Brain Imaging Findings Predict Blood Pressure Response to Pharmacological Treatment

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Abstract—Hypertension appears to alter brain morphology, as well as the cerebrovascular support for information processing. Because these effects might reflect progressive effects of essential hypertension on the brain, we asked whether structural and functional brain indices would predict the success of pharmacological treatment of hypertension among 45 previously unmedicated individuals. After initial structural MRI and functional positron emission tomography imaging, subjects were randomly assigned in a double-blind fashion for treatment for 1 year with either lisinopril or atenolol. Systolic and diastolic blood pressure decreases after treatment stabilization were correlated to a pretreatment index of brain aging (combined ratings of ventricle and sulcal size and white matter hyperintensities) and the pretreatment change in regional cerebral blood flow during working memory in the thalamus and posterior parietal regions of interest. In multiple regression analyses, the structural brain index and the blood flow response in the thalamus predicted 20% of the variance in the systolic blood pressure response to treatment controlling for pretreatment blood pressure, age, gender, and type and dose of medication. Alcohol use influenced the thalamic response measure, but covariates did not alter the relation between greater indices of brain aging and less successful blood pressure response to treatment. The state of the brain may be an important factor in the remediation of blood pressure. (Hypertension. 2008;52:1-2.)

Key Words: hypertension ■ MRI ■ positron emission imaging ■ atenolol ■ lisinopril ■ cerebral blood flow ■ blood pressure treatment

A number of factors suggest that cerebral structure and function might relate to success of BP treatment. First, hypertension has been characterized as accelerated aging, and aging changes in the brain are well established.13–16 Second, hypertension has been related to changes in both brain structure and cerebrovascular responsivity during information processing.6,9,17–19 Third, hypertension in mid-to-late life is associated with mild cognitive deficits.7,11,20 These observations, which distinguish hypertensive patients from similarly aged normotensive individuals, suggest that the brain is a target organ for essential hypertension. The impact of the disease on the brain may also interact with treatment efficacy.21 Treatment-induced reductions in BP require adaptation of central nervous system blood flow regulation, an adjustment that may be more efficient in a “younger” brain.22 Indirect evidence for this suggestion is difficulty in controlling hypertension in the elderly, the increasing use of multiple drugs, and the high prevalence of difficult-to-control hypertension.23–25 Taken together, brain indices were hypothesized to predict the degree of success of BP lowering, because the state of the brain may indicate both severity and progression of hypertensive disease and capacity for return to normal regulation of blood flow and pressure.

Based on this rationale, we examined the success of pharmacological treatment of BP as a function of brain...
structure and responsivity. Relevant results were available from a project comparing the effects of an angiotensin-converting enzyme inhibitor and a \( \beta \)-blocker on regional cerebral blood flow (CBF; rCBF).\(^{26} \) We used structural indices of brain aging (sulcal and ventricular size, as well as white matter hyperintensities) and used a measure of functional cerebrovascular responsivity, the rCBF response to information processing in 2 areas previously shown sensitive to both aging and hypertension, the posterior parietal cortex and thalamus.\(^{9,27-29} \) Responsivity was examined, because overall CBF does not seem altered by hypertension in midlife samples.\(^{9,18} \) In sum, using data collected in a 1-year clinical trial involving 45 hypertensive individuals, we tested the hypothesis that magnetic resonance (MRI)–derived indices of brain aging and positron emission tomography (PET) indices of functional response to working memory predict the magnitude of BP lowering with standard pharmacological treatment.

### Methods

#### Participants

Participants were a community sample recruited from the Pittsburgh area via radio, television, newspaper, and health fairs. Participants were between 35 and 65 years of age and had an average diastolic (fifth phase) BP of 90 to 109 mm Hg, systolic BP of 140 to 179 mm Hg, or both. Nonelderly individuals with mild-to-moderate hypertension were selected to enhance the likelihood that treatment would facilitate the reversibility of any cerebrovascular dysfunction. Seated BP was assessed after \( \geq 5 \) minutes of rest using the auscultatory technique with a mercury manometer. Baseline BP was calculated from the average of the last 2 of 3 readings done on 2 occasions. Participants were required to have either no previous pharmacological treatment for hypertension or \( \leq 6 \) months of BP medication within the past 5 years, with no BP medication taken in the 6 months preceding enrollment. Detailed inclusion/exclusion criteria for this study have been presented previously.\(^{26} \) Screening was designed to exclude secondary hypertension, use of drugs/substances interfering with accurate and safe treatment assessment, and the presence of other serious disease, notably coronary or cerebrovascular disease. The University of Pittsburgh Institutional Review Board approved all of the procedures as consistent with ethical principles, and subjects provided informed consent.

