Is hypertension more strongly linked to age-related cognitive decline in executive function than in elementary speed function?:

Effects of research methods on the findings

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加齢に伴う前頭葉機能低下において高血圧は遂行系機能に影響が大きいのか
―横断的データと縦断的データによる検討―
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要約

加齢に伴う高血圧と認知機能の低下との関連に関する研究において、血圧の影響は前頭葉機能の遂行系機能の方が情報速度処理系機能よりも大きいとする、Bucur and Madden (2010) の仮説を2種の研究法で検討した。研究1では八雲研究横断的データを用いて、高血圧群と正常群について認知機能検査（NU-CAB）のうち遂行機能を反映するとみなせる検査項目と情報処理速度を反映するとみなせる項目について比較した。その結果は概ね彼らの仮説を支持するものとなった。研究2では八雲研究縦断的データ（6年間）を使用し、多変量解析を用いて、遂行機能検査項目と情報処理速度検査項目に血圧変数と年齢変数が寄与する効果を検討した。その結果は、血圧変数と検査項目変数との間に交互作用を認めず、仮説は支持されるものではなかった。これらの結果は、Bucur and Madden（2010）の仮説は、方法論の影響を受けない堅牢な妥当性を有するとは言えないことを示唆している。

Key words

hypertension, ageing, executive function, elementary perceptual speed function, longitudinal data, cross-sectional data

1. Introduction

Since Wilkie and Eisdorfer's (1971) research on the relationship between hypertension and cognitive decline, many studies have examined the relationship between blood pressure (BP) and cognitive performance. With regard to the relationship between cognitive performance and cardiovascular measures, several recent meta-analyses suggested that chronically increased BP and hypertension are associated with decreased behavioral test performance in cognitive functioning (e.g., Gifford, Bada-racco, Liu et al., 2013; Tzourio, Laurent, & Debette, 2014).

Although there is a great amount of evidence showing a robust relationship between hypertension and both the risk of vascular brain injury and deterioration of cerebral function, it remains unclear which cognitive component is strongly reflected by the elevations in BP. In early stage studies, many studies have relied on the cognitive measure such as MMSE (Mini-Mental State Examination) that represents general cognitive functions. The MMSE has been used as a convenient tool to assess cognitive function for dementia-suspected elderly, however it is not clear what facets of cognitive components are involved from the view point of modern cognitive psychology (Iwahara & Hatta, 2016).

Bucur and Madden (2010) examined the relationship using

cognitive measures representing the correspondence between facets of cognitive function and brain region. In their study, they proposed first that hypertension relates to the decline both in speed-based performance measures (e.g., of attention and learning) and in executive function (e.g., speed in planning and keeping relevant components of information processing while avoiding irrelevant components). Their second proposal was that cognitive decline is more pronounced for executive function than for elementary perceptual speed tasks. A third consideration was that crystallized (knowledge-based) and verbal abilities might be less vulnerable than in fluid intelligence in relation to blood pressure-related decline. Then, recent studies have been conducted to clarify which cognitive component is strongly affected by high BP (see, e.g., Bucur & Madden, 2010; Waldstein, 2003) by two different research methods.

Our concern was their second proposal. To increase the validity of their proposal, it is necessary to gather further data using different experimental methods such as with different cognitive measures, with a different population, with different experimental paradigm. Therefore, in this study, a validity of this proposal was examined using both cross-sectional and longitudinal study methods. In their study, the Stroop test was used to address their purpose such that the color naming speed as a representative of elementary perceptual speed measure in the case of congruent between color name and color and color naming speed as a representing executive function measure in the case of incongruent. As a speed of processing is a major component of executive function, it is not easy to segregate perceptual speed and executive function clearly (Kramer & Madden, 2008; Madden, 2001; Miyake, Friedman, Emerson, Witzki, Howerter, & Wager, 2000; Salthouse & Madden, 2007). Bucur and Madden's proposal should be regarded such that they examined the relative degree to which the age-related decline in one cognitive domain influence the other domain. Therefore, it might be better to use the term low and high cognitive load tasks instead of the terms, elementary perceptual speed and executive function, to avoid troubles in the definition of executive function. However, to simplify the logic of this study, we dare use Bucur and Madden's term.

