On the nature and measurement of neurocognitive adaptability in older adulthood

by

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BSc, Laurentian University, 2006
MSc, Laurentian University, 2011

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Abstract

Objective: This dissertation was undertaken to explore the clinical utility of physiological and behavioural metrics of neurocognitive adaptability in the screening of older adults for possible early signs of pathological cognitive aging.

Methods: This was an intensive, multi-method study of 44 healthy (non-demented) Victoria-area older adults (ages 65 to 80 years). Study 1 examined timescale-specific differences in resting electroencephalographic (EEG) adaptability as a function of subtle cognitive decline. Study 2 described differences in retest practice effect -- within and across a burst of 4 to 6 occasions of computerized cognitive testing -- with respect to individual variation in estimated premorbid function and self-reported conscientiousness. Study 3 considered whether practice effects from Study 2 were related to individual differences in the resting EEG marker derived in Study 1, above and beyond the differences due to premorbid function and conscientiousness.

Results: Study 1 revealed that older adults with neuropsychological performance indicators of subtle cognitive decline also showed subtle, timescale-specific differences in resting EEG adaptability. Study 2 illustrated the differentiable effects of individual differences in estimated premorbid function and conscientiousness on within- and across-occasion improvement on a computerized attention-shifting (switch) task. Study 3 demonstrated the unique promotional effects exerted by conscientiousness and resting EEG adaptability on the rate of across-occasion improvement in cognitive performance.

Conclusions: Useful yet under-used tools for detecting early signs of neurocognitive decline include rigorous, standardized neuropsychological diagnostic criteria, the magnitude of practice-related improvement in cognitive performance, and characteristics of the brain's resting electrical activity. Future multi-method, ecologically-situated studies are needed to establish standardized protocol that can be used to screen growing worldwide numbers of older adults for losses in neurocognitive adaptability that may herald the earliest stages of pathological neurocognitive aging.

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Acknowledgments

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Dedication

This dissertation is dedicated to the participants and to the contagious altruism and enthusiasm for discovery that drove their participation.

General Introduction

Rationale

Population demographics in North America are shifting. As the post-World War II “baby boomers” reach older adulthood (ages 65 to 80 years) there are expected to be increasing numbers of individuals at heightened risk for dementia, bringing growing economic and social cost (Alzheimer Society of Canada, 2010). Dementia refers to syndromes of cognitive and neurobehavioural impairment beyond normal aging. The impact on cognitive function of interactions between age- and disease-related biological changes eventually compromise one's competence to meet everyday needs. It is significant that the problem of studying dementia in large part derives from the blurred lines between “normal” and “pathological” aging processes. Besides age (*i.e.* years since birth) there are a variety of lifespan-wide biological, psychological, and environmental variables that appear to impact a given individual's course of neurocognitive development and senescence. As a result, individual older adults show complex patterns of change and fluctuation in cognitive performance across time. In particular individuals, individual differences in trajectory are described by clinicians as periods of maintenance, decline, or improvement in various domains.

A significant proportion of older adults develop pathologic cognitive impairment and functional dependence late in life. Yet at the age of 60, these healthy individuals are often indistinguishable from those who will eventually develop dementia. There is a pressing need to prospectively identify, as early as possible, those older adults who are more likely to exhibit pronounced age- and disease-related declines in neurocognition. This will allow finite assessment and intervention energy and resources to be directed at maintaining or improving their quality of life and functional independence (Solomon et al., 2014).

Non-normative neurocognitive aging is often expressed as longitudinal declines in the

performance of standardized clinical neuropsychological tests and, eventually, as performance that falls in the impaired range relative to same-aged peers. This process typically takes years or decades to unfold. Neuropsychological assessment remains one of the most reliable and valid means for detecting older adults with neurocognitive function that (1) is impaired relative to same-aged peers, and (2) declines across several years of repeated assessment. While reliable, valid, and integral for comprehensive understanding and personalized care, this approach is time- and resource-intensive. As such, it is not suited to population-level screening of older adults for signs of early dementia (Block, Johnson-Greene, Pliskin, & Boake, 2017). The health and longevity of the growing older adult population depend on the development of assessment protocols that are sensitive to the earliest known signs of dementia and accessible to as many older adults as possible.

Recent developments in longitudinal and neuroscientific aging research have revealed that declines in neurocognitive adaptability may mark the earliest stages of dementia. Unfortunately, the concept of neurocognitive adaptability lacks theoretical integration. This fact hinders the development of potentially valuable clinical tools. The present body of work will take a theoretically integrative, multi-method approach to understanding the subtle losses of neurocognitive adaptability that may signal a heightened prospective risk of dementia. Some of the most promising neurocognitive adaptability markers are explored in the current series of studies.

Aging and dementia: trajectories emerge from the interplay of adaptation and decline

Over the course of a decade, the cognitive performance trajectories of individuals who will eventually develop dementia can be seen to decline from the “normative” to the “impaired” range relative to population-based norms (Collie et al., 2001; Howieson et al., 2008). Contemporary theory and research also suggest that the earliest stages of both normative and pathological cognitive aging are associated with slight (*i.e.* difficult-to-detect) shifts in cognitive performance (Caselli et al., 2014; Edmonds, Delano-Wood, Galasko, Salmon, & Bondi, 2015). Though subtle relative to late-stage

declines, these early stages of cognitive decline nonetheless appear to be linked with alterations in the structure and function of the central nervous system.

The most well-documented neuropathological indicators of dementia include cortical thinning, white matter degradation, amyloid deposition, cerebral infarction, accumulation of Lewy bodies, and modified functional dynamics (Sperling et al., 2011). With varying prevalence, combinations of these changes have been found in the brains of individuals diagnosed with conditions such as dementia of the Alzheimer's type, dementia with Lewy bodies, vascular dementia, or frontotemporal dementia. A considerable proportion of older adults with dementia show evidence of multiple etiologies (Kovacs et al., 2013; Schneider, Arvanitakis, Leurgans, & Bennett, 2009). Even among those older adults whose trajectory of neurocognitive aging seems normative, functional and structural evidence of changes in central nervous system consistently anticipate within-person declines in cognitive performance (Dodge et al., 2014; Hayden et al., 2011). In other words, the pathophysiological processes underlying dementing conditions often seem to manifest years or decades before obvious clinical impairment. The implications of this have fuelled the search for earlier and earlier markers of “preclinical” dementia (Knopman & Caselli, 2012), including subjective (Rabin, Smart, & Amariglio, 2017) and objective (Edmonds et al., 2015) markers.

