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Stability Of Default-Mode Network Activity In The Aging Brain

L.L. Beason-Held^{1,2}, M.A. Kraut², and S.M. Resnick¹

¹Laboratory of Personality and Cognition, National Institute on Aging, NIH

²Dept. of Neurology, Johns Hopkins University School of Medicine

Abstract

Activity attributed to the default-mode occurs during the resting state and is thought to represent self-referential and other intrinsic processes. Although activity in default-associated regions changes across the lifespan, little is known about the stability of default-mode activity in the healthy aging brain. We investigated changes in rest-specific activity across an 8 year period in older participants in the Baltimore Longitudinal Study of Aging (BLSA) neuroimaging study. Comparison of resting-state and recognition memory PET regional cerebral blood flow conditions from baseline and 8-year follow-up shows relative stability of rest-specific activity over time in medial frontal/anterior cingulate, hippocampal and posterior cingulate regions commonly associated with the default-mode. In contrast, prefrontal, parahippocampal and occipital cortical regions, which are not typically associated with default-mode activity, show changes over time. Overall, activity in the major components of the default-mode network remains stable in healthy older individuals, a finding which may assist in identifying factors that discriminate between normal and pathological aging.

Keywords

functional imaging; brain function; activation; age; fMRI; human; default activity

INTRODUCTION

Assessment of the neural networks thought to be active when the brain is at rest is an emerging area of interest in functional neuroimaging. Based on distinct patterns of activity observed when examining resting brain function, several processes are thought to occur during this baseline state. These patterns have been theoretically linked to visuoception, sensorimotor processes, memory, executive function, and functions referred to as 'default-mode' (Damoiseaux et al., 2006; Mazoyer et al., 2001; Raichle et al., 2001).

Default-mode activity was first noted as task-related deactivations in experiments where task conditions were contrasted with a baseline, often resting-state, condition. These early studies found that medial frontal/anterior cingulate, posterior cingulate/precuneus and inferior parietal regions exhibited greater activity during the resting state than during task performance (Raichle et al., 2001; Shulman et al., 1997). The spatial pattern of these regions originally prompted the theory of a baseline or default network involved in self-referential processes such as conscious awareness of the internal and external environment. Subsequent identification of medial temporal regions associated with this network expanded the proposed function of the default-mode system to include memory processes (Esposito et al., 2006; Greicius & Menon, 2004),

Correspondence to: L.L. Beason-Held.

Send Correspondence to: Dr. Lori Beason-Held NIA/LPC 251 Bayview Blvd. Baltimore, MD 21224-6825 Phone: 410-558-8655 Fax: 410-558-8674 Email: E-mail: heldlo@mail.nih.gov.

and more recent theories propose that more fundamental intrinsic processes are related to activity in default-mode regions (Buckner & Vincent, 2007; Raichle & Snyder, 2007).

Activity in this network appears generally stable in young adults when examined across repeated sessions (Damoiseaux et al., 2006). The older brain, however, shows subtle changes in regional rest-related default activity when compared to the younger brain. Older subjects decrease resting-state activity in medial frontal/anterior cingulate and posterior cingulate regions of the default-mode network relative to task performance to a lesser extent than younger subjects (Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006; Lustig et al., 2003; Persson, Lustig, Nelson, & Reuter-Lorenz, 2007). Older subjects also exhibit default activity in orbital and inferior frontal, parahippocampal and lateral temporal regions that are not involved in younger subjects (Greicius, Srivastava, Reiss, & Menon, 2004). Both types of findings suggest that changes in default-mode regional activity occur from young to older adulthood.

The extent to which activity within the default-mode regions changes as older individuals continue to age, however, remains unclear. Here, we present data from the Baltimore Longitudinal Study of Aging (BLSA) neuroimaging substudy where positron emission tomography (PET) regional cerebral blood flow (rCBF) scans were collected during rest and recognition memory performance at baseline and 8-year follow-up. Because assessment of activity patterns specific to the resting state relative to the recognition memory conditions was used to define regions within the so-called default-mode network, our prior findings of widespread longitudinal changes in both resting-state and recognition memory conditions in cognitively stable healthy agers (Beason-Held, Kraut, & Resnick, 2008a, 2008b) suggest that changes in rest-specific activity may also occur with advancing age. However, because longitudinal changes occur in *both* resting and task conditions, the relative difference between the two conditions, reflecting rest-specific default-related activity, could actually remain stable over time. In the present study, regions typically associated with the default-mode network show relative stability of rest-specific rCBF patterns, while regions outside of the network show subtle longitudinal changes in activity.