To address our concern, we designed two studies. In Study 1, cognitive performances between high BP and normal BP groups were compared with respect to elementary speed and executive function using t-test statistics as one of the most popular psychological research paradigm in a cross-sectional study. According to this paradigm, it is expected first that elderly participants in the high BP group should show lower performance in executive function than their counterparts in the normal BP group and it also expected that no substantial group difference should be evident in elementary perceptual speed function or verbal ability.

In Study 2, we used the longitudinal data of cognitive performances by participants over 60 years old over a period of 6 years using multiple regression analysis. Needless to say, trajectories of cognitive decline in elderly participants showed individual dif-

ferences. Specifically, some participants showed a steep decline with aging, whereas others maintained cognitive performance at a similar level. This is consistent with many other studies in which cognitive individual differences are shown to become prominent after the age of 60 (James, Boyle, Yu, et al., 2015; Hatta, 2010; Huntley, Gould, Liu, et al., 2015; Nissen, Eimstahl, Minthon, et al., 2015; Yamada, Lands, Mimori, et al., 2015). Therefore, in Study 2, we examined following hypotheses that if BP influenced on the executive function but not on elementary perceptual speed function, a significant interaction between the factors of BP and Time (6 years interval) will be shown only in the executive function measures. Further, if the proposal is valid, when BP is the dependent variable, the results of multiple regression analysis will show significant effect of the cognitive measures representing executive function while insignificant effect of cognitive measures of elementary perceptual function.

1.1 Database information

Yakumo Study: The Yakumo Study has been conducted since 1981 as a joint project between the town of Yakumo in Hokkaido, Japan and the Department of Preventive Medicine, Nagoya University Graduate School of Medicine. The team from the Department of Psychology, Nagoya University joined this project in 2001 and has administered neuropsychological tests. Professionals in the fields of epidemiology, internal medicine, orthopedics, neuropsychology, ophthalmology, otolaryngology, and urology have joined to the Yakumo Study. Participants had worked at a variety of jobs, including office and managerial work as well as employment in agriculture, fishing, and forestry. Therefore, this town can be regarded as a representative of modern Japanese society.

2. Study 1
2.1 Methods

The working hypothesis in Study 1 holds that the proposal of Bucur and Madden (2010) predicts that high BP participants should show decreased performance, compared to the normal BP participants, in cognitive measures that represent executive function. In addition, it implies that no differences between these groups should obtain in cognitive measures that represent elementary perceptual speed function and verbal function.

2.1.1 Participants

Participants consisted of members who joined the psychological section of the 2013 Yakumo Study. This study had middle-aged participants over 40 years old; however, the main finding of Bucur and Madden (2010) concerned participants aged 60-79 years. Therefore, we selected participants in this age range. The participants' age in the current research were over 60 years and were able to live on their own (that is, none were in long term care or hospitalized). All participants had previously participated in the Yakumo Study. In all three hundred

and eighty-two individuals participated in measurement of both blood pressure and NU-CAB (Nagoya University Cognitive Assessment Battery; Hatta, 2004).