#### Design

Initial BP assessment, medical screening and history, physical examination, administration of self-report questionnaires, and detailed consent followed telephone screening. The next session included the second BP assessment and neuropsychological examination. Separate sessions followed for brachial artery ultrasound, MRI, and PET examinations. All of the examinations were repeated after 1 year, except for the screening and self-report instruments. Details of psychological and neuropsychological testing and results will be presented elsewhere. This report focused on 43 of the 45 participants who completed the entire study. Participants were similar to noncompleting individuals in age, education, and personality factors; they differed in that continuing participants were significantly \( \chi^2 \) \( P<0.05 \) more likely to be male, white, and married.

#### Medication Procedures

Patients were treated for 1 year within a randomized, double-blind design using either lisinopril or atenolol, a choice of drugs based on the initial hypothesis that lisinopril would alter brain function more than atenolol.\(^{26} \) Medications were contained in unembossed capsules to ensure blinding. During a 6-week titration phase, drug dosage was gradually increased across 4 dosage levels: 10, 20, 30, and 40 mg for lisinopril and 25, 50, 75, and 100 mg for atenolol. During this phase, participants were seen every 2 weeks for dosage adjustment and determination of BP, compliance, and adverse effects. Upward titration stopped if a participant’s BP had fallen to \( \leq 135/85 \) mm Hg or if resting pulse fell to \( <50 \) bpm. If a participant’s BP remained \( >140/90 \) mm Hg on the full-dose treatment, 12.5 mg of hydrochlorothiazide was added (4 in lisinopril group and 7 in \( \beta \)-blocker group). Participants were withdrawn from the study if BP averaged \( >160/95 \) mm Hg on 2 consecutive visits during the maintenance phase (week 6 through the final visit at week 52). During visits, physical symptoms and impact of hypertension on quality of life were assessed with the Buphilt Hypertension Questionnaire, and ad- herence was estimated based on returned pill counts. The BP treatment effect was calculated from standardized BP assessment performed during the last regular clinical visit (approximately week 40). Estimates from final readings during the PET session (week 52) were deemed unrepresentative given the stress of that session.

#### Structural MRI Measures

All of the subjects underwent a structural MRI using a GE Signa 1.5 T scanner to provide a detailed image for mapping PET results and for assessment of white matter hyperintensities. A brief scout T1-weighted image was followed by an axial series oriented to the plane along anterior and posterior commissures: fast spin echo T2-weighted (effective echo time/repetition time: 102/2500 milliseconds, 1 excitation), proton density–weighted (effective echo time/repetition time: 17/2000 milliseconds, 1 excitation), and fast fluid-attenuated inversion recovery (FLAIR; effective echo time/repetition time: 56/9002 milliseconds, time to inversion: 2200 milliseconds, 1 excita- tion). Section thickness was 5 mm with a 1-mm intersection gap. A field of view of 24 cm and image matrix of 256\( \times 192 \) pixels were used for all of the axial magnetic resonance series. A volumetric spoiled gradient-recalled sequence with parameters optimized for maximal contrast among gray matter, white matter, and spinal fluid was acquired for purposes of region of interest (ROI) placement in the coronal plane (echo time/repetition time: 5/25 milliseconds, flip angle 40°, 1 excitation, section thickness 1.5 mm, 0-mm intersection). Severity of white matter hyperintensities, ventricle size, and sulcal size were graded using a 10-point scale (range of these summary measures: 0 to 27) by 2 trained raters using standards developed for the Cardiovascular Health Study.\(^{33} \) Percentage agreement on the ratings done from T1, T2, and proton density images was 93% and for FLAIR images was 94%. Participants showing evidence of significant lacunar or other infaracts (n = 2) were excluded from participation. These were identified from the MRI films by a board-certified neuroradiologist. Significant infarcts were those judged to potentially influence functional images and/or to influence cognitive processing.

Two summary measures of brain aging were created. Based on ratings of T2/T1/proton measures, we combined ventricular size, sulcal size, and white matter load (correlations between individual scores and index, \( r=0.69 \) to 0.84). Based on the FLAIR images, we combined overall brain ratings of ventricle size, of sulcal size, of periventricular white matter load, and of subcortical white matter load (correlations between individual scores and index, \( r=0.67 \) to 0.86). Ratings were scaled identically (0 to 9), so ratings from each category were simply added together (combined with equal weight- ing). Because of technical issues, 1 fewer patient had FLAIR indices available relative to the T2/T1 index. We only present FLAIR-based rating data, however, because this modality has greater specificity for white matter abnormalities. Both summary indices, however, related very similarly to BP results.