METHODS

Subjects

PET data from 32 older participants in the neuroimaging substudy (S. M. Resnick et al., 2000) of the BLSA were used in this analysis (14 female, 18 male; mean baseline age = 68.4 $\pm$ 6.8). All individuals remained in good cognitive and physical health through the follow-up period with no history of central nervous system disorders, major psychiatric disorders including depression, or severe cardiovascular disease. All participants also completed annual neuropsychological evaluations and were deemed cognitively normal by consensus diagnosis (Kawas, Gray, Brookmeyer, Fozard, & Zonderman, 2000) through the 8-year follow-up evaluation.

This study was approved by the local Institutional Review Board. All participants provided written informed consent prior to each assessment.

PET Scanning Conditions

Participants underwent PET scanning sessions at baseline (year 1) and at 8-year follow-up (year 9). During each imaging session, three PET scans were performed: rest, delayed verbal (word) recognition memory, and delayed figural (abstract design) recognition memory. During rest, participants were instructed to keep their eyes open and focused on a computer screen covered by a black cloth. During the delayed recognition tasks, the participants were asked to

identify stimuli that had been presented at the beginning of the session. During the imaging session, twenty novel distractor items were intermixed with the previously shown 20 target items and participants were asked to indicate whether or not they had seen each item before (see (Beason-Held et al., 2008a) for task details). Accuracy and reaction times were recorded throughout both recognition tasks.

PET Scanning Parameters

PET measures of regional cerebral blood flow (rCBF) were obtained using [^{15}O]water. For each scan, 75 mCi of [^{15}O] water were injected as a bolus. Scans were performed on a GE 4096+ scanner, which provides 15 slices of 6.5 mm thickness. Images were acquired for 60 seconds from the time the total radioactivity counts in brain reached threshold level. Attenuation correction was performed using a transmission scan acquired prior to the emission scans.

MRI Scanning Parameters

A 3-D spoiled gradient refocused (SPGR) MRI scan (124 slices, 256×256 matrix, 0.93×0.93mm voxel size, 1.5 mm slice thickness) was obtained on a 1.5 T GE Signa scanner at each imaging visit.

PET Data Analysis

For each subject, the PET scans were realigned, resliced with a voxel size of 2×2×2mm, spatially normalized into standard stereotactic and smoothed to a full width at half maximum of 12, 12, and 12 mm in the x, y, and z planes. To control for variability in global flow, rCBF values at each voxel were ratio adjusted to the mean global flow of 50 ml/100g/min for each image. The image data were analyzed using Statistical Parametric Mapping (SPM2; Wellcome Department of Cognitive Neurology, London, England), where whole brain voxel by voxel comparisons determined significant differences in rCBF using a single group 2 factor (task and time) design. All contrasts were adjusted for baseline age at year 1.

The data were analyzed in 4 stages. In the first step, we defined the voxels involved in default-mode activity in our sample. Rest-specific activity patterns, defined as activity occurring in the resting-state alone relative to the task activation states, were determined at each year separately by contrasting the rest condition with the mean of the verbal and figural recognition memory conditions at year 1 and year 9. Significance for each contrast was based on a magnitude of $p \leq 0.001$. To decrease the chance of false positive results resulting from multiple comparisons, an additional spatial extent threshold of >100 voxels was also used. Second, conjunction analyses were performed on the year 1 and 9 contrast images (magnitude $p \leq 0.001$, spatial extent >100 voxels) to determine spatial patterns of activity common to both years 1 and 9, and regions with spatial patterns of activity exclusive to year 1 or year 9 (masking thresholds of $p \leq 0.05$). Third, rCBF values were extracted from a 4 mm sphere centered on the local maxima of each region of interest identified in the conjunction analyses to examine the pattern of rCBF change over time. The rest-specific pattern of blood flow change (stable, decreasing, increasing) from year 1 to 9 was then determined for each common and exclusive region (paired sample t-tests, significance level $p \leq 0.05$). Finally, to determine the influence of tissue volume on the rCBF findings, the MRI scans were segmented into gray matter, white matter and cerebrospinal fluid and spatially normalized into stereotactic space using a high-dimensional elastic warping method and a volume-preserving transformation (Shen & Davatzikos, 2002). For each participant, binary maps of the common and exclusive regions from the conjunction analyses were registered with the MRI image. Total volumes of gray + white matter were subsequently calculated for each region of activity. The PET analyses were then repeated using tissue volume of each region at each time point as an additional covariate. It should be noted that volumes were unavailable for 1 participant due to inability to tolerate

the MRI scanner, and data from an additional participant was excluded from the analysis of the right insular and parahippocampal regions (areas showing rest-specific rCBF decreases over time) due to registration errors.