2.1.2 Cognitive measures

Participants assigned to the neuropsychology section were given a NU-CAB that included MMSE, memory test, verbal fluency test, Stroop test, D-CAT (digit cancelation test), as well as a visuo-spatial test by a trained examiner. The selection of cognitive tests was based on previous factor analytic studies, which found that age related cognitive measures consisted of those loaded highly on distinct factors representing executive function and elementary perceptual speed (Kramer & Madden, 2008; MacLeod, 1991; Miyake, Friedman, Emerson et al., 2000; Salthouse, Atkinson, & Berish, 2003). The D-CAT3 (three digits cancelation condition) and Stroop interference condition among NU-CAB items were employed as the representative of the executive function, and the D-CAT1 (one digit cancelation condition) and Stroop dot condition were used as the representative of the elementary perceptual speed function. In the D-CAT1, participants were required to search for a given target digit (6) and in the D-CAT, they were asked to search three digits, 8, 3, and 7 on a sheet of randomly arranged digit sequences and mark with a slash as many of these digits as they could in 60 s in the D-CAT3. The total number of digits that the participant checked was used as the measure in this study. The D-CAT was originally developed for the screening of attention defects in Traumatic Brain Injury (TBI) patients. Both the reliability and the validity (including imaging activation regions) of these tasks have been reported elsewhere (Hatta, Yoshizaki, & Ito, 2009; Hatta, Yoshizaki, Ito et al., 2012; Hibino, Mase, Shirataki et al., 2013).

The Stroop interference test stimulus consisted of an 8 by 5 dot (2 cm diameter) matrix where dot color names and corresponding dot colors were irrelevant; the Stroop dot test stimulus consisted of an 8 by 5 dot matrix where dot color names and colors were relevant. Participants were asked to read color name as fast as possible without error and response time (in seconds) was measured.

We also used the Japanese verbal fluency test (semantic fluency test); participants were asked to generate in 60 s as many Japanese nouns belonging to the categories of /sports/, /jobs/, and / animals/ as possible (Ito & Hatta, 2001). Subsequently, the total number of generated nouns was measured.

2.1.3 Blood pressure measurement

In the Yakumo Study, every participant first visited the reception desk and submitted a completed questionnaire to the public health nurse. They were then given their IDs and a map of examination sites for the day. The questionnaire had been distributed three weeks previously; participants were asked to complete questionnaire items on their health, medical history, and daily lifestyle. At the reception desk, public health nurses reviewed the questionnaire items with the participants; this lasted approximately 7-10 minutes. Then, the nurses (dressed of consideration to avoid white coat effect) measured the participants' blood pressure using a digital automatic blood pressure monitor (Omron hbp-9021). During the measurement, participants sat at a table with legs uncrossed and feet on the floor with their arm resting on the table. The cuff was placed on the participant's non-dominant arm. The digital automatic blood pressure monitor showed both systole BP (SBP) and DBP.

Data for 74 participants were excluded for any one of the following reasons: coronary disease, renal disease, arrhythmias, valvular disease, pulmonary disease, diabetes requiring insulin or hypoglycemic agents, cancer (other than skin cancer), drug abuse, alcoholism, or any psychiatric illness. From the database, 132 participants were classified as having high blood pressure and 176 as having normal blood pressure. Following Bucur and Madden (2010), participants with SBP < 130 mm Hg and DBP < 85 mm Hg were considered normotensive. The number and characteristics of the participants in the two groups are shown in Table 1.

Table 1: Characteristics of the participants in Study 1

	High BP ($N = 132$)	Normal BP ($N = 176$)
Age		
(Mean)	62.31	61.01
(SD)	(9.84)	(9.76)
Sex	132	176
(Male)	(77)	(58)
(Female)	(55)	(118)
Education		
(Mean yrs.)	11.55	11.80
(SD yrs.)	(2.27)	(2.13)
MMSE		
(Mean)	27.77	28.45
(SD)	(2.16)	(1.80)

2.2 Results

Cognitive performance in high BP and normal BP group participants are shown in Table 2. Statistical analyses showed a significant group difference in Stroop dot ($t = 3.61$, $df = 306$, $p < 0.01$), Stroop Interference ($t = 3.39$, $df = 306$, $p < 0.01$), and

