THE EFFECTS OF HYPERTENSION ON THE NEURAL CORRELATES OF COMPENSATION IN OLDER ADULTS:
AN fMRI INVESTIGATION

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Abstract

The present study examined the effect of hypertension on older adults’ brain activity during semantic and episodic memory tasks of two difficulty levels using functional Magnetic Resonance Imaging (fMRI). Previous research has shown that hypertension has both structural and functional effects on the aging brain and that aging is associated with poorer memory. Imaging studies have shown that older adults who perform as well as younger adults on memory tasks show a bilateral pattern of frontal activation while older adults who perform more poorly than younger adults show the same unilateral pattern of activation as younger adults. The bilateral activation has been interpreted as compensation for neurocognitive changes. The purpose of this experiment was to determine whether hypertension affects older adults’ ability to compensate. We hypothesized that if hypertension affects compensation, then hypertensive participants would show less compensatory frontal activation than normotensive participants and demonstrate poorer performance; if hypertension does not affect compensation, then hypertensive and normotensive participants would show similar activation and performance. The results showed that hypertensive participants were as accurate as normotensive participants on the tasks but slower to respond. During the semantic task, hypertensive participants had similar activation to normotensive participants; during the episodic task, they had a greater extent of activity, consistent with the hypothesis that the task was more difficult for them. Hypertensive participants also had more increases in activation and suppression of default network areas when the difficulty of the tasks increased. Since both groups exhibited bilateral activation, we conclude that hypertension is not what clearly determines older adults’ ability to engage in frontal bilateral compensatory patterns. Hypertension does have an effect on activity, however, in that hypertensive participants engaged in compensatory brain changes during the tasks to achieve a similar level of performance as normotensive participants.
1. Introduction

Hypertension, or high blood pressure, is a common problem among Americans. The Center for Disease Control estimates that in 2005-2006, hypertension was present in 28% of American adults; among older adults, it was more prevalent, with 67% of people over the age of 60 affected (Ostchega, 2008). Hypertension is usually defined as systolic blood pressure (BP) greater than or equal to 140 mm Hg or diastolic BP greater than or equal to 90 mm Hg (Ostchega et al., 2008). It has many negative health consequences, including increased risk of heart failure, stroke, and kidney disease (Chobanian et al., 2003).

Previous neuroimaging research has shown that hypertension also has negative effects on brain structure. Raz, Rodrigue, & Acker (2003) found that older adults with treated hypertension had lower prefrontal cortex (PFC) volumes than normotensive controls, as well as lower prefrontal white matter volumes and more frontal white matter hyperintensities (WMHs). The duration of the hypertension was associated with increased WMH volume—the longer the participants had hypertension, the more WMHs they had (Raz, Rodrigue, & Acker, 2003). Similar findings were reported by Knopman et al. (2005), indicating that hypertension and the use of antihypertensive medication was associated with bigger sulcal size and more WMH (Knopman et al., 2005).

Hypertension also affects the rate of age-related degeneration. Akiyama et al. (1997) conducted a 3-year longitudinal study and found that hypertension accelerated cortical atrophy, ventricular enlargement, and cortical perfusion declines in neurologically and cognitively normal older adults with both treated and untreated hypertension. Raz et al. (2005) also found that treated hypertension in older adults was associated with lower hippocampal volume at baseline, greater shrinkage in the orbitofrontal cortex (OFC) and hippocampus at a 5-year follow-up.
Regional cerebral blood flow (rCBF) is affected by hypertension as well. Dai et al. (2008) looked at resting state rCBF in cognitively normal older adults with treated hypertension and found that they had lower rCBF in several brain areas, including the putamen, globus pallidus, anterior cingulate gyrus, and left hippocampus, compared to normotensive controls (Dai et al., 2008).