The levels of some neuropathological indicators of dementia, or biomarkers, distinguish cognitive performance groups at baseline. Moreover, progression in certain biomarkers often predicts the incidence of detectable cognitive decline. However, currently identified “dementia biomarkers” in isolation do not tell the whole story. Some individuals (*e.g.* those higher in educational attainment) remain dementia-free until death despite significant postmortem evidence of neuropathology (Brayne et al., 2010). That is, while biomarkers contibute prediction of non-normal cognitive decline, research has yet to establish a 1:1 relationship between any given biomarker and later development of dementia. This suggests that there is some other process or variable that links biomarkers to manifest cognitive

function. Along with normative and pathological aging, differences in neurocognitive adaptability might also contribute to the considerable and largely unexplained individual differences in both level and rate of decline in cognitive performance with advancing age (*e.g.* see Hayden et al., 2011). Neurocognitive adaptability is an umbrella term that denotes the various mechanisms by which brain and cognition are dynamically adjusted in response to changing environmental demands (Table 1). Adaptive shifts in the structure or function of the physical brain underlie changes in cognition and overt behaviour. For this reason, neurocognitive adaptability can be measured directly from the brain, or indirectly through inferences based on behavioural (*i.e.* cognitive performance) measures.

Table 1. Examples of physiological and behavioural adaptations at various timescales and the corresponding environmental demands that drive them.

Timescale	Environmental demand	Physiological adaptation	Behavioural adaptation
Decade/year	Historical, technological, climactic epochs	Patterns of neuronal loss/preservation	Changes in vocabulary or personality
Month/day	Seasons; light-dark cycles; work schedule	Receptor, dendrite, and hormone dynamics	Learning to perform new routines smoothly
Minute/second	In-the-moment interaction with physical environment or other people	Autonomic dynamics (*e.g.* arousal, muscle tone)	Dealing effectively with an unexpected phone call
Subsecond	Driving; sports; combat; video games	Momentary changes in electrical topography	Rapid decision-making or precise movement execution

Alterations in brain and cognitive function across the continuum of healthy to pathological aging reflect a blend of normative age-associated changes, disease-related pathology, and adaptive shifts in neurocognitive processes; the latter are presumed to partially counteract the effects of aging and disease (Charles & Carstensen, 2010; Raz, 2009). Compared to existing understanding of normal and pathological aging processes, less is known about the mechanisms by which some individuals are able to adapt and maintain cognitive health and independence late in life or in the face of pronounced neuropathology. This complicated reality invites an idiographic approach (*i.e.* considering each person relative to themselves) that integrates multiple perspectives, including biological, behavioural, and

psychological dimensions.

Neural and psychological adaptation occurs via several distinct mechanisms and unfolds across adult developmental time in concert with normative and pathological aging processes. As such differences in the functioning of these mechanisms may explain the diversity and malleability of individual trajectories of aging as they emerge through bidirectional interactions between biology, behaviour, and physical/sociocultural environment (Lindenberger, Li, & Bäckman, 2006). Epidemiological work has revealed that involvement with various social, cognitive, and physical activities throughout life is protective against cognitive decline and dementia, suggesting that even in old age neurocognitive adaptability is preserved and can be fostered (Hertzog, Kramer, Wilson, & Lindenberger, 2009; Stern, 2012). It is possible that older adults who remain dementia-free (*i.e.* cognitively intact and functionally independent) remain so in part because they maintain some form of neurocognitive adaptability that allows them to meet day-to-day functional goals despite the increasing biological constraints of age and disease on neurocognitive functioning.

In order to detect the early, subtle signs of preclinical dementia it is necessary to consider the role that neurocognitive adaptability plays in the expression of or resistance to dementia. However, the absence of a comprehensive theoretical conceptualization of neurocognitive adaptability hampers its clinical assessment.

Theoretical perspectives on neurocognitive adaptability in aging and dementia

As previously discussed, the lack of a direct 1:1 relationship between brain function and manifest cognition underscores the need to identify individual differecnes that might mediate or moderate this relationship. In the current body of work, these individual differences are discussed in terms of neurocognitive adaptability. Unfortunately, to date, popular aging theory has largely ignored or over-simplified the role of adaptability in old age (Charles & Carstensen, 2010; Robinson, Briggs, & O’Neill, 2012). This is due in part to theoretical formulations based on cross-sectional studies as well

as longitudinal designs with relatively long (circannual) retest intervals; neither can capture the within-person dynamics associated with adaptation (Morcom & Johnson, 2015). As a result, many theoretical models tend to describe the continuum of normative and pathological cognitive aging in terms of binary differences between groups (*i.e.* young/old or healthy/declining) and gradual, linear declines in performance (*i.e.* at the scale of years or decades). These models are minimally useful in the assessment of a particular individual who presents at the clinic with a heretofore unknown level and rate of change in neurocognitive function, and an often blurred and uncertain diagnostic profile. That is, in real-time, individual aging trajectories are not characterized by static declines from a known level of "peak functioning". Growing evidence suggests that they are better expressed as complex variation (change and fluctuation) at multiple hierarchical timescales, in part driven by adaptive responses to various environmental demands and changes in physiological or motivational status (Molenaar, 2004). This ideographic complexity limits the generalizability of existing longitudinal studies, blurs the conceptual distinction between healthy and early-pathological aging, delays clinical intervention, and interferes with the development of novel prophylactic treatments (*i.e.* those based on bolstering neurocognitive adaptability).

