 hour Holter; QTc = mean rate corrected Q-T interval by 24 hour Holter; RAV /Long = Rey Auditory Verbal Learning Test (RAVLT) recall after 20 minute delay; RAV /Retention = Immediate recall after distraction – the fifth learning trial on the RAVLT; RAV /Short = RAVLT recall after distraction; RAV /TOT A1–5 = Sum of learning trials 1 –5 from the RAVLT; R/G = ratio of right insular / total grey matter rCBF by pMRI; R/L = ratio of right / left insular rCBF by pMRI; R/LUPSIT = ratio of right / left nostril UPSIT performance; RUPSIT = right nostril UPSIT; R/W = ratio of right insular / frontal white matter rCBF by pMRI; SBP = change in systolic blood pressure from sitting to standing; TRAILSA /B = Trail-Making Test Parts A /B.