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Extrastriatal dopamine D2 receptor binding modulates intraindividual variability in episodic recognition and executive functioning

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ABSTRACT

Intraindividual variability (IIV) reflects lawful but transient within-person changes in performance. Increased IIV in cognition shares systematic associations with numerous conditions characterized by alterations in dopamine (DA) neuromodulation (e.g., old age, ADHD, schizophrenia, and Parkinson's disease). In a group of normal middle-aged adults, we examined links between PET-derived measures of D2 receptor binding in striatum, orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and hippocampus (HC) and IIV for tasks assessing recognition memory and executive functioning. An index of IIV, the intraindividual standard deviation (ISD), was computed across successful response latency trials for each cognitive outcome. Lower D2 binding in OC, ACC, and HC, but not striatum, was associated with increasing ISDs for the memory and executive measures. Consistent with neurocomputational models, the present findings suggest a role for extrastriatal DA neurotransmission in modulating variability in cognitive functioning.

Intraindividual variability (IIV) reflects transient, within-person change in numerous types of behavior, most notably cognition. These fluctuations are indexed over short periods of time, typically seconds (e.g., variability across trials of a response latency task), and have been variously referred to as inconsistency, wobble, and lability (for reviews, see Hultsch, Strauss, Hunter, & MacDonald, 2008; Li, Huxhold, & Schmiedek, 2004). Recent research has focused on IIV as a common component of aging-related cognitive decline. Closer inspection of related literatures (lifespan developmental psychology, neuropsychology, and neuroscience) reveals that increased IIV is also linked to neurodegenerative diseases (e.g., Alzheimer's disease, fronto-temporal dementia, and Parkinson's disease), psychiatric disorders (schizophrenia and ADHD), traumatic brain injury, impending death, and even a specific allele (Val) of the COMT gene (for reviews, see Hultsch et al., 2008; MacDonald, Nyberg, & Bäckman, 2006). Converging evidence indicates that IIV in cognitive functioning is linked to these aforementioned outcomes independent of mean-level performance, underscoring the unique importance of variability.

Research on the origins of IIV remains sparse. At the cognitive level, postulated mechanisms include momentary lapses of attention (e.g., Bunce, MacDonald, & Hultsch, 2004; Bunce, Warr, & Cochrane, 1993) and failure to maintain executive control (e.g., West, Murphy, Armilio, Craik, & Stuss, 2002). Such accounts imply a disproportionately high number of very slow responses in the RT distribution among highly variable individuals, a supposition supported by recent findings (e.g., Williams, Hultsch, Strauss, Hunter, & Tannock, 2005). Although most extant research on IIV relies on such behavioral data, recent investigations have begun to delineate neural correlates. Rapid changes in IIV from one moment to the next in a cognitive task may reflect endogenous brain mechanisms, such as fluctuations in the connectivity of neuronal pathways (e.g., Kelly, Uddin, Biswal, Castellanos, & Milham, 2008), and the efficacy of neurotransmitter systems (e.g., Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006).

In a recent review of the available evidence (MacDonald et al., 2006), we argued that increases in IIV have multiple neural determinants: structural, functional, and neuromodulatory. Structural brain correlates of IIV include lesions to frontal grey matter (e.g., Sowell et al., 2003; Stuss, Murphy, Binns, & Alexander, 2003) as well as decreased white-matter volume, demyelination, and hyperintensities (e.g., Anstey et al., 2007; Britton, Meyer, & Benecke, 1991; Bunce et al., 2007; Walhovd & Fjell, 2007). The developmental evolution and involution of grey and white matter corresponds, at least

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grossly, to increasing then decreasing intellectual functioning (Kray, Eber, & Lindenberger, 2004; Li, Lindenberger et al., 2004) as well as decreasing then increasing intraindividual variability (MacDonald, Hultsch, & Dixon, 2003; Williams et al., 2005) across the life span. With regard to regional specificity, neuropsychological evidence suggests that frontal cortex integrity shares a strong association with IIV. Specifically, persons with fronto-temporal dementia are more variable than those with Alzheimer's disease for a similar level of disease severity (Murtha, Cismaru, Waechter, & Chertkow, 2002), and patients with circumscribed frontal lesions are more variable than those with comparable non-frontal lesions (Stuss et al., 2003).