#### Functional PET Measures

Four quantitative (arterial sampling) PET scans were performed that tested rCBF responses during information processing (working memory tasks). Two scans examined a control state and 2 the active memory state; task order was randomized. Each task used the same display and 2 button responses. The control memory task required the subject to respond by tapping the right. The 2-back memory task required the subject to respond by tapping the left of the screen and with the index finger for a letter appearing on the right. The 2-back memory task required the subject to respond...
with the thumb if spatial position of the letter currently appearing matched the spatial position, which appeared 2 times back, and the index finger if it did not. Each task lasted 5 minutes and started 2 minutes before tracer injection. An intertask interval of ~5 minutes rested the subject and permitted time for preparation and delivery of the tracer. See our previous article for further description.\textsuperscript{28} PET scans were acquired, in 3D imaging mode, using a Siemens/CTI ECAT HR+PET scanner (63 transaxial planes, 2.4-mm section thickness). PET data were corrected for radioactive decay, photon attenuation, and scatter.\textsuperscript{34} Data were reconstructed using filtered backprojection. The final image resolution was ~6 mm (transverse and axial). Head motion was minimized using a thermoplastic mask. A peripheral vein catheter was inserted for tracer injections and a radial artery catheter for arterial blood sampling. An initial 10-minute transmission scan was performed using rotating 68Ge/68Ga rods (attenuation correction). Nine millicuries of $[^1^\text{O}]$Owater were injected as a rapid bolus using an automated injector system. A 180-second emission scan was acquired in 20 sequential frames (10×3 seconds, 3×10 seconds, 4×15 seconds, and 3×20 seconds), followed by a 5-minute rest period for a total of 8 minutes between injections. Through calibration measurements, both blood and PET brain time-activity data were converted to microcuries per milliliter. All of the PET images were corrected for small head movements using Automated Image Registration,\textsuperscript{35} which was also used in a modified form to align and center the PET data.\textsuperscript{36}

### Quantitative CBF

The $[^1^\text{O}]$Owater data were analyzed using a 1-tissue compartment model.\textsuperscript{37,38} Model parameters corresponded with the clearance of water from blood to brain ($K_1$: mL/min per milliliter), brain-to-blood transfer ($k_2$: min$^{-1}$), and an arterial input function timing delay ($\Delta t$). The 3 parameters were simultaneously determined using an iterative least-squares curve fitting on a regional basis. $K_1$ is a clearance parameter that is directly proportional to flow, and $k_2$ was used as a blood flow measure (mL/min per milliliter).

ROIs were defined based on areas of activation that differed between patients and normotensive controls in a previous/separate study.\textsuperscript{9} The ROIs were regionally defined on the spoiled gradient-recalled MRI for each participant and manually drawn using a version of the Imagetool software (CTI PET Systems). ROI placement is illustrated in a previous online supplement.\textsuperscript{26} For current purposes, we examined the response to 2-back memory relative to control in the thalamic and posterior parietal ROIs, because these differed between hypertensive patients and controls in our previous work.\textsuperscript{9}

### Analysis

We tested the hypothesis that the brain aging index and rCBF response to working memory in thalamic or posterior parietal ROIs would predict treatment outcome using ordinary least-squares multiple regression (StatSoft, Inc). A hierarchical regression analysis was performed. In step 1 (basic model), age, drug assignment (lisinopril versus atenolol), and pretreatment systolic BP were used to predict change in systolic BP with treatment. Step 2 added variables to see whether they further explained variance in treatment response after adjustment for the basic model. Separate step 2 models were tested for parietal response during working memory, thalamic response during working memory, and brain aging index. Brain factors that significantly improved on the variance explained by the basic model were then entered together in a separate step 2 model to provide an estimate of overall prediction of BP treatment success using brain indices. Finally, covariates (see Table 1) were added to this model to see whether they altered the predictivity of brain factors. A covariate for dosage levels was used with a score corresponding to the dose level achieved at the end of treatment (1 to 4 for lisinopril or atenolol dose level and a 5 if hydrochlorothiazide was added). Because of the relatively small sample size, covariates were not added concurrently. The same analytic approach was repeated with diastolic BP and pulse pressure change during treatment as the dependent variable.