Hypertension not only affects the structure of the brain, but also the function. One study found that blood pressure levels at baseline were inversely related to poorer cognitive performance at follow-up 12-22 years later in untreated hypertensive older adults (Elias et al., 1993). Scores on subsets of the Weschler Adult Intelligence Scale (WAIS), the Weschler Memory Scale (WMS), and the Multilingual Aphasia Examination (MAE) were used to determine cognitive performance and demonstrated statistically significant negative correlations with BP for logical memory, visual reproductions, digits backward, and logical memory delayed (Elias et al., 1993). These results were supported by Kilander et al. (1998), who found that diastolic BP at 50 years of age was inversely related to cognitive function, as determined by the Mini Mental State Examination (MMSE) and the Trail-Making Test (TMT), at 70 years of age in hypertensive men; this relationship was statistically significant for participants with untreated hypertension. Poorer cognitive performance in hypertensive participants was further confirmed by Tzourio et al. (1999), who found an association between high BP at baseline and cognitive decline (defined as a drop in score on the MMSE) four years later; this was stronger for untreated high BP. Raz et al. (2003) found that not only was duration associated with increased WMH volume, but also with lower performance on executive function and working memory tasks. In the same participants as in the 2005 study, Raz et al. (2008) found that the smaller prefrontal volumes seen in hypertensive participants were associated with lower fluid intelligence.
Regardless of the presence of hypertension, aging has been associated with memory deficits. This pattern of memory loss differs among memory types and individuals. Semantic memory, or knowledge and general facts about the world, tends to stay relatively stable with age; on the other hand, episodic memory, or memory for specific events, declines (for review, see Hedden & Gabrieli, 2004). The field has shown that during memory tasks, younger adults show a unilateral pattern of frontal activation, while older adults show a bilateral pattern. For example, in a Positron emission tomography (PET) study, Cabeza et al. (1997) reported that during verbal recall, older adults showed a more bilateral pattern of PFC activation than younger adults. These results were confirmed during spatial and verbal working memory tasks in another PET study, as Reuter-Lorenz et al. (2000) reported young adults showed right lateralized activation for the spatial task and left for verbal task, while older adults showed bilateral activation for both.

Cabeza (2002) proposed that the bilateral pattern of activation seen in older adults was not task-specific and instead indicative of general aging in a model he called Hemispheric Asymmetry Reduction in Older Adults (HAROLD). The two main hypotheses for why this occurs are dedifferentiation and compensation. The dedifferentiation hypothesis holds that the bilateral pattern of activation seen in older adults is a result of age-related inability to recruit specialized neural mechanisms (inability to differentiate), while the compensation hypothesis proposes that it is a way of countering (or compensating for) age-related neurocognitive decline. To test these hypotheses, Cabeza et al. (2002) used PET to scan younger adults, low-performing older adults, and high-performing older adults during recall and source memory for words they had recently studied. The results showed that the younger adults and the low-performing older adults showed the same unilateral patterns of frontal activation, while the high-performing older adults (those who performed as well as the younger adults) showed a bilateral pattern of frontal
activation (Cabeza et al., 2002), which supports the compensation hypothesis over the dedifferentiation hypothesis.

It is unclear as to what separates the low-performing older adults from the high-performers, as there is a lack of functional studies that use hypertensive participants. Cabeza et al. (2002) excluded hypertensive participants in their experiment and thus the finding cannot be directly related to the problem of hypertension. However, one PET study did find evidence for compensatory brain activation in hypertensive participants. Jennings et al. (2005) reported that during spatial and verbal working memory tasks, untreated hypertensive participants showed lower increases in rCBF in posterior parietal areas and thalamus compared to normotensive participants; further, hypertensive participants who performed poorly on the verbal task further showed less PFC rCBF than normotensives (Jennings et al., 2005). Interestingly, hypertensive participants who performed well on the verbal task showed increased rCBF response in the right amygdala and hippocampus, which was correlated with prefrontal rCBF and with performance, and this activation has been interpreted as a form of compensation (Jennings et al., 2005). Therefore, it is possible that hypertension has an effect on the compensatory brain activation seen in older adults.

