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Intraindividual variability in performance on associative memory tasks is elevated in amnestic mild cognitive impairment

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ABSTRACT

Elevations in intraindividual variability (IIV) are an indicator of neurocognitive compromise and are seen on reaction time tasks in individuals with mild cognitive impairment (MCI). We examined IIV on memory tasks known to be sensitive to early cognitive change in a group of 24 individuals with amnestic MCI and 21 matched controls. Traditional measures of accuracy and speed, as well as indices of IIV statistically purified for systematic between-group and trial effects, were derived from performance on two computer-based associative recognition tests of word–word and face-name pairs. Accuracy and speed were reduced and IIV was elevated in the MCI group compared to controls on both tasks. Logistic regression analyses demonstrated that IIV, but not speed, was a unique predictor of group membership, over and above performance accuracy. Observed elevations in IIV in MCI are congruent with the notion that IIV may reflect disturbance in distributed neural networks, including medial temporal regions, in addition to frontal systems dysfunction. Present findings have diagnostic implications for accurate identification of individuals with MCI and add to the growing literature on IIV as an early indicator of cognitive decline in older adults.

1. Introduction

this special issue honouring Morris Moscovitch, we thought it fitting to present research exploring the cognitive mechanisms underlying complex memory tasks. In our past and present roles as Morris's trainees and colleagues, we have learned about the value of looking beyond the surface of our data and exploring novel measures that reflect the cognitive processes involved in behavioural tasks. For example, in past work with Morris using commonly administered tests of verbal fluency, we have discovered that analyzing behavioural patterns of clustering and switching provides unique information not captured by traditional measures of overall fluency output (Troyer et al., 1997). This initial finding led to a productive series of fluency studies in our own laboratories (Iskandar et al., 2016; Murphy et al., 2006; Troyer, 2000; Troyer et al., 1998a, 1998b) and many others (e.g., Raoux et al., 2008; Robert et al., 1998; Sauzéon et al., 2004; Tröster et al., 1998; Unsworth et al., 2010; Zakzanis et al., 2013). Over the years, we have found additional ways to take to heart this approach to data exploration (e.g., Troyer et al., 2008; Vandermorris et al., 2013b; Vandermorris et al., 2013a). In the current paper, we examine another type of measure – intraindividual variability – that provides insight into cognitive task performance that is not otherwise captured by traditional performance measures. We explored whether meaningful information could be gained by examining such variability on memory test performance in individuals with mild cognitive impairment.

Mild cognitive impairment (MCI) is a term used to identify individuals who show objective cognitive impairment, but do not meet full criteria for any dementia syndrome (Flicker et al., 1991; Smith et al., 1996). At the group level, individuals with MCI are at elevated risk for dementia (Petersen et al., 1999), but identification of those individuals with MCI who are most likely to decline is sub-optimal (for reviews see Bruscoli and Lovestone (2004) and Petersen (2004)). Although biomarkers and neuroimaging measures show promise for enhancing detection of those individuals at greatest risk of decline (Petersen et al., 2009), clinical assessment, including measurement of cognitive functioning, still forms the basis of diagnostic classification and prognostic inferences (e.g., Barnes et al., 2009; Grober et al., 2008; Petersen et al., 2009).

It is possible that clinically meaningful information in MCI could be gained from closer inspection of behavioural measures. Indeed, recent population studies have shown that elevated within-person across-task variability on a battery of cognitive tests yielded improved detection of those individuals who went on to

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develop dementia, over and above measures of cognitive performance level (Holtzer et al., 2008; Vaughan et al., 2013). In the present research, we sought to establish whether intraindividual (or within-person) variability (IIV) in the form of trial-to-trial fluctuations in performance on two associative memory tasks could distinguish a well-characterized clinical sample of individuals with amnestic MCI from matched controls, and whether measures of variability provide clinically meaningful information over and above measures of performance level.

1.1. Intraindividual variability as a marker of neurological disturbance

IIV is defined as short-term, rapid, reversible fluctuations in performance (Nesselroade, 1991), and is a reliable, measurable characteristic of an individual's behaviour (Hultsch et al., 2008; MacDonald et al., 2009b). According to a comprehensive taxonomy of "intraindividual dynamics" (Li et al., 2004), short-term, within-person, within-task changes are labeled as *variations* in *functioning*. To date, most studies of IIV have focused on the non-adaptive form of this variation, termed *fluctuation* (or "lack of processing robustness"). This form of IIV is defined as processing variability around an asymptotic level of functioning, and this is the focus of the current paper. Adaptive forms of variation in functioning, including *plasticity* (training gain), *diversity* (exploratory behaviour, strategy testing), and *adaptability* (variation in response to perturbations in the human-task environment), have not been as extensively studied to date.