Table 2: Cognitive performances in High BP and Normal BP

	High BP ($N = 132$)	Normal BP ($N = 176$)
Stroop dot	30.23 (9.55)	26.84 (6.85)
Stroop interference	45.57 (20.13)	39.16 (12.89)
D-CAT1	271.16 (68.74)	294.19 (66.45)
D-CAT3	166.76 (41.51)	180.72 (41.86)
Verbal fluency	8.12 (4.74)	9.09 (4.87)

D-CAT3 ($t = 2.90$, $df = 306$, $p < 0.01$). On the other hand, group difference was not significant in D-CAT1 ($t = 1.79$, $df = 306$, $p > 0.05$). As for the verbal fluency test, there was no significant difference ($t = 0.10$, $df = 306$, $p > 0.05$).

In sum, cognitive measures representing executive function, D-CAT3, and Stroop interference showed a significant difference between the high and the normal BP groups while measures representing elementary perceptual speed function and D-CAT1 showed no group difference. These findings support the working hypothesis; the Stroop dot results did not show group difference and the verbal fluency measure also failed to show group differences, therefore supporting Bucur and Madden's (2010) proposal that verbal abilities are less vulnerable to the effect of hypertension. The present results largely supported our working hypothesis that the high BP group would show lower performance in the executive function than the normal BP as well as our second hypothesis that no substantial group difference would found in the elementary perceptual speed function and verbal function, although the data in the current study consisted of that from a different cultural background and ethnicity than the data in Bucur and Madden (2010). A possible reason for the discrepancy in results between D-CAT 1 and Stroop dot task will be mentioned later.

3. Study 2

In Study 2, we examined the longitudinal database during the period of 6 years (60-65 years) by covariance analysis with age and sex as covariates and multiple regression analysis.

We examined following hypotheses: cognitive measures representing executive function (Stroop color, Stroop effect size, and D-CAT3) are reflected by BP (SBP and DBP) whereas BP scores do not affect cognitive measures representing elementary perceptual speed (Stroop dot and D-CAT1) and verbal function. More concretely, if proposal by Bucur and Madden (2010) is valid the results of covariance analyses are as follows:

First, a significant interaction between the factors of BP and Time (6 years interval) will be shown in the cognitive measures for Stroop color, Stroop effect size and D-CAT3, because a steeper cognitive decline is expected in High BP group while sustainable or mild decline is expected in normal BP group. Second, a significant interaction between the factors of BP and Time will not be shown for cognitive measures representing elementary perceptual speed such as Stroop dot and D-CAT1 and in VFT.

Further, if the proposal is valid, when BP is the dependent variable, the results of multiple regression analysis will show significant effects of the cognitive measures representing executive function while insignificant effect of cognitive measures of elementary perceptual function.

3.1 Methods
3.1.1 Participants

Participants were community residents who participated in the Yakumo Study on an almost yearly basis; they were selected

from the Yakumo database during the years 2001 to 2013 on the basis of the following criteria. First, they must exceed the age of 60 years at the time of first measurement. Second, they were participated in measurement of blood pressure and cognitive tests described below during the six-year period (therefore data were compared such that between 2001 and 2006 or between 2004 and 2009. Finally, participants must have shown no signs of mild cognitive dementia at first measurement (participants were omitted if they showed below point score 23 by MMSE). Many previous studies (Huntley, Gould, Liu et al., 2015; Nissen, Eimstahl, Minthon et al., 2015; Yamada, Lands, Mimori et al., 2015) as well as our previous cross-sectional analyses showed that the period from age 60 to 65 years old is the most crucial period for showing diversion of individual differences in cognitive performances (Hatta, 2010).

3.1.2 Cognitive measures

From the results of NU-CAB, performances in Stroop color, Stroop effect size, D-CAT3 were regarded as representing the executive function and performances in Stroop dot and D-CAT1 were regarded as representing the elementary speed function. The performance in verbal fluency test was also used as a control. Precise introduction about each measure was described in Study 1.

3.1.3 BP readings

BP measurement procedure was described in Study 1.