RESULTS

Neuropsychological Evaluation

Performance on the annual battery of neuropsychological tests (Beason-Held et al., 2008a) was compared across years (1 and 9) using repeated measures MANOVA with sex as a grouping factor. Only one change in performance levels was noted across time. There was a significant increase ($p=0.02$) in the number of errors on the Benton Visual Retention Test across the group as a whole. There was also a sex effect ($p=0.02$) on the Digits Forward test with males scoring higher than females at both years. There were no sex $\times$ time interactions in this group of participants. Performance levels are shown in Table 1.

PET Task Performance

Paired-sample t-tests were used to determine differences in performance levels between year 1 and 9. No significant differences were seen in task accuracy for either recognition memory condition (sensitivity scores: Verbal year1=0.45 (0.18 SD), year9=0.46 (0.19); Figural year1=0.50 (0.20), year9=0.43 (0.20)). Reaction times decreased over time for both tasks (Verbal year1=1384.4 (348.7), year9=1256.9 (409.2), $p=0.04$; Figural year1=1594.7 (316.3), year9=1432.8 (328.1), $p=0.02$), most likely reflecting effects of practice during repeating testing.

PET rCBF

We assessed rCBF activity patterns specific to the resting-state relative to the recognition memory conditions. The rest-specific patterns observed at years 1 and 9 were consistent with those reported to comprise the default-mode network of resting brain function. Over time, both similarities and differences in rest-specific activity patterns were observed between years 1 and 9.

In the voxel-based whole brain analysis, regions within frontal, temporal, parietal and occipital lobes show increased activity during rest relative to the recognition memory task conditions at both year 1 and year 9. Based on the conjunction analyses comparing years 1 and 9, the regional pattern of rest-specific activity was similar in medial frontal (Brodmann Area (BA) 11) and anterior cingulate (BA 24/32) areas over time, as were the patterns within lateral insular cortex, temporal pole (BA 38), inferior portions of the middle temporal gyrus (BA 21/39) and the hippocampus (Table 2, Figure 1). Posteriorly, mid-level middle occipital gyrus (BA 19/37) and inferior portions of the posterior cingulate/precuneus (BA 31) also show similar rest-specific spatial activity patterns across time. Using extracted rCBF values, rest-specific rCBF within these regions shows no significant change over time from Year 1 to Year 9 (paired-sample t-tests, p values ≥ 0.14), suggesting stability of activity levels with increasing age in these areas (Figure 2).

A few regions show relative decreases in rest-specific spatial activity patterns as a function of time in the voxel-based conjunction analyses. These areas include a portion of the left superior frontal gyrus (BA 10), right medial insula, bilateral parahippocampal gyri (BA 36), superior portions of the precuneus (BA 7/31) and superior portions of the middle occipital gyri (BA 19/37). The extracted rCBF levels from these regions show significant decreases in rest-specific activity over time (paired-sample t-tests, p values ≤ 0.04). The relative decrease is driven by decreased resting-state rCBF levels in conjunction with stable task-related rCBF in all regions with the exception of the right parahippocampal gyrus. The apparent decrease in

the right parahippocampal region is driven by an increase in task-related activity as opposed to a decrease in rest-related activity (Figure 3).

Two regions show an increased spatial pattern of rest-specific activity over time. These regions include the superior portions of the right middle temporal gyrus (BA 21) and inferior portions of the right middle occipital gyrus (BA 19/37). Rest-specific rCBF levels significantly increased over time (paired-sample t-tests, p values ≤ 0.01), resulting from increased resting-state activity combined with stable task-related activity.

To determine the potential influence of tissue volume loss on these findings, the PET analyses were repeated using tissue volume of each region at each time point as an additional covariate. There were no significant differences in size or location of any stable or changing rest-specific rCBF region after volume correction.

