Increased Response-time Variability is Associated with Reduced Inferior Parietal Activation during Episodic Recognition in Aging

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Abstract

■ Intraindividual variability (IIV) in cognitive performance shares systematic associations with aging-related processes, brain injury, and neurodegenerative pathology. However, little research has examined the neural underpinnings of IIV, with no studies investigating brain correlates of IIV in relation to retrieval success. Using functional magnetic resonance imaging, we examined links between IIV, recognition memory performance, and blood oxygenation level dependent activations. Nineteen older adults (70–79 years) were presented with 80 words at encoding, with brain scans and response latencies obtained during subsequent recognition. An index of IIV, the intraindividual standard deviation (ISD), was computed across successful latency trials. Decreasing ISDs were systematically associated with better recognition, faster latencies, and increased activation in the inferior parietal cortex (BA 40). Demonstrated links between less behavioral variability and parietal activations are consistent with the known importance of the parietal cortex for retrieval success. In support of extant findings and theory from neuroscience, neuropsychology, and cognitive aging, the present results suggest that behavioral IIV represents a proxy for neural integrity. ■

INTRODUCTION

Most cognitive research examines group differences in mean levels. Complementary research on intraindividual variability (IIV) has been overshadowed by this tradition (Li, Huxhold, & Schmiedek, 2004). IIV is defined as lawful but transient within-person changes in performance, such as trial-by-trial fluctuations on a reaction-time (RT) task or day-to-day variations of cognitive performance (e.g., MacDonald, Nyberg, & Bäckman, 2006; Li et al., 2004). Failure to consider such markers of intraindividual dynamics is a serious oversight, for as IIV increases and represents systematic as opposed to random error, performance indexed from any given measurement occasion can yield flawed estimates of mean-group differences (Hultsch, Strauss, Hunter, & MacDonald, 2007; Hultsch & MacDonald, 2004; Nesselroade, 2002). Increased IIV in cognitive performance across the adult life span has been linked to cognitive deficits (MacDonald, Hultsch, & Dixon, 2003; Hultsch, MacDonald, & Dixon, 2002; West, Murphy, Armilio, Craik, & Stuss, 2002; Rabbitt, Osman, Moore, & Stollery, 2001), sensory and physiological losses (Strauss, MacDonald, Hunter, Moll, & Hultsch, 2002; Li, Aggen, Nesselroade, & Baltes, 2001; Anstey, 1999), as well as terminal decline and mortality (MacDonald, Hultsch, & Dixon, submitted; Shipley, Der, Taylor, & Deary, 2006). Such within-person fluctuations may correspond to as much as several decades of between-person age differences (Nesselroade & Salthouse, 2004). IIV is of particular relevance to clinicians as it may serve as an early marker of age-related cognitive impairment, uniquely predicts neurological status independent of mean-level performance, and implies that a single assessment may be insufficient to accurately characterize performance (for reviews, see Hultsch et al., 2007; Hultsch & MacDonald, 2004).

Increased performance IIV not only is a common component of aging-related cognitive decline but is also associated with other brain-based conditions including neurodegenerative pathologies such as dementia (Murtha, Cismaru, Waechter, & Chertkow, 2002; Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000; Gordon & Carson, 1990; Knotek, Bayles, & Kaszniak, 1990), mild cognitive impairment (Dixon et al., 2007), and Parkinson's disease (Burton, Strauss, Hultsch, Moll, & Hunter, 2006), as well as other brain-related disorders including traumatic brain injury (Stuss, Murphy, Binns, & Alexander, 2003; Hetherington, Stuss, & Finlayson, 1996; Stuss, Pogue, Buckle, & Bondar, 1994), ADHD (Bellgrove, Gill, Hawi, Kirley, & Robertson, 2005; Castellanos & Tannock, 2002), schizophrenia (Manoach, 2003; Manoach et al., 2000), and epilepsy (Bruhn & Parsons, 1977). Considering the diverse populations that exhibit increased IIV and concomitant cognitive deficits, more variable

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cognitive functioning may reflect a variety of structural, functional, and neuromodulatory brain changes (Lindenberger & Oertzen, 2006; MacDonald et al., 2006; Li, 2004).