Consequently, the aim of the present experiment was to employ functional Magnetic Resonance Imaging (fMRI) to investigate whether hypertension affects older adults’ ability to engage in compensatory brain activity. In order to test this, we administered two memory tasks, semantic and episodic, to hypertensive and normotensive older adults in the scanner. While we expected the semantic memory task to be easy for the participants, we expected the episodic task to be more difficult and thus better demonstrate the effects of hypertension. The stimuli used also had two levels of difficulty, easy and hard, which we expected would further differentiate the
hypertensive participants from the normotensive ones. We hypothesized that if hypertension has
an effect on compensation, then hypertensive participants would show less compensatory frontal
activation than normotensive participants and demonstrate poorer cognitive performance. If
hypertension does not have an effect on compensation, then hypertensive participants would
have similar activation to the normotensive participants and demonstrate similar cognitive
performance.

2. Methods

2.1. Participants

Eleven older adults (eight females), ages 63 to 83, were included in the study, six
hypertensive (HT) and five normotensive (NT). Participants were recruited through an existing
database of older individuals who had participated in the AD Risk project in the Cognition and
Neuroimaging Laboratories (CNL) at the University of Arizona. All participants were right-
handed, native English speakers, and cognitively normal (as defined by a score of 25 or higher
on the MMSE; Folstein, Fosltein, & McHugh, 1975). They were screened for exclusionary
criteria, including history of neuropsychological or psychiatric disorders, head trauma, alcohol or
drug abuse, stroke, or current depression.

Hypertension was defined as a self-report of physician-diagnosed hypertension. Five of
the six HT participants were on antihypertensive medication at the time they participated in the
study. Four measurements of BP were collected during the experiment (See Procedures below).
2.2. Neuropsychological Testing

Participants underwent neuropsychological assessment that included the Geriatric Depression Scale (GDS; Yesavage et al., 1983), a 30-item self-report measure used to identify depression in older adults, with a score of 0-9 considered normal. The assessment also contained the North American Adult Reading Test (NAART; Blair & Spreen, 1989), which is a measure of verbal intellectual ability. The MMSE was also administered. This 30-point questionnaire measures cognitive function using tasks such as orientation, mental math, and memory, and is used to screen for cognitive impairment and dementia. Scores on the vocabulary section of the Wechsler Abbreviated Scale of Intelligence (WASI; Psychological Corporation, 1999), which is a measure of word knowledge, were also included and obtained from the latest neuropsychological testing session of the AD Risk project, which had taken place roughly within the year before the participant was scanned in the current study.

2.3. Materials and Procedures

2.3.1. Materials

Participants were presented with word pairs, either similar or opposite in meaning. The word pairs had two levels of difficulty, easy and hard, based on written frequency value norms from Francis & Kucera (1982) and separated into high and low frequency. The stimuli were collected online at http://wordplay.geneseo.edu (which provided frequency information) and were organized into two lists containing the same word pairs but with items in a different random order in each list and the lists counterbalanced in presentation.

High frequency pairs were made up of words common in the English language, such as “damp-moist.” The average frequency for the words at this level was 19.4 and the average word
length was 7.6 letters. Low frequency pairs were made up of words that are found on standardized tests, such as the Graduate Record Examination. An example of such a word pair is “garrulous-taciturn.” The average frequency for the words at this level was 2.0 and the average word length was 8.1, comparable to the high frequency words.

The stimuli in the semantic task consisted of 96 total word pairs, half of which were similar and half opposite. The word pairs were also divided into half high frequency and half low frequency. In this task, the easy level was made up of high frequency words and the hard level of low frequency words. This is because the high frequency words are more common and participants were more likely to know the meanings. The task also included 40 controls, in which the participants saw either the word “left” or the word “right”, paired with “xxxx” for visual consistency, and had to press the left or right mouse button, respectively. Each pair was presented for four seconds with an intertrial interval of one second.