3.2 Results
3.2.1 Statistical analysis

An analysis of covariance (ANCOVA) was conducted to determine whether there was a difference in cognitive change overtime between those of high and normal BP measurements. All participants had two observations spaced 6 years. Table 3 shows the baseline demographic characteristics of participants according to two occasions with BP reading. Table 4 shows the results of covariance analyses for each cognitive measure. As seen from the table, the expected signify interaction between BP and Time was shown only in Stroop dot measure ($F_{1, 143} = 12.583$, $p < 0.001$, $\eta_2 = .081$). Executive function measures, Stroop color, Stroop effect size, and D-CAT3, did not show significant interaction ($F_{1, 143} = 0.885$, $p < 0.349$; $F_{1, 143} = 0.869$, $p < 0.353$; $F_{1, 143} = 0.006$, $p < 0.943$, respectively) and VFT was also did not show signify interaction ($F_{1, 143} = 0.469$, $p < 0.495$). These results did not support our working hypothesis that BP has different relation between executive cognitive measures and elementary perceptual speed function. The result of multiple regression analysis was shown in Table 5 where dependent variable was BP. As seen in Table 5, not only executive function measures but also elementary perceptual speed function measures were insignificant (Stroop dot, Stroop color, Stroop effect size, D-CAT1, D-CAT3, and VFT: $F_{1, 143} = 0.467$, $p < 0.469$; $F_{1, 143} = 0.051$, $p < 0.822$; $F_{1, 143} = 0.834$, $p < 0.303$; $F_{1, 143} = 0.103$, $p < 0.749$; $F_{1, 143}$

Table 3: Longitudinal cognitive performance data in High BP and Normal BP groups at the first year and six year later measurement

Characteristics	Hyper group (*N* = 75) Men: 32, Women: 43		Normal group (*N* = 72) Men: 31, Women: 41	
	First year	Five years later	First year	Five years later
Age (years) Mean	66.40	71.40	61.05	66.05
SD	8.46	8.46	7.22	7.22
Education (years) Mean	11.10		11.57	
SD	1.86		2.20	
SBP (mmHg) Mean	144.61		122.73	
SD	10.28		10.00	
DBP (mmHg) Mean	85.75		76.37	
SD	8.17		6.70	
Stroop dot (sec) Mean	30.81	29.68	28.30	29.68
SD	7.51	5.98	6.19	8.71
Stroop color (sec) Mean	45.51	45.14	42.06	42.92
SD	14.73	17.20	11.54	15.60
D-CAT1 (number of marked) Mean	262.94	248.81	284.85	265.85
SD	69.48	66.26	69.36	65.28
D-CAT3 (number of marked) Mean	163.56	152.39	169.57	163.27
SD	40.19	40.07	39.50	37.85
Verbal fluency (number of words) Mean	8.19	7.83	8.41	7.87
SD	3.37	4.45	3.76	3.85

= 0.335, $p < 0.564$; $F_{1, 143} = 0.100$, $p < 0.753$, respectively). The reason of these findings due to the fact that age factor played the crucial role between BP and cognitive functions. Age effect was signify in all cognitive measures (Stroop dot, Stroop color, Stroop effect size, D-CAT1, D-CAT3, and VFT: $F_{1, 143} = 23.453$, $p < 0.000$, $\eta_2 = .141$; $F_{1, 143} = 34.5201$, $p < 0.000$, $\eta_2 = .194$; $F_{1, 143} = 7.967$, $p < 0.005$, $\eta_2 = .53$; $F_{1,143} = 25.289$, $p < 0.000$, $\eta_2 = .150$; $F_{1, 143} = 21.501$, $p < 0.000$, $\eta_2 = .131$; $F_{1, 143} = 4.258$, $p < 0.041$, $\eta_2 = .029$, respectively). These results clearly show our second working hypothesis is not confirmed and does not support the proposal by Bucur and Madden (2010).