IIV provides unique information about behaviour that is not otherwise captured by traditional measures of performance accuracy or speed. Over and above these other measures, IIV tends to uniquely predict meaningful outcomes such as everyday functioning (Burton et al., 2009), falls (Graveson et al., 2015), the presence of cognitive impairment (Collins and Long, 1996), cognitive decline (Sugarman et al., 2014), and even impending death (MacDonald et al., 2008), among others. Increased variability is seen in normal cognitive aging. Measures of IIV are elevated in older relative to younger adults (e.g., Anstey, 1999; Bielak et al., 2014; Hultsch et al., 2002; Nesselroade and Salthouse, 2004; Iskandar et al., 2016; Vandermorris et al., 2013a; Murphy et al., 2007; West et al., 2002; Williams et al., 2005), and variability tends to increase over time, especially in the oldest old (Bielak et al., 2014; Bielak et al., 2010; Lövdén et al., 2007; MacDonald et al., 2003). In addition, longitudinal changes in IIV and cognitive performance in older adults are coupled, in that increases in IIV over time correspond with decreases in cognitive performance across a variety of tasks, and in some cases, IIV precedes and predicts cognitive decline (Bielak et al., 2010; Lövdén et al., 2007; MacDonald et al., 2003).

These and other findings provide evidence that IIV may reflect wide-ranging neural disturbance. That is, elevated IIV has been documented in a number of neurological populations, including epilepsy, attention deficit disorder, traumatic brain injury, multiple sclerosis, and focal frontal lesions. It is also elevated in neurological conditions that are more prominent in older populations, including cerebrovascular conditions, Alzheimer's disease, Parkinson's Disease, frontal-temporal dementia, and other dementias (for a recent review, see Vandermorris and Tan, 2015).

1.2. Intraindividual variability in MCI

There is emerging evidence that IIV is elevated in MCI. Although there have been some exceptions (e.g., Gorus, 2008; Tales et al., 2012), a number of studies have demonstrated increased within-person, within-task variability in MCI relative to normal control groups, including on tests of simple or choice reaction time (Christensen et al., 2005; Dixon et al., 2007), visual search (McLaughlin et al., 2010; Phillips et al., 2013), complex attention requiring inhibition and switching (Strauss et al., 2007), speeded lexical- and semantic-decision making (Dixon et al., 2007), and speeded cued recall (Ramratan et al., 2012). There have been contradictory findings regarding utility of IIV as a predictor of MCI diagnosis, with some studies showing positive prediction (Dixon et al., 2007; Strauss et al., 2007) and another showing no prediction (Christensen et al., 2005). There is additional evidence that, within individuals with MCI, IIV is predictive of the development of dementia over the subsequent 2–3 years (Tales et al., 2012).

To date, IIV in *associative memory performance* response times has not been fully examined in MCI. This kind of cognitive task may be of particular relevance in this population given that some of the most sensitive tests for detecting early cognitive decline are measures of associative memory (e.g., Atienza et al., 2011; Irish et al., 2011; Karantzoulis et al., 2006; Troyer et al., 2008, 2012). Although one previous study (Ramratan et al., 2012) demonstrated increased IIV in MCI during cued speeded recall of word pairs, it can be preferable to focus on recognition (rather than recall) of associative information. Because associative recall is limited by the number of items recalled, the use of associative recognition paradigms permits one to examine memory for all items, not just those explicitly recalled. In addition, speeded memory tasks where participants are asked to recall information as quickly as possible are less naturalistic than unspeeded tasks where participants have time to reflect and strategize before responding. This, in the present study, we sought to explore patterns of IIV on unspeeded associate recognition tasks in a well- characterized clinical sample of individuals with amnestic MCI and a demographically matched control group. To date, the utility of IIV on memory tasks for *predicting* diagnostic status has not been examined. We hypothesized that (1) individuals with MCI would show heightened IIV compared to healthy controls and (2) IIV would uniquely predict MCI group membership, independent of measures of performance accuracy.

2. Methods

2.1. Participants

Participants were 24 individuals with single-domain amnestic MCI and 21 matched controls with age-normal memory ability. Participant characteristics and diagnostic procedures have been described in detail previously (Troyer et al., 2012). Briefly, all participants underwent clinical evaluation including a clinical interview, cognitive testing, and administration of self-report questionnaires. All participants were screened for medical and psychiatric disorders, medications affecting cognition, substance use, and current mood symptomatology.

Diagnosis of amnestic MCI was done according to well-established criteria (Knopman et al., 2003). Each participant reported a subjective memory complaint and obtained scores that were lower than expected for age, education, and verbal IQ on at least two memory tests (Hopkins Verbal Learning Test – Revised; Brandt and Benedict, 2001; Brief Visuospatial Memory Test – Revised; Benedict, 1997; Rey-Osterreith Complex Figure recall; Spreen and Strauss, 1998; Digit Symbol incidental recall; Wechsler, 1997). Performance was normal for age on general and non-memory cognitive tests (Mini-Mental State Examination; Folstein et al., 2000; Digit Span; Wechsler, 1997; Boston Naming Test; Kaplan et al., 1983; Rey-Osterreith Complex Figure copy; Spreen and Strauss, 1998; Trail Making Test switching; Delis et al., 2001). Participants had no substantial interference with normal daily activities.