Functional brain imaging correlates of IIV have also been identified. Bellgrove, Hester, and Garavan (2004) found that increased IIV in a response-inhibition task (Go-NoGo) was associated with lower inhibitory success, slower responding, and increased brain activity in left and right middle frontal regions. Persons with higher IIV activated inhibitory regions to a larger extent, likely reflecting greater demands for executive control to maintain task performance. More recently, IIV across latency trials of a word recognition task was examined in relation to the magnitude and anatomical brain location of BOLD activations (MacDonald, Nyberg, Sandblom, Fischer, & Bäckman, 2008). Low variability for successful word retrieval was associated with better recognition sensitivity, faster response latencies, and heightened BOLD activations in the supramarginal gyrus of the parietal lobe, a structure implicated in sustained attention, deep semantic encoding, and retrieval success (e.g., Cabeza & Nyberg, 2000; Shannon & Buckner, 2004; Wagner, Shannon, Kahn, & Buckner, 2005). These associations support the hypothesis that behavioral IIV is a proxy for neural integrity and associated changes in functional networks.

Finally, dysfunctional modulation of select neurotransmitters, including dopamine (DA) and acetylcholine, has been associated with increased neural noise (Bäckman et al., 2006; Li & Lindenberger, 1999) which might contribute to increased IIV in cognitive performance. Alterations in DA neuromodulation have been documented for select populations (Bäckman et al., 2006) that also exhibit increased behavioral IIV, including the elderly (Hultsch, MacDonald, & Dixon, 2002; Rabbitt, Osman, Moore, & Stollery, 2001), ADHD children (Bellgrove, Gill, Hawi, Kirley, & Robertson, 2005; Castellanos & Tannock, 2002), schizophrenics (Manoach, 2003), and Parkinson patients (Burton, Strauss, Hultsch, Moll, & Hunter, 2006). Evidence from neurocomputational models suggests that DA regulates the signal-to-noise ratio of neural information processing (e.g., Li & Lindenberger, 1999; Servan-Schreiber, Bruno, Carter, & Cohen, 1998; Servan-Schreiber, Carter, Bruno, & Cohen, 1998). In these models, DA is commonly assumed to facilitate the responsivity of neural networks in activity transmission both within and between neural networks. Through enhancing the neural signal relative to background noise, DA is thought to promote the firing frequency of innervated neurons (e.g., Daniel et al., 1991; Oades, 1985; Sawaguchi, Matsamura, & Kubota, 1988). In an application of this type of modeling, Li and Lindenberger (1999) and Li, Lindenberger, and Sikström (2001) demonstrated that reduced DA activity (via adjustment of the signal-to-noise ratio thereby simulating age-related losses) increased neural noise, resulting in less distinct cortical representations manifest as decreased cognitive performance and increased behavioral IIV. Genetic findings also support the putative importance of DA neuromodulation in IIV. Specifically, the catechol O-methyltransferase (COMT) enzyme degrades DA in the frontal cortex, with carriers of the Val allele of the COMT gene having lower extracellular DA levels in prefrontal cortex than Met carriers due to greater enzymatic activity (Weinshilboum, Otterness, & Szumlanski, 1999). Consistent with the hypothesized DA–IIV link, Stefanis et al. (2005) demonstrated that Val carriers of the COMT gene were more variable than Met carriers in a rapid perceptual comparison task.