The stimuli in the episodic task consisted of the 96 pairs presented in the semantic task plus 48 previously unseen pairs (lures). The lures were similar to the original word pairs in frequency and length, with the high frequency averaging 14.9 and 7.1 letters and the low frequency averaging 1.8 and 7.5 letters. The word pairs were again divided into half similar, half opposite and half easy, half hard. In this task, the easy level was made up of low frequency words and the hard level of high frequency words. This was done to account for the novelty effect, which implies that the words participants had a harder time defining are those they are more likely to remember. This task included 42 of the same controls as in the semantic task. Each pair was presented for four seconds with an intertrial interval of one second.
2.3.2. Experimental Tasks

The stimuli were presented to the participants with DMDX stimulus presentation software (Forster & Forster, 2003) through high-resolution digital goggles (VisuaStim, Resonance Technology, CA). Participants made responses using an MR compatible computer mouse.

In the semantic task, participants were presented with pairs of words and were asked to judge if the two word were similar or opposite in meaning. There was also a third option in this task where participants could choose “don’t know,” although they were encouraged to make educated guesses if possible. This task was broken down into two sessions of 6.5 minutes each.

In the episodic task, participants were again presented with pairs of words; however, rather than judging their meanings for similarity, they were asked to determine if they had seen the pair in the previous task or not. This task was broken down into three sessions of 6 minutes each. Figure 1 illustrates a typical sequence of stimuli presentation in the semantic and episodic tasks.

Figure 1: Visual representation of the semantic and episodic tasks.
2.3.3. Procedures

Participants were contacted via telephone and screened for contraindications to MRI. When they arrived at the scanner at the University Medical Center, they were seated and underwent written consent and neuropsychological testing. Immediately following, BP was measured using an automatic cuff by one experimenter. Participants were then trained on the semantic task and practiced until they understood the instructions. BP was collected again (roughly five minutes after the first measurement) by the same experimenter, with the participants having been seated the entire time. Participants were then familiarized with the MRI procedure. Once they were clear of all metal, they lay down on the scanner bench, were equipped with ear plugs, head phones, microphone, and goggles, and were moved into the scanner. Structural images were first collected. The participants then completed both sessions of the semantic task, were instructed on the episodic task, and completed all three sessions. Each participant was in the scanner for a total of approximately 60 minutes.

After exiting the scanner, participants were seated and performed an extra behavioral task pertaining to the meaning of the pairs of words they were presented with in the semantic task. This was to make sure that they actually knew the words they responded to correctly during the semantic task and were not just guessing. BP was collected again, this time by a different experimenter, and then participants were asked about their medical history pertaining to hypertension. BP was collected a fourth and final time. Participants had been seated for at least ten minutes before each of the four measurements, as per BP collection guidelines. Additionally, two different experimenters collected BP to insure reliability across experimenters. Finally, participants were debriefed. The entire duration of the study lasted approximately two hours.
2.4. Image Acquisition

Participants were scanned on a General Electric 3.0 Tesla HD Signa Excite long bore scanner (Milwaukee, WI). A 3-plane localizer image was acquired, followed by a 3D spoiled gradient-echo MRI (3D SPGR) pulse sequence with a section thickness of 1.5 mm. The functional data was acquired parallel to the anterior-posterior commissure plane in a spiral in-out sequence (inferior to superior direction, TR = 2100 ms, 32 sections, thickness = 3.8 mm, FOV = 24 cm) with 240 total trials in five sessions, two of which were 6.5 minutes and three of which were 6 minutes.

2.5. Image Analysis

Functional data was analyzed using SPM5 in MatLab 6.5. Each participant’s data was slice timed, realigned, normalized to the Montreal Neurological Institute (MNI) template, and smoothed with a 7-mm full-width half-maximum (FWHM) Gaussian smoothing kernel. For first-level analysis, each possible condition (semantic easy hit, semantic easy miss, episodic hard hit, etc.) was modeled for each individual. The activation during semantic hits was compared to the activation during controls in the semantic task and the activation during episodic hits was compared to the activation during controls in the episodic task. Individual contrasts were entered. For second-level analysis, HT and NT group contrasts were entered. A difficulty analysis was also performed, in which the model included a parametric modulation of difficulty. This is a linear regression with 1 entered for the easy levels of the task and 2 for the hard levels that computes the increases and decreases in activation as the difficulty level increased from easy to hard.
3. Results

3.1 Demographics

Demographic and neuropsychological test information for the participants is presented in Table 1. Group differences were assessed using t-tests with hypertension status as the between-participants variable. HT and NT participants were matched on age, education, GDS scores, NAART scores, MMSE scores, and WASI vocabulary scores ($t < 0.2$, ns).