### Results

#### Participant Characteristics

Figure 1 diagrams selection and retention characteristics of the sample. Medication was well tolerated, but a substantial number of patients were excluded after initial consent because of our medical exclusions (see above) and because of their loss of interest before treatment but after further consideration of the demands of the study.

Table 1 provides details of subject characteristics. To provide evidence of the variability in treatment response and to allow examination of factors related to treatment response, the sample was divided by median systolic BP response. Most baseline characteristics and medication type (lisinopril or atenolol) did not significantly influence BP response; however, higher initial systolic BP was associated with a greater decrease in systolic BP with treatment.

Overall, patients showed values of white matter and rCBF response indices comparable to previous work. Ratings from the FLAIR images showed mean values (SEs) for ventricle size of 2.30 (0.14), sulcal size of 2.70 (0.15), periventricular white matter of 1.40 (0.13), and subcortical white matter of 1.50 (0.27). These values are comparable to those from our previous study\textsuperscript{9} and appear appropriate for age in comparison with epidemiological data.\textsuperscript{33} Similarly, values observed were somewhat higher but comparable to ours and others for mean rCBF in the thalamic area (63.8 [(2.1] mL/min per milliliter) and response in this area to the 2-back memory task (3.9 [0.9] mL/min per milliliter).\textsuperscript{9,39,40}

#### Association With Treatment Response

MRI indices of brain aging, as well as the responsivity of the thalamic ROI during PET scanning, were associated with a subsequent degree of BP lowering with treatment. Table 2 shows the results of the hierarchical multiple regression analyses. Step 1 in the analysis tested a basic model that included age, medication type, and initial BP (factors typically assumed to alter treatment response). The table shows the standardized $\beta$ weights for the predictors as related to the change in BP in millimeters of mercury. For example, pretreatment BP shows a negative $\beta$ weight, indicating that the higher initial pressure was related to a greater decrease in BP with treatment. Step 2 analyses then asked if further variance in treatment outcome could be explained by brain variables. Step 2a added the brain aging index. Step 2b added only the responsivity in the thalamic ROI. Step 2c added the brain aging index and the thalamic responsivity concurrently. The increment in variance explained associated with each step 2 analysis is shown in the far right column. Addition of the parietal ROI is not shown, because responsivity in this area failed to relate to BP treatment response. Note that the “n” with different analyses differs somewhat, eg, the “n” for the PET response is decreased because of refusal of the arterial catheter by 4 participants. The step 2c model with both the FLAIR index and thalamic responsivity predicted 60% of the variance in SBP treatment outcome. Brain indices added 20% to the prediction of the basic model. The regression results in Table 2 are supplemented by Figure 2, which
illustrates the basic bivariate relationship between the systolic BP treatment outcome and brain aging.

The combined model, ie, brain aging and thalamic responsivity, together with the factors in the basic model, was further tested using diastolic BP and pulse pressure rather than systolic BP as the dependent variable. The results for diastolic BP completely paralleled the results for systolic BP shown in Table 2. Statistical significance at \( P < 0.05 \) or better was consistent with the systolic BP results throughout. The combined model showed significant standardized \( \beta \) for initial diastolic pressure (-0.429, \( t = -2.98, P < 0.001 \)), FLAIR aging index (0.374, \( t = 2.19, P = 0.03 \), and rCBF change in the thalamic ROI (-0.351, \( t = 2.42, P = 02 \). Results for pulse pressure remained significant only for the FLAIR
FLAIR MRIs (43).

white matter lesions and ventricle and sulcal size derived from

All of the $P<0.001$, FLAIR aging index at 0.318 ($t=2.28$, $P=0.03$), and rCBF change in the thalamic ROI at $-0.143$ ($t=-1.17$, $P$ value not significant).

Covariates were added to the combined model to check for potential confounding. Race, body mass index, educational level, gender, number of cigarettes, dosage level, percent compliance, resting CBF, and estimated intelligence quotient all failed to make any significant change in the associations among the FLAIR brain aging index, thalamic ROI rCBF responsivity, and systolic BP treatment outcome ($P<0.05$ in all cases). Number of alcoholic drinks per week did not alter the influence of the brain aging index but did reduce the variance attributed to thalamic responsivity ($t=-1.52$, $P$ value not significant).

Discussion

A substantial fraction of the variability between patients in the success of 2 standard pharmacological treatments of BP was accounted for by a combination of structural and functional indices of the brain. Structural and functional indices were independently related to treatment outcome and were also independent of the influences of chronological age, medication type, and initial BP. Furthermore, a substantial number of covariates, which potentially could have accounted for our findings, failed to alter the results (body mass index, gender, race, drug dosage level, smoking, estimated intelligence, and percent compliance). Level of alcohol use did alter the strength of the functional, but not the structural, index’s relationship to treatment outcome.