Because task reaction times changed over time in our group of participants, we examined the relationship between changes in these measures and changes in the extracted rest-specific rCBF values using Pearson correlations. No significant correlations were seen between reaction time and rCBF in regions of stable activity. In regions of changing activity, decreased figural task reaction time was associated with decreased rCBF in the right parahippocampal gyrus (BA 36; $r=0.38$, $p=0.04$), and decreased verbal reaction time change was associated with increased rCBF in the right middle temporal gyrus (BA 21; $r=-0.41$, $p=0.03$) over time. The two significant correlations would not withstand correction for multiple comparisons, however.

DISCUSSION

Default-mode activity was originally defined as activity specific to the resting-state relative to task performance. Our results show that by contrasting rest with recognition memory conditions, we observe a pattern of rest-specific activity that is consistent with the resting-state default-mode network described in previous studies. Our results further show that over a period of eight years, most regions commonly associated with this network retain stable activity levels over time in the brains of healthy older, cognitively normal individuals. Although the major components of this network are not significantly affected by advancing age in older individuals, a number of discrete cortical areas located in prefrontal, medial temporal and occipital regions show changes in resting-state activity levels over time. These changes are reflected as longitudinal decreases or increases in rest-specific activity relative to the task conditions.

A number of potential networks of brain activity have been identified during the resting-state (Damoiseaux et al., 2006; Mazoyer et al., 2001; Raichle et al., 2001), yet the rest-specific activity patterns revealed in our study closely fit those previously defined as components of the so-called default-mode system. Default-mode activity was originally proposed to be involved in self-referential processes (Gusnard, Akbudak, Shulman, & Raichle, 2001; Shulman et al., 1997), spontaneous or stimulus-independent thought (Raichle et al., 2001) and random episodic memory processes (Andreasen et al., 1995; Greicius & Menon, 2004). More recent theories propose that default-related activity may also involve fundamental intrinsic processes related to the stabilization and coordination of information (Buckner & Vincent, 2007; Raichle & Snyder, 2007). Although the role of this resting-state network remains unclear, the network of activity referred to as the default-mode appears to be fairly consistent in younger subjects, as the same general pattern of rest-specific activity is seen when contrasted with a variety of task modalities (Mazoyer et al., 2001; Raichle et al., 2001) and across multiple imaging sessions (Damoiseaux et al., 2006).

Although there is overlap in the major components of the default network in younger and older individuals, modifications in the aging brain have also been observed. First, the network of regions involved in resting-state activity appears to be larger in the older brain than that

observed in the younger brain. In older adults, several regions in the inferior, middle and orbital frontal cortex, as well as medial and lateral temporal cortex show resting-state activity that is not apparent in the young (Greicius et al., 2004). This finding suggests that the older brain may rely on some areas beyond those typically used in the younger brain during default-mode processes, a finding similar to many previously noted age-related activation changes attributed to functional reorganization in the aging brain (Cabeza, Anderson, Locantore, & McIntosh, 2002; Park, Polk, Mikels, Taylor, & Marshuetz, 2001). Second, the magnitude of activity in some regions associated with the proposed default-mode network changes as a function of age. Studies have shown that activity in medial frontal/anterior cingulate and posterior cingulate/precuneus show less task-related deactivation due to greater task-related activity levels in older compared to younger and middle-aged individuals (Grady et al., 2006; Lustig et al., 2003; Persson et al., 2007). This increased activity in regions commonly associated with the default-mode during task performance has been interpreted as an inability of the older brain to effectively reduce or shift resources from intrinsic default-mode processes to those involved in the task at hand, perhaps contributing to age-related declines in cognitive performance (Grady et al., 2006; Lustig et al., 2003). Other studies have also shown age-related decreases in resting-state activity alone within default-mode regions (Damoiseaux et al., 2007) and decreases in the functional connectivity between regions from young adulthood to older age (Andrews-Hanna et al., 2007), suggesting that lifespan changes may occur in rest-related default-mode processes.

Unlike cross-sectional comparisons between age groups, we find that activity in the major components of the default-mode network remains stable across time in the older brain. When contrasting rest with recognition memory conditions, our participants show similar spatial patterns and consistent levels of rest-specific activity in medial frontal/anterior cingulate, posterior cingulate/inferior precuneus and hippocampal regions across the 8 years. Given the advantage of repeated assessments in the same individuals, these findings suggest that instead of further changes occurring with advancing age in older individuals, the activity levels in some regions may plateau in healthy aging.