Table 1: Demographic information and neuropsychological test results. HT and NT participants were matched on age, education, and neuropsychological test scores.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Age</th>
<th>Education</th>
<th>GDS</th>
<th>NAART</th>
<th>MMSE</th>
<th>WASI Vocabulary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>11</td>
<td>74.6 (63-83)</td>
<td>15.7 (12-20)</td>
<td>3.2 (0-7)</td>
<td>48.5 (34-64)</td>
<td>28.4 (25-30)</td>
<td>67.8 (54-77)</td>
</tr>
<tr>
<td>HT</td>
<td>6</td>
<td>76.8 (3.1)</td>
<td>15.8 (1.3)</td>
<td>3.7 (0.84)</td>
<td>49.7 (3.2)</td>
<td>28.8 (0.5)</td>
<td>68.3 (3.2)</td>
</tr>
<tr>
<td>NT</td>
<td>5</td>
<td>71.8 (1.6)</td>
<td>15.6 (1.0)</td>
<td>2.6 (1.17)</td>
<td>47.6 (4.0)</td>
<td>27.8 (0.9)</td>
<td>67.2 (3.9)</td>
</tr>
</tbody>
</table>

When averaging across the BP measurements, nine of the eleven participants had normal BP, as defined by systolic BP lower than 140 mm Hg and diastolic BP lower than 90 mm Hg (Ostchega et al., 2008). This demonstrates that the hypertension was effectively controlled by medication in HT participants and that NT participants did indeed have normal BP. BP data for one NT participant was missing due to the participant being scanned before the BP collection was implemented and another NT participant only had two BP measurements instead of four. The participant with BP above normal was the one HT participant not currently on antihypertensive medication and had an average measurement of 145/74. Interestingly, this participant’s BP was normal prior to the scan and high afterwards.
3.2 Behavioral Performance

To analyze performance, mixed factor ANOVAs were performed with HT status as the between-groups variable and difficulty level as the within-groups variables. For the semantic task, accuracy was defined by the number of hits. HT and NT participants performed similarly on the task, as Figure 2 shows that there was no difference in their number of hits ($F(1,9)<1$, ns). Additionally, the two groups had the same number of “don’t know” responses and no responses ($F(1,9)<1$, ns). A main effect of difficulty was observed in this task, with HT and NT participants having more hits on the easy level than on the hard ($F(1,9)=26.332$, $p<0.01$).

To determine accuracy on the episodic task, the number of corrected recognitions was analyzed. Corrected recognitions consist of hits minus false alarms and are a measure commonly used to indicate accuracy. This measure was not used in the semantic task because there were no false alarms. As Figure 2 shows, HT and NT participants had similar numbers of corrected recognitions ($F(1,9)<1$, ns). Additionally, the two groups also had the same number of no responses ($F(1,9)<1$, ns). Participants also showed a main effect of difficulty on this task, having a higher corrected recognition score on the easy level than on the hard ($F(1,9)=14.045$, $p<0.01$).

To analyze reaction time, mixed factor ANOVAs were calculated with HT status as the between-groups variable and difficulty as the within-group variable. In the semantic task, reaction times during hits were compared while the reaction times for both hits and false alarms were analyzed in the episodic task. On both tasks, HT participants were slower to respond than NT participants. As Figure 3 shows, HT participants had slower reaction times during both semantic hits ($F(1,9)=6.642$, $p<0.05$) and episodic hits ($F(1,9)=4.885$, $p=0.054$). Since corrected recognitions could not be used for reaction times, we also analyzed the reaction times for false alarms and found that there was no difference between the two groups ($F(1,8)<1$, ns).
A main effect of difficulty on reaction times was observed in the semantic task. Participants were faster to respond on the easy level than on the hard level for semantic hits ($F(1,9)=20.792, p<0.01$), but there was no difference between the two levels during episodic hits ($F(1,9)<1, \text{ ns}$).