In the present investigation, we for the first time attempt to directly link an in vivo marker of dopaminergic neurotransmission to IIV in cognitive performance. Dopamine D2 receptor binding in striatum and three extrastriatal brain regions (orbitofrontal cortex [OFC], anterior cingulate cortex [ACC], and hippocampus [HC]) was determined using positron emission tomography (PET) and the radioligands [^{11}C]raclopride and [^{11}C]FLB 457, and then correlated with IIV in response latencies during a recognition memory task and a task assessing executive functioning. Region of interest (ROI) selection was guided by extant findings implying that frontal and medial-temporal regions may differentially influence IIV (Bellgrove et al., 2004; Murtha et al., 2002; Takahashi et al., 2007), with the episodic and executive tasks chosen for their established association with IIV (see Hultsch et al., 2008). Relative to other DA receptors, D2 binding may be especially relevant for the study of IIV. D2 receptors have been argued to serve a critical role in facilitating rapid shifts between different targets (cf. IIV), in contrast to D1 receptors that are more germane to tonic DA levels involved in maintaining a specific cognitive set (e.g., Bilder, Volavka, Lachman, & Grace, 2004; Cohen, Braver, & Brown, 2002).

1. Method

1.1. Subjects

Sixteen participants (8 women and 8 men), ranging in age from 41 to 65 years (M = 56.06, S.D. = 7.67), were recruited by advertising in daily newspapers. The subjects had no history of significant psychiatric or somatic illness as assessed by medical interview, physical examination, routine blood tests, and brain MRI. On PET assessment days, participants were required to abstain from products containing caffeine. Regular prescription medications were consumed (e.g., estrogen substitution and bronchodialators for asthma) but none were judged to interfere with the study. The study was approved by the Ethics and Radiation Safety committees of the Karolinska Institutet. Informed consent was obtained from all subjects.

1.2. Measures

1.2.1. Cognition

Several tasks were administered from the Cambridge Neuropsychological Test Automated Battery (CANTAB), a series of computerized non-verbal tests of memory and executive function (Strauss, Sherman, & Spreen, 2006). For the present purposes, participants completed two measures. First, for the test of pattern recognition memory (PRM), each participant was presented with a series of 12 visual patterns, shown one at a time in the middle of a computer screen. Each individual pattern was designed so that they could not be easily ascribed verbal labels. After seeing all 12 patterns, a test of immediate recognition was administered, requiring forced-choice discrimination between the 12 previously seen vs. 12 novel patterns. Both accuracy and response latency for each trial were recorded.

The second CANTAB measure, intra–extra dimensional set shifting (IEDSS), assesses rule acquisition and attentional set shifting similar to the Wisconsin Card Sorting test. Stimuli are comprised of white lines and color-filled shapes. Participants initially observed simple stimuli (two color-filled shapes) and were required to press one of them on a touch-screen display. Feedback was provided to teach the participant which stimulus was associated with a correct response. Following 6 correct responses, the stimuli and associated rules for responding were switched, with these shifts initially intra-dimensional (responses based on the color-filled shapes) followed by extra-dimensional shifts (where the relevant dimension for responding was based on the white lines shown together with the colored shapes). Participants progressed to the next stage after satisfying the learning criterion (6 consecutive correct responses for a given stage). The test terminated when the participant failed to produce 6 correct responses for 50 trials at a given stage. Per trial response accuracy and latency were recorded.

1.2.2. PET

Dopamine D2 receptor availability was indexed in striatum using the radioligand [^{11}C]raclopride and in extrastriatal brain regions using [^{11}C]FLB 457. To minimize head movement, a plaster helmet was made for each subject. PET assessments were performed on an ECAT Exact HR system (CTI/Siemens, Knoxville, TN) run in 3D mode (Wienhard et al., 1994). The transaxial resolution of the system is 3.8 mm full width at half maximum (FWHM) at the centre of the field of view and 4.5 mm FWHM tangentially and 7.4 mm radially at 20 cm from the centre. Axial resolution is 4 mm FWHM at the centre and 6.8 mm at 20 cm from the centre. Prior to each emission scan, a transmission scan of 10 min was performed using three rotating ^{68}Ge–^{68}Ga sources. The information from the transmission scan was used for attenuation correction.

As described elsewhere, [^{11}C]raclopride and [^{11}C]FLB 457 were prepared from [^{11}C]methyl triflate (Langer et al., 1999; Sandell et al., 2000). The radioligands were