Some theoretical perspectives do consider the role of neurocognitive adaptability in the maintenance of cognitive performance and functional independence in old age. Most notably, the theory of cognitive reserve (Stern, 2009a) and the theory of selective optimization and compensation (SOC; Baltes, 1997) both posit a crucial role for neurocognitive adaptation in older adulthood. In both cases, adaptability is seen as a moderator of the effect of age- and disease-imposed biological constraints on cognitive and functional status. In the case of cognitive reserve, the adaptive mechanism remains obscure (Morcom & Johnson, 2015), and "reserve" is most often quantified using educational attainment as a proxy. However, recent formulations of cognitive reserve theory (Stern, 2012) have emphasized that the protective benefits of reserve can be enhanced throughout the lifespan, such as

through continued education or other cognitively stimulating activities. In other words the reserve model treats education alternately as a *marker* and *mechanism* of neurocognitive adaptability.

In contrast, formulations of SOC theory have explicitly stated the importance of particular psychological mechanisms, namely selection (focusing resources on specific personal goals), optimization (investment of energy in achieving the selected goals), and compensation (achieving a personal goal via alternative means), to effective adaptability and everyday competence in old age (Tuokko & Smart, 2014). In addition to its formulation of purely psychological mechanisms of adaptation to age and disease, SOC has also served as a meta-model for the science of aging in terms of successful adaptation to a changing environment despite and/or as a result of alterations in biological function (Baltes & Carstensen, 1996). Like psychological mechanisms of adaptation, many proposed neural mechanisms of adaptation show quantitative and qualitative differences across individuals and across the lifespan. Specific adaptive neural mechanisms include transient disinhibition, receptor/neurotransmitter dynamics, growth of neural processes, synaptogenesis, neurogenesis, gliogenesis, and angiogenesis (Mercado, 2008; Will, Dalrymple-Alford, Wolff, & Cassel, 2008). Differences between persons, and within persons over time, in psychological and biological mechanisms of adaptability might help to explain the relative resilience of some older adults to detrimental effects of age and disease, and the relative susceptibility of others.

Acceptance of the theories of cognitive reserve and of SOC have been widespread. Yet many adaptive mechanisms nonetheless remain poorly understood, as do their relationships to various risk and protective factors (*e.g.* health behaviours, education). In part, this reflects a reliance on metaphors to understand adaptability. This situation is not uncommon in cognitive science, as in, for example, the widely-used “resource-allocation” and “filter” models of attention, where the nature and quantifiability of “cognitive resources” and “filters” are unclear (Fernandez-Duque & Johnson, 1999).

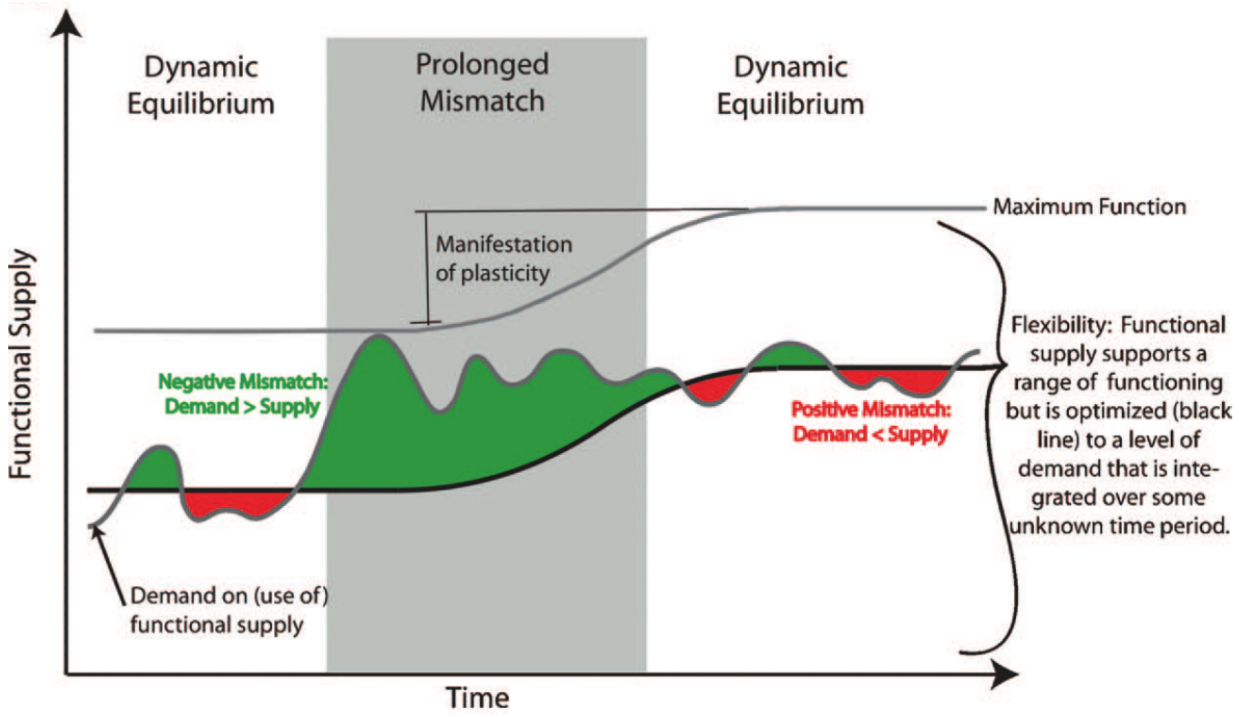

Figure 1. Conceptual model illustrating the contributions of flexibility and plasticity to neurocognitive adaptation across time. Adapted from Lövdén et al., 2010.