Interestingly, the interaction between HT status and difficulty almost reached significance in the episodic task. Specifically, reaction times on the hard false alarms were approaching significance ($t(9)=2.041, p=0.072$), with HT participants ($M=2279.42, SE=157.57$) responding slower than the NT participants ($M=1830.38, SE=148.95$). On the easy false alarms, there was no difference between the HT participants ($M=2161.03, SE=88.53$) and the NT participants ($M=2180.97, SE=176.15, t=-0.101, p>0.05$).

Finally, all participants performed well in the definitions task, indicating that they knew the meanings of the words and were not simply guessing on the semantic task. HT and NT participants performed similarly on the definitions task ($F(1,9)<1, \text{ ns}$) and both groups performed better on the easy level than on the hard ($F(1,9)=12.158, p<0.01$).
Figure 2: HT and NT participants had similar accuracies on both the semantic and episodic tasks.

Figure 3: HT participants were slower to respond than NT participants on semantic and episodic hits.
3.3. Functional Data

HT and NT participants had very similar patterns of activation for semantic hits, with both groups displaying bilateral activity in the lingual gyrus and inferior frontal gyrus, as can be seen in Figure 4. Additionally, HT participants exhibited bilateral activation in the middle temporal gyrus, lentiform nucleus, and cuneus, while NT participants exhibited bilateral activation in the insula and superior temporal gyrus.

Figure 4: Semantic Hits at p=0.01 for HT (red) and NT (blue). The two groups displayed similar patterns of activation during this task.

For the episodic hits, HT and NT participants displayed similar patterns of activation; however, HT participants displayed a greater extent of activation, while NT participants displayed less and more circumscribed areas of activation, as can be seen in Figures 5 and 6. Figure 5 shows that both groups displayed bilateral activity in the cuneus and middle occipital gyrus, as well as activity in the right insula and right cingulate gyrus. As can be seen in Figure 6, HT participants additionally displayed activation in the left cingulate gyrus, as well as bilateral activation in the middle temporal gyrus, hippocampus, precentral gyrus, and superior frontal gyrus.
Figures 5 and 6: Episodic Hits at \( p=0.01 \) for HT (red) and NT (blue). Figure 5 shows that both groups showed activity in the bilateral cuneus, bilateral middle occipital gyrus, right insula, and right cingulate gyrus. HT participants had a greater extent of activation, especially in the left cingulate gyrus, bilateral middle temporal gyrus, hippocampus, precentral gyrus, and superior frontal gyrus, as can be seen in Figure 6.

Figures 7 demonstrates the areas of activation that are greater in the HT participants compared to the NT participants (H>N) for semantic hits. As it can be seen from the figure, there is very little such activation, with very small areas in the right cingulate gyrus and the left middle temporal gyrus (not pictured). There is slightly more activation for NT greater than HT (N>H), with small areas in the right lingual gyrus, left precuneus, left inferior occipital gyrus, right middle frontal gyrus, right superior temporal gyrus, left precentral gyrus, right middle temporal gyrus, and right inferior frontal gyrus, as can be seen in Figure 8.
Figures 7 and 8: H>N semantic hits at p=0.01 (left; red) and N>H semantic hits at p=0.01 (right; blue). There is very little activation for H>N, with a small area in the right cingulate gyrus. There is slightly more activation for N>H, with small areas in the right lingual gyrus, left precuneus, left inferior occipital gyrus, right middle frontal gyrus, right superior temporal gyrus, left precentral gyrus, right middle temporal gyrus, and right inferior frontal gyrus.

Figure 9 shows areas of activation that are greater in the HT participants compared to the NT (H>N) for episodic hits. HT participants have more activation bilaterally in the middle occipital gyrus, middle temporal gyrus, hippocampus, and postcentral gyrus, as well as in the left insula, and right middle frontal gyrus. NT participants have more activation than HT participants (N>H) in the right insula, left precentral gyrus, and left middle frontal gyrus, as Figure 10 shows.