Although we found no significant change in the rest-specific activity levels of most regions commonly associated with the default-mode network, we detected longitudinal changes in several other regions in healthy aging. While we found that the hippocampus proper exhibits similar rest-specific activity levels across time, the left parahippocampal gyrus shows decreased activity with advancing age. Decreased activity was also observed in superior frontal gyrus, and superior levels of the precuneus and occipital cortex. Often, age-related decreases in activity levels are interpreted as declines in neuronal efficiency (Grady & Craik, 2000; Reuter-Lorenz et al., 2001). Although historically these declines have been discussed in relation to task performance, the changes observed here suggest that declines in efficiency or processes carried out by these regions during the resting state also occur with advancing age. The question that remains, however, is whether or not these activity changes represent age-related changes in the default-mode network or in different resting-state brain networks. Although the precuneus has been identified as a component of the default-mode system, the other regions showing decreased activity over time are not typically associated with the default-mode in younger subjects. Further study is needed to determine the relationship between these regions and proposed resting-state brain processes.

Longitudinal neuroimaging and neuropsychological studies provide sensitivity for the detection of subtle age changes, yet one challenge with this type of design is the need to consider practice effects from repeated task exposure. We observed significant decreases in reaction time, but not accuracy, for the verbal and figural recognition memory tasks over time. Although change in activity in two brain regions correlated with improvements in reaction time, only the right parahippocampal gyrus showed an apparent decrease rest-specific activity that was related

to an increase in task-related activity as opposed to a decrease in rest-related activity. These results suggest that practice effects based on behavioral performance measures had little effect on the rCBF patterns of rest-specific change or on the patterns of stable activity over time.

Another methodological consideration in studies of age-related changes in brain function is the potential effect of brain atrophy on regional brain activity. It has been shown that tissue volume in frontal, temporal and parietal regions declines over time to a greater extent than occipital regions in normal aging (Raz, 2005; S. Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003). Although we did see changes in activity in some of these cortical areas, controlling for tissue volume in the PET analyses did not have a significant effect on either location or size of activity. This suggests that atrophy did not play a major role in the relative changes in regional blood flow.

While our results show general stability of rest-specific activity in the major components of the default-mode network in healthy aging, other data suggest that regions associated with the default-mode may not be stable in pathological aging. Subjects with mild cognitive impairment (MCI) and Alzheimer's disease (AD) show early changes in cerebral glucose metabolism and blood flow in frontal, medial temporal, and posterior cingulate/precuneus areas of the brain (De Santi et al., 2001; Herholz et al., 2002; Kogure et al., 2000; Minoshima et al., 1997), suggesting that the default-mode network which relies on these regions may be compromised in MCI and AD. Indeed, studies specifically examining the default network have shown that alterations in frontal, hippocampal and posterior cingulate regions occur in individuals with MCI and AD above and beyond that observed in cognitively normal older individuals (Greicius et al., 2004; Lustig et al., 2003; Rombouts, Barkhof, Goekoop, Stam, & Scheltens, 2005). As this evidence points to alterations in default-mode activity in MCI and AD, the relative stability of these patterns in healthy aging may aid in the identification of individuals at risk for cognitive impairment.

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Figure 1. Longitudinal Patterns of Default-Mode Activity

Legend: Top row illustrates default-mode regions commonly active during the resting state relative to task performance at years 1 and 9; these regions also show relative stability of rest-specific rCBF levels over time. Bottom row illustrates rest-specific regions that are active exclusively in years 1 or 9 and also show a significant increase (red) or decrease (blue) in resting-state relative to task-related rCBF levels over time.

Figure 2. Regions of Stable Longitudinal Activity

Legend: Average (SEM) blood flow values are shown for rest and task conditions at years 1 and 9. These examples show regions of no significant change in resting-state relative to task rCBF over time ($p > 0.14$).

Figure 3. Regions of Decreasing Longitudinal Activity

Legend: Average (SEM) blood flow values are shown for rest and task conditions at years 1 and 9. These examples show declining resting-state rCBF over time (p values ≤ 0.001) in conjunction with stable task-related rCBF, with the exception of the right parahippocampal gyrus ($p=0.02$). The apparent change in default-mode activity in this region is driven not by a decrease in resting rCBF but by an increase in task-related rCBF.