Although plausible IIV–brain links have been suggested (Hultsch et al., 2007; Hedden & Gabrieli, 2004; Hultsch & MacDonald, 2004; Braver, Reynolds, & Donaldson, 2003; Stuss et al., 2003), extant evidence is largely indirect. To date, but a single investigation has directly examined the neural correlates of variability using functional magnetic resonance imaging (fMRI; Bellgrove, Hester, & Garavan, 2004). Findings demonstrated an association between IIV and brain activation during a response inhibition task (go/no-go) for a group of healthy young adults. More variable response latencies on go trials were associated with increased brain activity during successful response inhibition in middle frontal regions, likely reflecting greater demand for executive control in order to maintain task performance.

The main purpose of the present investigation was to examine the association between IIV and brain activity in regions related to successful episodic memory retrieval for a sample of healthy older adults. Previous studies of younger adults have implicated fronto-parietal and medial-temporal regions in retrieval success (e.g., Iidaka, Matsumoto, Nogawa, Yamamoto, & Sadato, 2006; Achim & Lepage, 2005; Wagner, Shannon, Kahn, & Buckner, 2005; Herron, Henson, & Rugg, 2004; Kahn, Davachi, & Wagner, 2004; Shannon & Buckner, 2004; Dobbins, Rice, Wagner, & Schacter, 2003; Wheeler & Buckner, 2003; Rugg, Otten, & Henson, 2002; Buckner & Wheeler, 2001; Donaldson, Petersen, & Buckner, 2001; Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Konishi, Wheeler, Donaldson, & Buckner, 2000; Lepage, Ghaffar, Nyberg, & Tulving, 2000; McDermott, Jones, Petersen, Lageman, & Roediger, 2000). There is less direct evidence for the neural basis of successful retrieval in older adults, so in view of reported differences in the neural correlates of various episodic memory processes for younger and older adults (e.g., Cabeza et al., 2004; Morcom, Good, Frackowiak, & Rugg, 2003; Grady, McIntosh, Rajah, Beig, & Craik, 1999; Bäckman et al., 1997; Cabeza et al., 1997), we first examined brain regions that were related to successful word recognition in our elderly sample. The second but primary analysis examined whether activity in these regions was related to IIV in response latency during word recognition. In light of the inverse association between IIV and cognitive performance, we hypothesized that lower variability would be associated with increased activations in retrieval success regions.

METHODS

Participants

Participants were 19 healthy adults (9 women, 10 men), between 70 and 79 years of age, recruited via newspaper advertisement. The mean age was 73.21 years (SD = 3.24) with an average of 13.36 years of education (SD = 2.39). All participants were right-handed; reported no previous or current psychiatric, neurological, or serious medical conditions; and were not taking hypertensive medications. Informed consent was obtained prior to the investigation, which was approved and conducted in accordance with established ethical committee guidelines at the Karolinska Hospital in Stockholm, Sweden.

Measures

Word Recognition

A total of 160 concrete nouns were used to create an encoding and recognition word list. The nouns were equivalent with respect to visual and tactual imagery, meaningfulness, and frequency, as determined from a normative Swedish study (Molander, 1984). Selected words were no less than three letters and no more than eight letters in length. The encoding list was shown during the anatomical MRI scan, with 80 single words presented consecutively at the rate of one word per 3 sec with a 1-sec gap between words. This was followed by a recognition memory test in which the 80 target words were presented along with 80 lures, yielding a total of 160 response latencies (msec). During the recognition phase, words were shown for 2 sec, with a 4-sec gap before subsequent word presentation. Using their right hand, participants were required to press one of two buttons on a fiber-optic response box to indicate previously seen versus unseen words. Performance indicators of mean response latency (msec), recognition sensitivity (hits [H] − false alarms [FA]), and behavioral IIV were obtained per individual.