Figures 9 and 10: H>N episodic hits at p=0.01 (left; red) and N>H episodic hits at p=0.01 (right; blue). For H>N, there are many areas of activation, including middle occipital gyrus, middle
temporal gyrus, hippocampus, postcentral gyrus, left insula, and right middle frontal gyrus. For N>H, there are fewer areas of activation, specifically in the right insula, left precentral gyrus, and left middle frontal gyrus.

By including a parametric modulation of difficulty, it is possible to look at the increases and decreases in activation as the difficulty of the task increases. This statistical procedure is based on the idea that there will be more activation for the more difficult items. Therefore, the analysis includes a regressor with 1 corresponding to the easy level and 2 to the hard level of each task, and regions that show increases and decreases in activation as the difficulty increases (goes from 1 to 2) are identified. In the semantic task, HT participants mostly increased in activation bilaterally in the insula and in the right inferior frontal gyrus, as illustrated by Figure 11; Figure 12 shows they decreased activation in the left medial and superior temporal gyri, as well as the left insula and left medial and superior frontal gyri. The NT participants increased in activation bilaterally in the middle occipital gyrus, the left ligual gyrus, and the left inferior frontal gyrus, as is demonstrated by Figure 13; they decreased in activation in the left middle and superior temporal gyri, the left postcentral gyrus, and the left insula, as is shown in Figure 14.

Figures 11 and 12: HT increase (left) and decrease (right) in activation as difficulty increases in semantic hits at p=0.01. HT participants had increases in activation in the insula and right
inferior frontal gyrus, and decreases in the left medial temporal gyrus, left superior temporal gyrus, left insula, left medial frontal gyrus, and left superior frontal gyrus.

![Brain scan images](image1.jpg)

Figures 13 and 14: NT increase (left) and decrease (right) in activation as difficulty increases in semantic hits at p=0.01. NT participants had increases in activation in the middle occipital gyrus, left ligual gyrus, and left inferior frontal gyrus, and decreases in the left middle gyrus, left superior temporal gyrus, left postcentral gyrus, and left insula.

In the episodic task, HT participants increased in activation bilaterally in the precuneus, cuneus, insula, and cingulate gyrus, as well as in the right precentral gyrus, as Figure 15 demonstrates; Figure 16 shows they decreased in activation bilaterally in the inferior frontal gyrus and anterior cingulate, as well as in the right middle occipital gyrus and left caudate. The NT participants increased in activation bilaterally in the middle temporal gyrus, as seen in Figure 17; they had almost no decreases in activation, only exhibiting small areas in the left inferior occipital gyrus, left inferior temporal gyrus, and left superior frontal gyrus, as Figure 18 demonstrates.
Figure 15: HT increase in activation as difficulty increased in episodic hits at $p=0.01$. Increased activation was observed in the precuneus, cuneus, insula, cingulate gyrus, and right precentral gyrus.

Figure 16: HT decrease in activation as difficulty increased in episodic hits at $p=0.01$. Decreases were observed in the inferior frontal gyrus, anterior cingulate, right middle occipital gyrus, and left caudate.
4. Discussion

HT and NT participants were equally accurate on the semantic and episodic tasks, which is in disagreement with the general trend in the literature. However, there have been several other studies with similar findings. Although they used a different memory task, Jennings et al. (2005) found that there were no differences on spatial and verbal working memory abilities between HT and NT participants. Additionally, Beason-Held et al. (2007) reported that there was no
impairment in cognitive function in HT participants relative to controls, as judged by a battery of neuropsychological tests evaluating six different cognitive domains, despite HT participants having greater rCBF decreases prefrontally.

HT participants were slower to respond than NT participants on both the semantic and episodic tasks, a result that is consistent with other findings in the literature. For example, Harrington et al. (2000) found that untreated HT participants were slower to respond than NT participants in several domains: memory scanning, immediate word recognition, delayed word recognition, picture recognition, and spatial memory. Additionally, Efimova et al. (2007) reported that HT participants had slower psychomotor speed during the Digit Symbol Test. Interestingly, Reuter-Lorenz et al. (2000) found that the older adults who were faster during spatial and verbal working memory tasks showed bilateral PFC activation, while the slower older adults only showed right PFC activation. Although they do not specify whether they included HT participants, this study nonetheless serves as a link between reaction time and activation patterns.