Given the diversity of putative adaptive mechanisms, Lövdén, Bäckman, Lindenberger, Schaefer, & Schmiedek (2010) created a trans-theoretical framework for the study of neurocognitive adaptation as it unfolds at multiple hierarchical timescales. According to Lövdén et al. (2010), adult neurocognitive adaptation, in general, reflects two inter-related categories of time-varying processes. The first category, *flexibility*, refers to processes that serve to optimize in-the-moment performance given existing biological constraints (*i.e.* brain structure). The second category, *plasticity*, denotes processes underlying the alteration of these biological constraints, over time, in response to persistent shifts in environmental demand. Thus the model predicts that when neurocognitive adaptation occurs, it reflects the resolution of a supply-demand mismatch: while *flexibility* is the range in performance that is possible given existing neurostructural limitations (what the authors refer to as “functional supply”), *plasticity* is the resolution of protracted mismatches between functional supply and environmental demands (Figure 1). Thus, variation mechanisms supporting flexibility and/or plasticity may help to

explain individual differences in the effect of dementia-related neuropathology on cognitive performance and functional independence.

While a useful heuristic, the framework of Lövdén et al. (2010) is an echo of previous perspectives on the issue of adaptability and aging (*e.g.* Horn, 1972), re-packaged for the "neuro" generation. This framework also has the potential to create a false binary between "static" and "time-varying" processes underlying neurocognitive adaptability. All adaptation, being a process, requires time in order to manifest. Flexibility and plasticity refer to this single construct – adaptation – unfolding at two extremes of timescale. Adaptation is thus observable as within-person changes in structure or function to meet shifting demands. At one end, *flexibility* allows for shifts in neurocognitive function that are rapid, transient, and limited in magnitude. At the other end, *plasticity* allows for dynamic alterations to the range of immediately available responses through alteration of anatomical and physiological constraints. Shifts as a result of plasticity tend be slower, more stable, and allow for a greater magnitude of change in order to keep pace with persistent changes in environmental pressure.

Neurocognitive adaptability in the clinic

Considering the diverse mechanisms and measurable manifestations of neurocognitive adaptability on a timescale continuum sheds light on potentially useful clinical examples of these phenomena. Many instances of manifest neurocognitive adaptation encountered in clinical neuropsychological practice are not recognized as such. For example flexibility determines the peak level of performance that could be obtained by a particular individual at a particular moment in time, without the benefits of environmental support (*e.g.* scaffolding, instruction, feedback). In practical terms, flexibility is the individual's capacity for accommodating the demands of a particular assessment task given contemporaneous neurostructural constraints. In fact, Lövdén et al. (2010) considered flexibility "a synonym to terms such as intelligence, functional capacity, brain functioning, and

experience in order to emphasize a simple but important point, the inherently adaptive and variable nature of cognitive and brain functioning" (p. 661).

At the other, plasticity end of the spectrum, adaptation is commonly conceived of as "experience-dependent change in brain structure". It manifests at the observable behaviour level as performance improvement as a result of simple exposure to a particular paradigm (retest or practice effects; Yang, Krampe, & Baltes, 2006), or of "testing the limits" by providing scaffolding, training, or performance feedback (Baltes, Kühl, & Sowarka, 1992). Both retest and targeted training prompt individuals to explore and refine alternative neural circuits and cognitive strategies relevant to the demonstration or achievement of a particular cognitive task or functional goal (Park & Reuter-Lorenz, 2009). Thus clinicians can consider neurocognitive adaptability as a superordinate domain with a variety of potential lower-order mechanisms and indicators, and these may be used to improve conceptualization of the clinical and day-to-day functioning of older adults.

Conclusion

Various adaptive mechanisms seem to buffer older adult cognitive and functional status against age- and disease-related biological changes. Explicit assessment of neurocognitive adaptability thus has the potential to reveal why individual older adults vary in terms of their resilience/susceptibility to functional declines with advancing age and/or dementia pathology. The following series of studies represents an attempt to advance the clinical neuropsychological care of older adults by pursuing the measurement of neurocognitive adaptability via multiple complementary approaches.

Thus, on the one hand, these studies will consider a sample of healthy (non-demented) older adults in terms of differences in standardized neuropsychological performance, estimated premorbid/reserve capacity, and aspects of personality (*i.e.* conscientiousness). These dimensions, all based on standardized instruments, are perhaps at present more common in the clinical assessment of older adult neurocognitive function; they were measured at a single time-point (baseline), and provide

an invaluable cross-sectional reference. On the other hand, this series of studies will also exploit recent advances in cognitive science, the neurosciences, and longitudinal design/analysis to provide a time-varying perspective on neurocognitive adaptability in older adulthood. In particular, the present studies employed repeated computerized testing to capture within-person fluctuation and change in cognitive performance (behaviour) at the scale of days (occasions) and seconds (trials), and resting electroencephalographic (EEG) recordings to quantify fluctuation in neural function at the scale of subseconds. Although some of the more novel approaches used in the ensuing studies may be less familiar to clinicians, these techniques nonetheless hold promise for imminent clinical application pending further validation and standardization.

To reiterate, there is a pressing need to identify individual older adults as early as possible in the course of pathological neurocognitive aging (*i.e.* in the "preclinical dementia" stage). Approaches from a variety of disciplines have factored in a broadened conceptualization of early-pathological neurocognitive aging; further advances in conceptualization and clinical care of at-risk older adults are hampered by a lack of integration across lines of investigation and levels of analysis. A focus on "dementia biomarkers" is not enough: many older adults remain dementia free despite significant "dementia neuropathology". This resilience may be attributable to individual differences in one or more mechanisms of neurocognitive adaptability; these are presumed to mitigate the impact of neuropathology on cognition. Indeed, the evidence reviewed in this body of work suggests that subtle losses in neurocognitive adaptability may mark the earliest detectable stages of non-normative neurocognitive aging. It will be argued that a multi-method, multiple time-point approach is likely to yield increased sensitivity to early signs of loss in neurocognitive adaptability relative to any one indicator in isolation.

Study 1: Neuropsychological and resting-state electrophysiological markers of older adult neurocognitive adaptability

Worsening over time in biomarker- or performance-based indices of preclinical dementia reflects the progressive loss of an individual older adult's neurocognitive adaptability, and an increased prospective risk of dementia. Clinical neuropsychologists track the loss of neurocognitive adaptability in single individuals as reliable decline in performance on standardized neuropsychological measures across repeated assessments separated by one or more years (Duff, 2012). Likewise, because within-person declines in performance are often mirrored by changes in neuroanatomy and neurophysiology (Mormino et al., 2014), clinicians also often consider longitudinal neuroimaging data in order to determine whether a particular patient is stable or declining.