Behavioral IIV

Behavioral IIV reflects within-person fluctuations across RT latency trials (Hultsch et al., 2007; Hultsch & MacDonald, 2004). Here, behavioral IIV was operationalized as intraindividual standard deviations (ISDs) computed across successful word recognition latency trials per individual. These ISDs were conditionalized on H trials to ensure that between-person differences were not a function of differences in response accuracy. Systematic between-person differences and practice effects may also influence raw score differences in ISDs, necessitating the dissociation of systematic between- and within-person changes from changes that reflect inconsistency in performance (Hultsch et al., 2002). Using split-plot regression, between-person differences in mean RT were partialled prior to computing the ISDs. The data were not detrended because the mean changes across RT trials were not reliable (p =.33), and thus, the computed ISDs are not confounded by systematic variation across trials (Nesselroade & Salthouse, 2004).

Between-subject age confounds were minimized by using a relatively age-homogeneous elderly sample. Chronological age was not significantly correlated with recognition accuracy ($r = .26$, *ns*) or response latency ($r = -.03$, *ns*), possibly reflecting the narrow age range and small sample size. ISDs were standardized and linearly transformed as *T* scores, with higher ISD estimates reflecting more inconsistent latencies across trials.

Functional Magnetic Resonance Imaging

Data Acquisition

Participants were positioned supine on a padded scanner bed in a dimly illuminated room, and wore foam ear plugs as well as external ear protection to attenuate scanner noise. Words were projected onto a rectangular screen approximately 3 m in front of the subject using a Philips Hopper HG 20 Impact LCD projector (Philips, Netherlands) placed inside the scanner room. Participants viewed stimuli on the screen via a mirror system mounted on top of the head coil (approximately 2 cm above the participants' eyes). Whole-brain images were acquired on a 1.5-T GE Signa Echospeed MR scanner (GE Medical Systems, USA) using a standard circular head coil. Functional images were acquired (3×88 image volumes, FOV = 220×220 mm, in-plane resolution = 3.44×3.44 mm^2) using a T2*-sensitive gradient-echo EPI sequence (TR = 4.2 sec, TE = 40 msec, flip angle = 90°). A total of 42 horizontal slices (4 mm thick) were obtained with a 0.4-mm gap between each slice. All images were acquired sequentially. To account for magnetic saturation effects, three dummy scans from the beginning of the session were discarded in the statistical analysis.

Data Analysis

Functional images were first realigned and unwarped to account for movement-by-field inhomogeneity interaction effects (Andersson, Hutton, Ashburner, Turner, & Friston, 2001), slice-time corrected, and normalized to a standard template using SPM2 (Wellcome Department of Cognitive Neurology, England). Normalized images were spatially smoothed with a Gaussian filter of 12 mm full width at half maximum. Within subjects, high- and low-frequency noise and differences in global signal were removed using a low-pass filter, a high-pass filter, and global scaling. Subsequent fMRI activation contrasts were conditionalized on correct memory performance, H − Misses (M), to examine links between ISDs and blood oxygenation level dependent (BOLD) activation independent of performance differences. Analyses were performed in two steps, with individual contrasts (H − M) for recognition activations first computed using a fixed-effects model (Friston, Jezzard, & Turner, 1994) followed by the computation of between-subject contrasts using a random-effects model (Holmes & Friston, 1998). Effects were modeled by convolving the event train with a canonical hemodynamic response function.

Whole-brain analyses were initially conducted to identify neural correlates of successful memory retrieval. To identify regions recruited across participants that were relatively more activated during correct word recognition, a one-sample *t* test was computed on these contrast images to create a statistical parametric map (SPM) depicting differences in brain activation between H and M recognition trials (thresholded at $p < .05$ using an FDR correction for multiple comparisons; Genovese, Lazar, & Nichols, 2002).