HT and NT participants had similar activation patterns in the semantic task but different patterns in the episodic task, with the HT participants displaying a greater extent of activation. This difference in the episodic but not in semantic can be explained by the fact that the semantic task is easy for both groups and the episodic is hard for both; the semantic task is not challenging enough to induce differences in activation but the episodic task is harder for the HT participants and therefore leads to recruitment of additional resources.

When considering the parametric analysis of difficulty, HT participants increased in activation more than the NT participants for both tasks, especially in the episodic task. They also decreased in activation in more areas. An increase in activation as difficulty increases is associated with finding the hard level of the task more difficult than the easy level. Therefore,
this suggests that the HT participants were finding the increase in difficulty level in both tasks more challenging than the NT participants. A decrease in activation is often interpreted as a suppression of the default network, which suggests that the HT participants engage in greater suppression of the default network. This is yet another sign that HT participants were finding the increase in difficulty level more challenging than the NT participants.

These findings point to the conclusion that in this small sample, hypertension affected brain function but not enough to notice a difference in accuracy. Both tasks were more difficult for the HT participants (the semantic less so than the episodic), as evidenced by their slower reaction times, but not difficult enough to lead to a decrease in accuracy. Semantic memory tasks are easier for older adults in general; therefore, while the HT found the semantic task more difficult than the NT (as evidenced by slower reaction times), it was not difficult enough to induce recruitment of additional areas. The episodic task, however, is difficult for older adults in general. The HT participants found it especially more difficult than the NT participants, as evidenced by the slower reaction times and recruitment of additional areas of activation. Additionally, when the difficulty increased in both tasks, HT participants recruited additional areas and suppressed more areas than the NT. This further demonstrates that HT participants found the tasks more difficult than the NT participants and required more activation of key areas and suppression of default network areas to perform at the same level.

In terms of the original hypothesis concerning compensatory brain activity, both HT and NT are showing bilateral activity. Thus, these results support the conclusion that hypertension is not a factor that independently separates the high-performing older adults who demonstrate bilateral prefrontal activity from the low-performing ones who have the same unilateral pattern of activity as younger adults. Additionally, the bilateral activation seen in both groups is
evidenced in several brain regions, not just in the frontal areas, and HT participants are demonstrating more activity overall.

However, the HT participants seem to be engaging in compensatory brain activity in other areas besides the frontal lobe. The results show that HT participants had significantly more activation during the episodic task than the NT participants but had similar accuracy levels; they also displayed greater increases in activation and suppression of default network as the difficulty level increased in both tasks. Therefore, it seems as if the HT participants are recruiting additional areas of activation in order to achieve a similar performance level as the NT participants. Consequently, hypertension seems to have an effect on compensatory activity in this sample, as HT participants are able to engage in compensatory brain changes that maintain their performance.

The present study is greatly limited by the small sample size. If this study were to be reproduced with a larger sample size, it is likely that differences in performance would be noticed between the HT and NT participants and that the two groups would both separate into high and low performers, much as in the Cabeza et al. (2002) study. The current study may additionally be limited by the fact that all but one of the hypertensive participants were on antihypertensive medication. Several previous studies have found differences in the effects of hypertension based on whether it was treated or not (Kilander et al., 1998; Tzourio et al., 1999). Therefore, it would be beneficial to conduct a functional study in which treated and untreated hypertensives are separated and the effects analyzed individually, as such a study would help further tease out the effects of hypertension on brain functioning in older adults.

While the results of this study do not support the conclusion that hypertension is the factor that independently separates the high-performing older adults who engage in frontal
compensatory activity from the low-performing older adults who do not, they do provide some insight into what is happening in the brains of hypertensives. The results point to the conclusion that hypertension does affect brain functioning: hypertensive older adults require the recruitment of additional areas during memory tasks, engaging in compensatory brain changes that allow them to achieve a similar level of performance as normotensive older adults.
References