Yet clinicians are often asked to make a determination of dementia-risk status (or “dementia stage”) at a given individual's initial assessment. They typically do not have the luxury of access to prior assessments when they are called to do so. The utility of older adult neurocognitive assessment would be enhanced by the development of cross-sectional proxies that signal the earliest stages of dementia. Among the most promising early markers of an individual's potential for future cognitive and functional deterioration are performance-based evidence of “subtle cognitive decline” (Edmonds et al., 2015) and biomarkers of nascent neural pathology (Sperling et al., 2011). Combined assessments that include both biological and performance-based measures of neurocognition have proven to be more sensitive to early/subtle decline than either in isolation (Gomar, Bobes-Bascaran, Conejero-Goldberg, Davies, & Goldberg, 2011).

Two potential early-dementia markers are considered in this initial study. The first involves an actuarial diagnostic classification based on standardized neuropsychological performance measures. Groups based on these criteria were then considered in terms of differences in a metric of neural

adaptability, derived from resting-state electroencephalographic (EEG) signals, that is known to be sensitive to aging and dementia.

Standardized neuropsychological testing as a proxy for within-person decline

In the absence of prior data, the simplest means of inferring cognitive decline is through comparison of individual performance at a single time point with that of a healthy, demographically similar reference sample. Recently, Edmonds et al. (2015) proposed an actuarial neuropsychological operationalization of "subtle cognitive decline", the earliest detectable stage of preclinical dementia. This operationalization reflects a more parsimonious conception than previous criteria, such as those based on biomarker cascade hypotheses (Sperling et al., 2011). For diagnostic classification decisions, the approach of Edmonds et al. (2015) relies solely on the presence of impaired-range neuropsychological test scores defined by norm-based cutoffs. A relatively sensitive (less stringent) cutoff for impairment (>1 SD below the reference sample mean) allows the earliest (subtle) stages of cognitive performance decline to be detected. In the interest of increasing the reliability of diagnosis, the method considers those with ≤1 impaired-range score to be normal; among healthy older adults a small number of impaired-range scores is common and often uninformative (Binder, Iverson, & Brooks, 2009; Mistridis et al., 2015; Schretlen, Munro, Anthony, & Pearlson, 2003). The proposed classification rubric also takes advantage of the fact that obtaining one impaired score in each of two domains is far more common (~20%) than obtaining two impaired scores in the same domain (~5%) (Palmer, 1998).

However there are limitations to this diagnostic approach. The authors themselves note that a particular shortcoming of their "criteria for subtle cognitive decline is that they may be too strict to capture all individuals with very early cognitive changes (*i.e.* those who have declined cognitively but are still performing in the normal range on neuropsychological testing...)" (Edmonds et al., 2015, p. 240). In other words a method based on impairment relative to population-referenced cutoff scores

alone may sometimes be insensitive to within-person decline. This might be particularly true when applied to individuals who may have previously performed in the high- or above-average range.

In theory, estimates of premorbid function allow clinicians to capitalize on those cognitive processes which are thought to be resilient to age- or disease-related declines. So-called “hold skills” can be used as a standard against which to describe possible declines “with respect to self” in other domains. While many demographic- and performance-based methods exist to estimate premorbid level, irregular word reading tests provide a brief, reliable, and standardized assessment that is valid and useful for most situations (Lezak, Howieson, Bigler, & Tranel, 2012). Applied to the single client, an unexpected discrepancy between (estimated) “peak” and current function would suggest a within-person loss of neurocognitive adaptability. In fact grouping individual older adults based on the presence or absence of premorbid IQ-adjusted cognitive impairment has been used to predict subsequent longitudinal decline and to highlight group differences in brain metabolic activity at baseline (Rentz et al., 2007). IQ-adjusted norms have been developed especially for detection of early-stage decline among higher-performing older adults (Rentz et al., 2006).

These results suggest that the sensitivity of the actuarial approach put forth by (Edmonds et al., 2015) might be further improved by adjusting current neuropsychological performance for estimated premorbid IQ. IQ-adjusted neuropsychological performance may provide a single-occasion estimate of within-person decline, and hence lost neurocognitive adaptability, which could inform more accurate and individualized assessment for early-stage preclinical dementia.

Brain signal variability as a marker of neurocognitive adaptability

Clinical-neuropsychological testing remains the most valid and reliable means for objective measurement of current cognitive function. However, as previously noted, such testing may lack sensitivity at the most subtle levels of impairment, meaning that older adults who test “normally” may actually be false-negatives with regards to estimating risk of future decline. This is particularly true of

those higher in education and/or premorbid function (Jonker, Geerlings, & Schmand, 2000). In those with more subtle levels of impairment, adaptability – particularly flexibility – may be a more sensitive, additional marker to estimate future decline, yet this is not typically ascertained within a standardized assessment. The use of real-time, functional neural data could shed light on an individual's adaptability, and enhance the understanding and interpretation of what might be apparently normal test scores.

In practice clinical neuropsychologists most often infer neural function from objective cognitive performance and subjective report data. Yet many are increasingly exposed to findings from neuroimaging that can refine case conceptualization. Macrostructural features considered on MRI (*e.g.* size and shape of gyri, sulci, major white matter tracts) are tied to relatively stable neurocognitive constraints. However "structural" (static) neuroimages cannot capture the time-varying complexity that is the *sine qua non* of brain function. Neuroimaging modalities with high time-resolution provide the unique opportunity for many repeated measurements of neural processes, at a subsecond timescale, within a single measurement occasion. Moment-to-moment fluctuations in synaptic, ion channel, haemodynamic (fMRI BOLD), and scalp electrical/magnetic field (EEG/MEG) signals reflect the dynamic, adaptive range of the nervous system (given existing structural constraints), and might be considered as the brain's fundamental "temporal structure" or "temporal organization" (Beharelle, Kovačević, McIntosh, & Levine, 2012; Garrett et al., 2013). The brain's inherent, malleable spatiotemporal dynamics underlie its ability to represent, integrate, and respond to a diversity of information derived from experiences and interactions with the environment (Mercado, 2008; Seeley et al., 2007). Brain signal variability provides a view of neurocognitive flexibility (Lövdén et al., 2010), and may prove a useful and readily-acquired index of neural adaptability to inform the assessment of older adult neurocognitive function in cases of suspected preclinical dementia.