Table 1
Neuropsychological Performance (Mean(SD))

Domain	Test	Measure	Year 1	Year 9
Memory	CVLT BVRT	total correct 5 trials	60.4 (7.4)	61.3(11.6)
		total errors	3.5 (2.6)	4.4 (3.2)*
Verbal Fluency	Letters Categories	mean correct	15.5 (3.6)	14.4 (3.8)
		mean correct	16.9 (2.3)	16.1 (3.2)
Attention & Working Memory	Digits Forward Digits Back Trails A Trails B	total correct	8.9 (2.5)	9.6 (2.3)
		total correct	9.0 (2.2)	8.3 (2.6)
		time in seconds	32.7 (12.0)	33.3 (10.7)
		time in seconds	70.9 (25.8)	79.6 (24.6)
Visuospatial	Card Rotation	correct-incorrect	95.3 (36.7)	100.0 (42.4)

Legend: CVLT = California Verbal Learning Test; BVRT = Benton Visual Retention Test.

* significant change in performance levels over time (p=0.02).

Table 2

Regional Rest-Specific Activity Over Time

Region	Side	Coordinate				p value	Size (# voxels)
		x	y	z	T-value		
Stable Activity							
Med Frontal Gyrus (10)	B	-2	58	-4	9.20	<0.001	6,507 [*]
Ant Cingulate Gyrus (32)	B	2	24	-12	6.68	<0.001	6,507 [*]
Insula	R	62	-14	2	4.15	<0.001	623
Insula	L	-58	-8	14	4.31	<0.001	2,452 ⁺
Temporal Pole (38)	R	40	16	-36	5.69	<0.001	2,294
Temporal Pole (38)	L	-40	14	-30	3.45	<0.001	2,452 ⁺
Mid Temporal Gyrus (39)	R	50	-72	18	5.32	<0.001	18,372 [‡]
Mid Temporal Gyrus (21)	R	62	-2	-24	5.63	<0.001	2,266
Mid Temporal Gyrus (21)	L	-56	-10	-18	3.70	<0.001	2,452
Hippocampus	R	24	-6	-20	3.23	0.001	1,084
Hippocampus/Parahipp Gyrus (36)	L	-24	-2	-34	3.16	0.001	6,507 [*]
Post Cingulate/Precuneus (31)	B	0	-66	20	11.34	<0.001	18,372 [‡]
Mid Occipital Gyrus (19/37)	R	52	-74	4	3.87	<0.001	18,372 [‡]
Mid Occipital Gyrus (19/37)	L	-42	-74	4	3.44	<0.001	18,372 [‡]
Decreased Activity							
Sup Frontal Gyrus (10)	L	-14	50	8	4.81	<0.001	153
Insula	R	42	-16	0	3.80	<0.001	875 [§]
Parahippocampal Gyrus (36) [*]	R	28	-26	-18	4.41	<0.001	875 [§]
Parahippocampal Gyrus (36)	L	-24	-24	-26	5.25	<0.001	428
Precuneus (7)	R	8	-36	50	5.09	<0.001	463 [€]
Precuneus (31)	L	-8	-46	36	4.05	<0.001	463 [€]
Mid Occipital Gyrus (19)	R	8	-90	20	5.54	<0.001	2,472
Mid Occipital Gyrus (19/37)	L	-40	-74	32	4.98	<0.001	2,763

Region	Side	Coordinate			T-value	p value	Size (# voxels)
		x	y	z			
Increased Activity							
Mid Temporal Gyrus (21)	R	54	-14	-10	3.90	<0.001	192
Mid Occipital Gyrus (19/37)	R	50	-68	0	4.32	<0.001	1,195

Legend: Local maxima within default-mode regions exhibiting either stable or changing resting-specific activity from year 1 to year 9 as determined by the patterns of rCBF change in each area. Stereotaxic coordinates are listed; Brodmann areas are indicated in parentheses. *denotes change due to an increase in task-related rCBF as opposed to a decrease in resting rCBF.

* Regions contained within the same cluster

+ Regions contained within the same cluster

‡ Regions contained within the same cluster

§ Regions contained within the same cluster

¶ Regions contained within the same cluster