After demonstrating regions of activation for retrieval success, a second set of contrasts examined whether BOLD activations for correct retrieval in these regions were systematically associated with ISDs. Multiple regression was used to examine the magnitude and location of activations for correct retrieval in relation to ISDs entered as a continuous covariate. Hypothesis-driven regional analyses were computed using a 7-mm radius sphere for areas of peak activation identified in the initial analysis that correspond to regions linked to retrieval success (Achim & Lepage, 2005; Wagner et al., 2005; Herron et al., 2004; Kahn et al., 2004; Shannon & Buckner, 2004; Dobbins et al., 2003; Wheeler & Buckner, 2003; Donaldson et al., 2001; Konishi et al., 2000). Small-volume corrections (SVC) for these regions of interest (ROIs) have the advantage of increasing power by minimizing the number of multiple comparisons and by increasing signal-to-noise ratio by averaging voxels within the ROI (Wheeler & Buckner, 2003). To identify potential neural correlates of IIV outside of these ROIs, a whole-brain exploratory analysis was computed for the same contrast (FDR corrected, $p < .05$). The logic of this exploratory analysis (cf. Head, Snyder, Girton, Morris, & Buckner, 2005) is that this investigation is among the few to examine potential neural correlates of behavioral IIV, and the first to do so for successful episodic retrieval. A nonlinear transformation (www.mrc-cbu.cam.ac.uk/Imaging/mnispace.tml) was used to convert all MNI coordinates to Talairach and Tournoux (1988) coordinates.

RESULTS

Behavioral Data

For recognition sensitivity (H − FA), participants averaged 39.10 (*SD* = 10.17, skewness = −0.37) out of a maximum of 80. Mean response latency for correct word recognition was 1178.38 msec (*SD* = 326.60, skewness = 1.19), with reliably slower responses ($p < .001$) observed for misses ($M = 1366.77$, $SD = 423.47$, skewness = 1.03), underscoring the need to conditionalize the ISD computation on correct performance. Behavioral IIV, computed

across H trials per individual, yielded an average ISD of 9.96 (SD = 1.61, range = 6.17–12.90) in T-score metric. Even subsequent to partialling for systematic between-person differences in response latency, ISDs were negatively correlated with recognition accuracy ($r = -.37$, $p = .06$) and positively correlated with response latency ($r = .66$, $p < .01$). The correlation between accuracy and latency was $-.57$ ($p < .01$).

fMRI Data

BOLD Activations during Correct Word Recognition

The first contrast examined brain regions with greater relative activation for correct word recognition trials. As predicted, fronto-parietal activation was related to recognition success. Table 1 lists spatial coordinates and statistical properties for peak activations. Activations in the left hemisphere were observed in the frontal lobe (middle and medial areas, BA 10/46), the dorsal anterior cingulate gyrus (BA 32), and the supramarginal and angular gyri (BA 40/39) of the inferior parietal lobe. Right hemisphere activations were observed for the medial frontal lobe (BA 10) and the supramarginal gyrus (BA 40). Activations from these left and right hemisphere locations are consistent with neural correlates of correct word retrieval found in prior research (e.g., Wagner et al., 2005; Cabeza & Nyberg, 2000; Lepage et al., 2000; McDermott et al., 2000).

BOLD Activations during Correct Word Recognition in Relation to Performance Variability

A second set of fMRI contrasts examined whether variability was differentially associated with BOLD activation patterns for correct recognition (see Table 1), controlling for individual differences in the number of hit trials. Decreasing variability was associated with retrieval success activations in the left supramarginal gyrus (see Figure 1), overlapping with the left hemisphere parietal activation in Table 1. Beyond Table 1 regions, the strongest association for decreasing ISDs was observed in the right parahippocampal region ($x = 29$, $y = -30$, $z = 3$, $T = 5.71$, $p < .001$ uncorrected). Corresponding SVC contrasts for increasing ISD yielded no significant activations for any Table 1 ROIs. Notably, the fact that decreasing, but not increasing, ISDs were linked to activations in regions subserving retrieval success is consistent with numerous findings in the variability literature documenting an inverse association between IIV and cognitive performance (e.g., Hultsch et al., 2007).