Even if restricted to measurement at a single occasion, EEG signals derived from resting-state (as opposed to task-associated) recordings have particular potential as population-level clinical

screening tools. For one, the EEG approach relies on relatively inexpensive, non-invasive, and portable technologies that are already in routine use for the clinical assessment of neurocognitive function. Recordings of resting brain activity (*i.e.* in the absence of an explicit task) also reflect similar network dynamics as task-associated recordings (Sala-Llonch, Bartrés-Faz, & Junqué, 2015) and tend to reflect contributions from those networks with the most metabolic activity (Ganzetti & Mantini, 2013). Because of its implication in myriad clinical syndromes and psychological processes, the resting or "default" state has moreover been the focus of intensive recent neuroimaging research (Greicius, Krasnow, Reiss, & Menon, 2003; Greicius, Supekar, Menon, & Dougherty, 2009).

It is convenient that resting (task-free) recordings also appear to provide the most reliable estimates of some EEG metrics because they are not contaminated by task-related activations or differences in motivation or task performance (Garrett et al., 2013). In brief, whereas task-associated brain signals reflect evoked or induced activity that depends on understanding, attending to, and performing a given task, resting brain signals reflect a default state of flexible readiness (Garrett et al., 2013). This methodological point facilitates ready comparison and integration of human findings with those from experimental non-human neuroscience. Resting-state recordings are suitable for the clinical assessment of neurocognitive adaptability with individuals from a wide variety of developmental, socioeconomic, cultural, geographic, educational, and diagnostic backgrounds.

Multiscale sample entropy as a metric of brain signal variability. Variability across time in brain signals (*e.g.* fMRI and EEG) is most pronounced between the frequencies of 0.01 and 100 Hz (oscillations on the scale of seconds/subseconds). Visual detection by experts of regional differences in resting-state EEG waves can be used to differentiate subtypes of early dementia (Micanovic & Pal, 2014). The most common quantitative approach to studying brain wave oscillations involves analysis of spectral power in various frequency bands. This approach is analogous to a decomposition of the EEG wave in to a linear combination of sine waves (and a residual signal), whose amplitudes are then

estimated (Niedermeyer & Lopes Da Silva, 1999).

Low-frequency brainwave oscillations in the delta (1-4 Hz) and theta (4-8 Hz) frequency bands have received particular attention in the aging and dementia literature. Aging and the progression of dementia have been associated with increased power in the low-frequency bands (Dauwels, Vialatte, & Cichocki, 2010). This is due in part to the increasingly local (as opposed to distributed) nature of interactions between neuronal populations (Vakorin, Lippe, & McIntosh, 2011). There are many high-quality studies of resting low-frequency EEG spectral power. Yet the nature of the relationship of these electrophysiological markers to healthy and pathological aging is obscured by mixed and sometimes contradictory findings. This is in part due to across-study variability in the protocols used to process and analyze EEG data (Caplan, Bottomley, Kang, & Dixon, 2015).

Though it continues to be a rigorous and widespread method of EEG analysis, recent investigations suggest that linear decomposition methods such as spectral analysis lead to a loss of unique information that is orthogonal to average activity (Faisal, Selen, & Wolpert, 2008). As a result, useful information embedded in EEG signals is often seen as a nuisance, systematically (and usually implicitly) eliminated by many popular functional neuroimaging approaches including spectral analysis, functional connectivity analysis, and even those ERP, BOLD, MEG, and NIRS paradigms that involve signal averaging within voxels and/or across multiple recording epochs (Garrett et al., 2013; Garrett, Kovacevic, McIntosh, & Grady, 2011).

Non-human primate work has revealed that variation in cortical electrical activity is not unidimensional. It oscillates at multiple timescales simultaneously and these multiscale fluctuations reflect local and long-range structural and functional interactions (Honey et al., 2007). In other words, resting brain signal variability represents a blend of signals reflective of various local and distant interactions between spatially disparate and differentially-specialized brain loci. These simultaneous oscillations across a range of subsecond timescales reflect a dynamic balance between functional

segregation and global integration (Tononi, Sporns, & Edelman, 1994). Characteristic spatiotemporal "blends" identify dissociable, distributed functional networks (McDonough & Nashiro, 2014). These multiscale temporal characteristics appear to emerge in part as a result of neurostructural constraints on functional interactions. Simulation work suggests that timescale-specific fluctuations in brain electrical activity depend on fundamental physical features of the nervous system that are potentially impacted by aging or dementia pathology, including conduction velocity, coupling strength, and noise levels (Sporns et al., 2009).