Ratings based on FLAIR images of the brain were combined to provide a general index of brain aging. This index was related to BP treatment outcomes. Scores going into the index were morphological changes in the ventricles and sulci, as well as the presence of small lesions in white matter. Subsequent checks on the contribution of these individual scores to the treatment effects showed that each score demonstrated the same direction of relationship with BP change, albeit with some variation in the strength of the relationship. The FLAIR index was recomputed without the subcortical white matter index, which was not an original scoring dimension in the Cardiovascular Health Study. Results remained essentially the same. Given this, the combined indices should provide more reliable and replicable measures than the individual scores.

Our results show poorer responses to treatment among hypertensive individuals with greater brain aging relative to their chronological age. This may imply that hypertension accelerates brain aging or that a third factor influences both hypertension and brain aging. Interestingly, accelerated aging has been postulated previously as an effect of hypertension based on physiological data unrelated to brain function or structure. Alternatively, Diz and Lewis recently reviewed results suggesting that the brain renin-angiotensin system may have parallel effects on aging and BP. Given the evidence that BP reduction can be resistant to treatment in a significant portion of cases, particularly among the elder-
ly, 23–25 our results suggest that an aging brain may impede successful therapy.

The thalamic rCBF response to working memory tasks but not to the posterior parietal rCBF response related to the success of BP treatment, although this effect was not significant for pulse pressure or when alcohol use was controlled. Among the ROIs studied in our previous work, only the thalamic and posterior parietal showed a diminished rCBF response to working memory relative to our normotensive controls. 9 Given this, we examined these 2 ROIs to see if the degree of diminished perfusion would relate to success of treatment. The thalamus shows reduced metabolic activity with aging 27,45 and less gray matter volume with age in some but not all of the studies. 20,46 Changes with age in thalamic activity during working memory tasks have been less consistently identified. 28,47 Overall, however, the thalamus may be more susceptible to age-related, and possibly alcohol-related, changes than the posterior parietal regions. This susceptibility appears to extend to the influence of hypertension and potentially accounts for the relationship of thalamic responsivity, but not posterior parietal responsivity, to the efficacy of BP treatment.

Except for the influence of alcohol use on the thalamic relationship just noted, neither basic demographic factors nor health -relevant factors modified the relationship between brain indices and treatment success. Compliance to treatment was uniformly high in this sample and unrelated to either BP or brain measures. There was minimal dropout after treatment was initiated. Overall, however, no covariate of our brain measures provided a convincing alternative explanation of the link between brain indices and treatment outcome.

Our interpretations are limited by our data. Our sample size and representativeness were constrained by the requirement for initially nonmedicated patients and the general acceptability to potential participants of imaging procedures. This limits the generalizability of our results. We did not use a placebo-treated control group for ethical and cost reasons and, thus, cannot control for the effect of time and spontaneous changes in BP. Duration of heightened BP, indices of vascular aging, and related longitudinal data were not available but would be very important for refining our interpretation. Finally, we compared only 2 common BP medications, and the results may be specific to these medications.

Overall, however, we found a surprisingly strong relationship between brain indices and the success of standard pharmacological treatment of hypertension. We do not know of any physiological mechanism that would provide a convincing, definitive explanation of how brain aging or responsivity would influence treatment outcome. Two speculative implications may be worth noting, however. First, the pathology of essential hypertension may not solely influence BP but may have systemic effects that have suggested to many that it hastens biological aging. If so, then an early target of these processes may be the brain. A close examination of factors such as the actions of the angiotensin system in the brain and interactions with brain stem BP control areas would seem warranted based on this speculation. 21 Second, the systemic reaction to BP lowering, per se, may involve adjustments in the brain. Autonomic nervous system regulation of vascular tone, sensitivity of baroreceptors, and other regulatory systems should adjust to altered pressure profiles. Such adjustment may be more effective in those with “younger,” more responsive brains. Studies throughout the course of treatment could assess whether such changes occur and whether they directly contribute to treatment success.

Perspectives
The correlation between brain indices and treatment outcome would suggest that more aggressive treatment early in the course of hypertensive disease may be beneficial for brain structure and function. At present, the expense of brain imaging precludes diagnostic use, but technical advances may permit evaluation of the use of early treatment for brain structure and function in the foreseeable future.

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Disclosures
None.

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