DISCUSSION

Short-term fluctuations in cognitive performance are associated with multiple unfavorable outcomes including age-related cognitive deficits, neurodegenerative pathology, and traumatic brain injury, suggesting that behavioral IIV may be a useful proxy for structural, functional, or neuromodulatory brain changes. The present study extends previous cognitive research by examining the neural underpinnings of within-person variability, with this study being the first to examine brain correlates of IIV in episodic retrieval. The behavioral findings replicated previous research, with decreasing ISDs associated with more advantageous cognitive outcomes including shorter response latencies and better recognition memory.

Corresponding fMRI analyses showed that correct word recognition was associated with specific activations in the left prefrontal cortex (BA 10/46), supramarginal gyrus (BA 40), and anterior cingulate (BA 32). Right hemisphere activations were observed for homotopic frontal (BA 10) and parietal (BA 40) sites. The parietal and frontal activations denote retrieval success, consistent with numerous previous investigations (e.g., Wagner et al., 2005; Shannon & Buckner, 2004; Rugg et al., 2002; Konishi et al., 2000; McDermott et al., 2000).

Table 1. Fronto-parietal Regions Activated for Correct Word Recognition Trials (Hits − Misses)

Brain Region	*Hemisphere*	*Brodmann's Area*	*x*	*y*	*z*	*Cluster Size (Voxels)*	*t*
Frontal pole (*middle frontal gyrus*)	Left	10, 46	−28	57	10	388	4.73
Frontal lobe (*medial frontal gyrus*)	Left	32, 10	−6	45	5	246	4.32
Parietal lobe (*inferior lobule, supramarginal gyrus*)	Left	40, 39	−44	−52	45	162	5.18
Frontal pole (*medial frontal gyrus*)	Right	10	6	54	−3	246[a]	4.20
Parietal lobe (*inferior lobule, supramarginal gyrus*)	Right	40	50	−23	14	572	4.65

Spatial coordinates are for peak activation(s) in fronto-parietal regions corrected for multiple comparisons ($p < .05$) using the false discovery rate. Underlined Brodmann's areas indicate the local maximum for a given cluster activation. Coordinates are in millimeters and correspond to the stereotactic atlas of Talairach and Tournoux (1988). Negative values are in the left hemisphere for the x-coordinate (right–left), are posterior to the zero point located at the anterior commissure for the y-coordinate (anterior–posterior), and are inferior to the plane defined by the anterior and posterior commissure for the z-coordinate (superior–inferior).

[a]Corresponding activation subpeak for the cluster of activations reported in the left hemisphere.