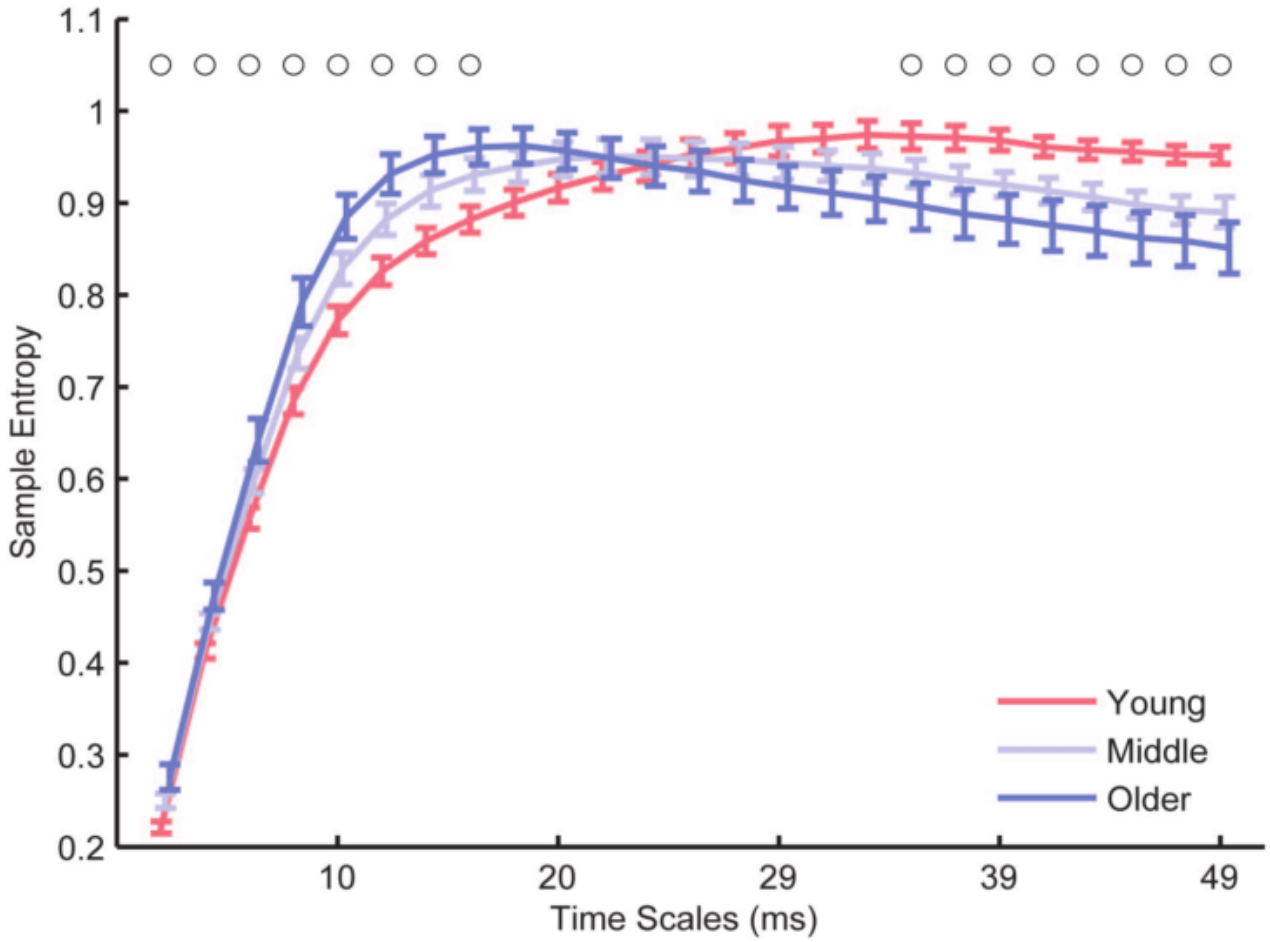

Figure 2. Plot of brain signal variability (entropy) across multiple timescales. Note the contrasting differences at finer (~12 ms) and coarser (~40 ms) timescales between younger-, middle-, and older-aged individuals, with an inversion of the direction of effect at ~20 ms. From McIntosh et al., 2014.

Multi-timescale brain signal variability is captured in the raw by most existing fMRI and EEG methodologies, however it must be extracted using particular analysis algorithms lest it is eliminated as unwanted noise in the course of signal filtering and averaging. Recent research with human participants has quantified multi-timescale brain signal variability with a metric known as multiscale sample entropy, or MSE (Costa, Goldberger, & Peng, 2002, 2005). Similar to global cognitive performance, the magnitude of brain signal entropy shows an inverted-U pattern across the lifespan: there is a generalized (across-timescale) increase from birth through the 20s and an asymptote/decrease thereafter (Lippé, Kovacevic, & McIntosh, 2009; McIntosh et al., 2014; McIntosh, Kovacevic, & Itier, 2008). Broad-timescale developmental increases in brain signal entropy are also associated with increases in performance accuracy and consistency (Garrett et al., 2011; McIntosh et al., 2008).

Recently, McIntosh et al. (2014) harnessed MSE to demonstrate that healthy young-, middle-, and older-aged adults showed *timescale-specific* differences in EEG entropy. Using event-related EEG, they found that cross-sectional increases in age were associated with increased EEG entropy at fine-grained timescales (~2 – 15 ms) but decreased entropy at coarse-grained timescales (above ~20 ms) across nearly all of the brain regions examined (Figure 2). The authors theorized that their MSE-based method captured the progressive shift from long-range functional interactions (reflected in coarse-grained entropy) to local processing (reflected in fine-grained entropy) that is associated with healthy aging. This basic result has been replicated at least once using a dataset that included both task-associated and resting-state EEG (Sleimen-Malkoun et al., 2015). This pattern of changes with development and senescence echoes trajectories of executive cognitive functions (Zelazo, Craik, & Booth, 2004). Executive functioning has been hypothesized to underlie many compensatory strategies employed by healthy, functionally independent older persons (Tuokko & Smart, 2014).

Therefore, contrary to views of non-linear brain signal variability as tantamount to “neural noise” resulting from experimental apparatus or an “old, inefficient” brain, EEG, MEG, and fMRI

signal entropy appears to reflect an adaptive state of flexibility and readiness. These are characteristic of a healthy brain, where a wide dynamic range allows rapid response to environmental stimuli of uncertain frequency and quality (Faisal et al., 2008; Garrett et al., 2011; Grady & Garrett, 2014). MSE provides an all-important multi-timescale perspective on brain variability, and may have untapped potential for use in clinical applications. That is, MSE could serve as a real-time measurement of *flexibility*, previously defined as processes that serve to optimize in-the-moment performance given existing biological constraints (*i.e.* brain structure).