4. Discussion

In this study, we examined a proposal of Bucur and Madden (2010) regarding the role of the neural mechanism in the relationship between BP and cognitive development in elderly individuals using two different, cross-sectional and longitudinal, research paradigms. To confirm the validity of a proposal, it is indispensable to replicate the findings using not only similar research methods with a different population but also using different research paradigm to ascertain if this proposal is robustly valid and not culturally specific or whether it is restricted only to a certain limited population and under specific conditions.

Results of Study 1 largely supported the above proposal that high BP is more likely to lead to decline in the so-called executive function related behavioral cognitive measures than in the so-called elementary perceptual function related behavioral cog-

nitive measures. In Study 1, high BP participants showed lower performance levels for measures representing executive function in D-CAT3 and Stroop interference than normal BP participants. On the other hand, there was no significant group difference in measures representing elementary perceptual speed function in D-CAT 1 and verbal fluency. Possible reasons why the Stroop dot measure did not coincide with the working hypothesis appear to depend on the nature of the task; that is, participants are asked to call out the name of the dot as quickly as possible in the Stroop dot task. This task seems to require more cognitive demand compared to the D-CAT1 in which participants are requested to find a targeted single digit. Therefore, this result suggests that the Stroop dot task might have stronger components related to executive function (e.g., identify the color, retrieve proper color name and verbalize it) than D-CAT1, and it might reflect on the comparison between high BP and normal BP participants.

In Study 2, we used the Yakumo Study longitudinal database to evaluate the validity of Bucur and Madden's (2010) proposal further using different research paradigms, multiple factor analyses.

The advantage of a longitudinal design over cross-sectional design in cognitive developmental research is that a longitudinal design does not involve confounding effects of maturational change and those of cohort membership. Developmental change by a cross-sectional design tends to overestimate the magnitude of actual age difference due to cohort-related unidentified influences (Sharie, 1995; 1977; Uttl & Van Alstine, 2003). Although a longitudinal design has shortcomings such as contamination of

Table 4: Results of covariance analysis for each cognitive measure

Stroop dot	df	MS	F-score	P-score	η^2
Time (6-year interval)	1	56.947	4.312	.040	.029
Time x Age	1	70.794	5.361	.022	.036
Time x Sex	1	.102	.008	.930	.000
Time x BP	1	166.172	12.583	.001	.081
Error	143	13.206			
Stroop color					
Time (6-year interval)	1	30.604	.412	.522	.003
Time x Age	1	90.023	1.211	.273	.008
Time x Sex	1	69.744	.938	.334	.007
Time x BP	1	65.734	.885	.349	.006
Error	143	74.317			
Stroop effect size					
Time (6-year interval))	1	.037	.413	.521	.003
Time x Age	1	.010	.106	.364	.001
Time x Sex	1	.075	.830	.364	.006
Time x BP	1	.078	.869	.353	.006
Error	143	.090			
D-CAT1					
Time (6-year interval)	1	2092.565	1.115	.293	.008
Time x Age	1	4363.925	2.326	.129	.016
Time x Sex	1	4.057	0.002	.963	.000
Time x BP	1	1690.723	0.901	.344	.005
Error	143	1876.008			
D-CAT3					
Time (6-year interval)	1	2794.634	4.871	.029	.033
Time x Age	1	3078.384	5.365	.022	.036
Time x Sex	1	776.703	1.354	.247	.009
Time x BP	1	3.306	.006	.940	.000
Error	143				
Verbal fluency					
Time (6 year interval)	1	6.005	.635	.427	.004
Time x Age	1	17.162	1.816	.180	.013
Time x Sex	1	6.845	.724	.396	.005
Time x BP	1	4.432	.469	.495	.003
Error	143	9.451			

Table 5: The result of multiple regression analysis where dependent variable was BP

	df	MS	F	p	η_2
Stroop dot	1	18.895	.467	.496	.003
Stroop color	1	7.001	.051	.822	.000
Stroop effect	1	.092	.834	.363	.006
D-CAT1	1	424.509	.103	.749	.001
D-CAT3	1	459.290	.335	.564	.002
Verbal fluency	1	1.254	.100	.753	.001

a learning effect, because the same cognitive test measures are employed at different developmental stages, the evidence still provides more reliable prospective implications rather than that in a cross-sectional research. Thus, if a longitudinal examination supports Bucur and Madden's proposal, this would strengthen the validity of their findings.