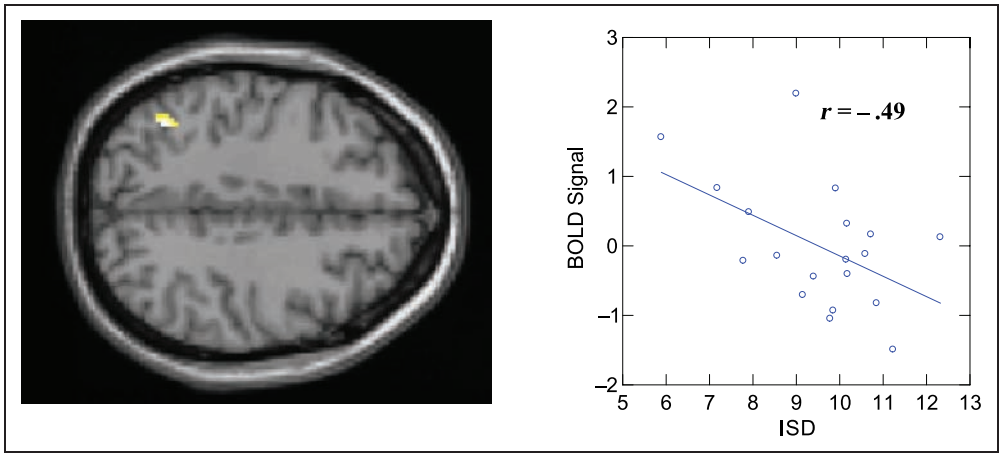

Figure 1. A multiple regression model examined blood oxygenation level dependent (BOLD) activations for successful recognition, controlling for the absolute number of hits, in relation to decreasing intraindividual standard deviations (ISDs). An inferior parietal ROI (peak location −40, −54, 46, with 7-mm radius sphere) was identified based on overlap among previously reported neural correlates of retrieval success (e.g., Wagner et al., 2005; Kahn et al., 2004; Dobbins et al., 2003; Wheeler & Buckner, 2003; Donaldson et al., 2001; Konishi et al., 2000). Statistical maps for this volume, with activations represented in yellow ($p < .05$, small-volume corrected), are superimposed upon the T1 template in SPM2. Lower variability was associated with higher activity in the left inferior parietal region (BA 40, Talairach coordinates $x = -38$, $y = -56$, $z = 44$, $k = 102$). The associated scatterplot shows the fitted regression line for the BOLD signal at the peak voxel as a function of normalized ISDs in *T*-score metric ($p < .05$).

Subsequent contrasts examined whether these activations shared differential associations with decreasing versus increasing ISDs. The relevant data showed that less-variable participants exhibited distinct patterns of activation relative to the more variable. Specifically, decreasing variability was associated with more pronounced activation in the left inferior parietal cortex (BA 40) and the right hippocampal formation. Of the significant activations from Table 1, the BA 40 cluster was the only one to share a reliable association with ISD. The emergence of the supramarginal gyrus as an important neural correlate of decreasing variability (see Figure 1) is consistent with research implicating this structure in retrieval success (e.g., Wagner et al., 2005; Shannon & Buckner, 2004; Cabeza & Nyberg, 2000). Similarly, there is much evidence to link the hippocampal complex to successful recognition (e.g., Eldridge et al., 2000).

By contrast, increasing ISDs shared no systematic association with any activations for correct retrieval. From an fMRI analytic perspective, the lack of association implies more transient patterns of activation between persons. Specifically, more variable individuals exhibited fewer regions of overlapping neural activations (yielding an unreliable association between any Table 1 activation cluster and increasing ISD), whereas less variable individuals showed more overlapping activations (yielding the significant association between select Table 1 activations and decreasing ISD). Thus, increasing IIV in behavior may be a proxy for increasing IIV in the BOLD signal itself (see MacDonald et al., 2006; Yamaguchi, Hale, D'Esposito, & Knight, 2004). Of relevance to this point, parietal cortex alterations (including a diminished BOLD response) reliably predict memory decline for a word categorization task in nondemented apolipoprotein E-ε4 carriers (Lind, Persson, et al., 2006), with such patterns perhaps foreshadowing an increased risk for future dementia (Lind, Ingvar, et al., 2006). Previous neuropsychological research has also clearly established links between greater variability and dementia (e.g., Murtha et al., 2002; Hultsch et al., 2000). Thus, both functional activation and behavioral variability patterns are markers of impairment, with the present study serving to associate the two. From the perspective of broader cortical networks, reduced parietal activation for more variable individuals could reflect factors such as decreased input due to upstream changes in hippocampus or corpus callosum (Lind, Persson, et al., 2006). The absence of prefrontal cortex engagement as a function of variability in the present study may be due to the analytic contrast and retrieval task employed (successful retrieval as opposed to retrieval mode and a retrieval task with low demands for strategic search and other self-initiated operations).