The working hypotheses in Study 2 were not supported. First working hypothesis was that if

BP reflects on cognitive measures representing executive function (Stroop color, Stroop effect size, and D-CAT3) significantly but not on cognitive measures representing elementary

perceptual speed (Stroop dot and D-CAT1) and verbal function. More concretely, if proposal by Bucur and Madden (2010) is a significant interaction between the factors of BP and Time (6 years interval) will be shown in the cognitive measures for executive function, because a steeper cognitive decline is expected in High BP group while sustainable or mild decline is expected in normal BP group. On the other hand, a significant interaction between the factors of BP and Time will not be shown for elementary perceptual speed measures such as Stroop dot and D-CAT1 and in VFT. Second, if the proposal is valid, when BP is the dependent variable, the results of multiple regression analysis will show significant effects of the cognitive measures representing executive function while insignificant effect of cognitive measures of elementary perceptual function.

As seen Table 3, 4 and 4, a significant interaction between BP and Time (relative cognitive decline for 6-years interval) was not shown and statistical results strongly suggest robust effect of age on BP rather than cognitive measures.

Here, we consider again what Bucur and Madden (2010) proposed. They proposed a model in which a deterioration of blood vessels, associated with aging, causes high blood pressure, and the resulting hypertension destroys brain tissue, especially the white matter. This process is especially notable in the prefrontal lobe area and therefore, the executive function exhibits a steeper decline than do elementary perceptual speed and verbal ability. Brain imaging evidence also converges to strengthen Bucur and Madden's proposal. For example, Pardo, Lee, Sheikh, et al. (2007) measured brain activity of normal elderly individuals using fluorodeoxyglucose and positron emission tomography and found that the largest declines were localized to a medial neural network including the anterior cingulate/medial prefrontal cortex, dorsomedial thalamus, and sugenual cingulate/basal forebrain. These findings suggest that hypertension may induce metabolic changes in medial prefrontal networks that invite dysfunction in the anterior attention system. Recent brain imaging studies by Raz and colleagues examined the relation of brain volume and function whether the "bigger is better" hypothesis is proper (Raz, Ghistella, Rodrigue et al., 2010; Raz, Rodrigue, & Acker, 2003; Raz, Rodrigue, Head et al., 2004; Raz, Rodrigue, Kennedy et al, 2007; Yuan, Bender, & Raz, 2014). For example, recent meta-analysis of brain imaging studies by Yuan and Raz (2014) examined the relation between prefrontal cortex volumes with executive function in healthy adults using 31 samples in vivo. They found a strong relation between executive function (Wisconsin Card Sorting Test) and prefrontal cortex volume. This means shrinkage of brain regions with aging, especially in prefrontal cortex, invites functional decline; furthermore, one important cause of regional shrinkage might be hypertension. Bucur and Maden's model seems to be reasonable theoretically, however as the present two different type of studies show the proposal possesses a certain level of support on validity with one type of research paradigm whereas it was not supported when using different research paradigm with elderly Japanese elderly population. This means that the proposal does not supported by strong validity level across research paradigm, other populations and cultures.

In sum, present study strongly suggested first that any proposal concerning neural mechanisms should be examined using different type of plural different type of research paradigms, and second that the relation between BP and cognitive function is crucially influenced by aging of participants in the case of healthy community dwelling elderly people.

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