It is critical to note that group comparisons of raw-score ISDs are confounded by mean performance differences, where those with slower response latencies are often more variable (e.g., Shammi, Bosman, & Stuss, 1998; Hale, Myerson, Smith, & Poon, 1988). To address this concern, we controlled for between-subject confounds as well as differentiated systematic versus unsystematic within-subject sources of variability (see Hultsch et al., 2007). Specifically, between-subject age confounds were minimized by using an age-restricted sample, with chronological age not reliably associated with recognition accuracy or latency. Further, differences in mean response latency were statistically partialled in a random-effects regression model prior to computing the ISDs. As the actual number of H trials was partialled from the analyses to equate for statistical power, subsequent between-person associations between IIV and neural activation were not due to differences in response accuracy. Finally, as there were no reliable individual differences in learning across latency trials, this source of systematic within-subject variance was ruled out as a

potential confound. Pursuant to these controls, the observed associations between IIV and brain activation is not an artifact of within-subject differences in learning or between-subject differences in mean level accuracy or latency.

Although the present analyses partialled group differences in response latency, it is still the case that variability and level of performance are correlated at the individual level. Thus, an important question concerns whether measures of IIV predict performance independent of mean level. A growing number of studies have demonstrated that IIV in both cognitive (e.g., Hultsch et al., 2002) and physiological (e.g., Li, Aggen, et al., 2001) functioning uniquely predicts performance in various domains (e.g., perceptual speed, working memory, episodic memory, crystallized IQ) independent of mean-level influences. Similarly, IIV uniquely discriminates group differences in neurological integrity (demented vs. nondemented; Hultsch et al., 2000), cognitive impairment (mild cognitive impairment vs. controls; Dixon et al., 2007), and mortality status (survivors vs. decedents; MacDonald et al., submitted) independent of mean-level accuracy and latency. Taken together, these findings support the claim that IIV is an important indicator of cognitive aging and neural integrity, and is not an artifact of mean level confounds.

Concluding Remarks and Future Research

Results from the present study complement those of Bellgrove et al. (2004), and are the first to demonstrate a link between fMRI correlates of episodic memory and behavioral IIV. It is our hope that subsequent investigations will similarly combine correlational and experimental approaches (see Thompson-Schill, Braver, & Jonides, 2005) to further elucidate neural correlates and mechanisms of performance variability. Moreover, recent technological advances in event-related fMRI (e.g., high-field 4-T MRI) facilitate the direct measurement of variability in brain itself by computing an index of IIV across BOLD signal trials, with the distribution of activations reflecting the outcome of interest (Yamaguchi et al., 2004; see MacDonald et al., 2006). If extant hypotheses about variability are accurate, then indices of brain IIV should share systematic links to behavioral IIV and mean cognitive performance.

Potential mechanisms underlying increased performance variability desperately require systematic study. Changes in dopaminergic (DA) neurotransmission represent one candidate of interest. Many groups or conditions that exhibit increased IIV (e.g., schizophrenia, older adults, ADHD children) exhibit dysfunction in DA neuromodulation, which may lead to increased neural noise (Cohen & Servan-Schreiber, 1992) resulting in less distinct cortical representations as well as increases in behavioral IIV and subsequent cognitive deficits (Li, 2004; Li, Lindenberger, & Sikström, 2001). Consistent with this view, impaired attention, memory, and motor performance are known sequelae of alterations in the DA system (Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006; Bäckman et al., 2000). Examining links between measures of DA function (e.g., receptor densities), cognitive functioning, and performance variability would directly speak to the modulating influence of DA on IIV. Ultimately, IIV in both behavioral and BOLD responses may be a consequence of neural noise due to structural (e.g., white matter changes) or neuromodulatory (e.g., DA dysregulation) brain changes (for further discussion, see MacDonald et al., 2006). Linking these lines of research constitute intriguing avenues for future investigation.

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