Single-subject application of this technique could benefit from considering the different clinical correlates of distinct timescale bands in brain signal entropy, where healthy aging appears to involve relative loss of coarse- and enhancement of fine-grained EEG entropy (McIntosh et al., 2014; Sleimen-Malkoun et al., 2015). From an aging as "wear and tear" perspective, the loss of coarse-grained entropy, also characteristic of traumatic brain injury (TBI; Beharelle et al., 2012), may thus index reduced biological integrity with advancing biological age. On the other hand many older persons might experience relative preservation or enhancement of fine-grained variability as a reflection of the adaptive response to primary alterations known to underlie healthy neurocognitive aging (Baltes, 1997). Older adults diagnosed with pathological cognitive decline (MCI or dementia) seem to exhibit an additional loss of this (potentially adaptive) fine-grained variability relative to their healthy same-aged peers (Mizuno et al., 2010; J.-H. Park, Kim, Kim, Cichocki, & Kim, 2007). However, other studies have found that specific losses of fine-grained EEG entropy differentiate those with Alzheimer type dementia from healthy controls (Yang et al., 2013). As such, between-person differences in the relative levels of fine- and coarse-grained brain signal entropy may serve to distinguish older adults at increased risk for cognitive decline from those who are likely to remain stable for several more years.

Therefore, resting-state EEG MSE has potential as a practical, economical early dementia screening tool. The recent adoption of reproducible diagnostic criteria for subtle cognitive decline and

mild cognitive impairment (Edmonds et al., 2015) presents an opportunity to take a first step towards the validation of resting-state EEG MSE for use as a prodromal dementia screener by examining timescale-specific differences between diagnostic groups.

Objectives and predictions

Accelerated population growth, and the accelerating prevalence of dementia (Alzheimer Society of Canada, 2010), motivate the demand for more sensitive and efficient approaches to the standardized, multi-method neurocognitive assessment of older adults. The present study undertook an empirical examination of putative cross-sectional indices of neurocognitive adaptability in a sample of healthy older adults. First of all, this study employed performance-based scores from standardized neuropsychological tasks adjusted for estimated premorbid IQ in order to improve their approximation of within-person losses in neurocognitive adaptability. The IQ-adjustment procedure was deemed particularly relevant due to the highly-educated nature of the older adults comprising the community sample in question (Rentz et al., 2006). Age-adjusted and age-and-IQ-adjusted cut-scores were then used to group participants according to proposed actuarial neuropsychological criteria for subtle cognitive decline and mild cognitive impairment (MCI) (Edmonds et al., 2015). This diagnostic determination of increasing dementia-risk was then used to examine group differences in multiscale EEG entropy.

Besides providing a baseline description of the study sample in terms of demographic and neuropsychological indicators, a major objective of this study was to illustrate the derivation of potential cross-sectional proxies of within-person decline. Another aim was to assess the validity of the EEG marker by examining across-timescale differences between diagnostic groups defined by standardized performance data gathered at the same assessment occasion. The extant research reviewed above suggested that (1) adjusting neuropsychological performance for premorbid IQ increases sensitivity to subtle neurocognitive impairments; and (2) older adults with greater dementia-risk status

will show progressive losses of coarse- and then fine-grained brain signal entropy.

Based on this foundation, the main hypotheses of the present study are that resting-state EEG MSE would:

(1) be lower across all timescales for those classified as MCI relative to those classified as normal (no impairment);

(2) be lower across fine- but not coarse-grained timescales for those classified as MCI relative to those classified as subtle cognitive decline (SCD);

(3) be lower across fine- but not coarse-grained timescales for those classified as SCD relative to those classified as normal; and

(4) show a larger association with dementia-risk status when the latter was based on age- and premorbid IQ-adjusted relative to age-adjusted neuropsychological cutoff scores.

Study 1 Methods

Participants

The sample used in the present study is from a 3-year longitudinal, intensive-measurement study of prospectively-recruited, non-demented older adults. Individuals were recruited from the Victoria, British Columbia area by means of flyers posted in older adult service and recreation centres; via email announcements through local older adult organizations; and through a notice published on the website and in the newsletter of the University of Victoria Institute on Aging and Lifelong Health (IALH). Recruitment messaging requested the participation of healthy older adults (no significant neurological history) who either (1) had no concerns about their cognitive functioning, or (2) had some concerns about their cognitive functioning. A self-report telephone interview (Rabin et al., 2007) was used to determine study eligibility. To be included in the study, participants had to (1) be between ages 65 and 80, (2) be free of significant neurological history (*e.g.* stroke, Alzheimer's, Parkinson's), (3)

report intact instrumental activities of daily living (Lawton & Brody, 1969), (4) have access to an informant (friend or family member) who knew them well (at least 10 hours per week of direct or telephone contact) and who could accompany them to their first laboratory visit, and (5) be willing to participate in all of the study activities. Recruitment and enrollment ran from April 2013 until July 2015, and 52 potential participants between ages 65 and 80 contacted the primary investigator during this period. Six were excluded due to positive neurological history and 1 eligible participant completed the phone screen and then declined further participation. Of the 45 who were enrolled, 1 participant did not complete all assessment activities required for at least 1 complete wave of measurement. This left a sample of 44 participants eligible for inclusion in the present analyses.

Measures

In addition to the telephone screen, the 44 study participants also completed self-report scales (Table 2), underwent neuropsychological testing (Table 3), and attended multiple "measurement burst" appointments comprised of self-report and computer tasks. Resting electroencephalographic (EEG) recordings were also obtained from each participant, immediately following and at the same testing occasion as the neuropsychological assessment. Self-report and computerized cognitive assessment measures were not considered in this first study.

Standardized neuropsychological testing. Neuropsychological testing was conducted by the primary investigator (clinical neuropsychology doctoral student). Resultant raw scores were evaluated by two methods: (1) by correction for age only through reference to MOANS norms (Mayo's Older Americans Normative Studies) when possible (Ivnik et al., 1992; Ivnik et al., 1996; Lucas et al., 1998), and test publisher norms otherwise; and (2) by correction for age and premorbid function, in which the age-adjusted participant scores were further adjusted based on each individual's estimated premorbid IQ. Other means such as educational attainment and socioeconomic status are also used to represent premorbid function (Lezak et al., 2012), and education-corrections are available for many common

neuropsychological tests (including those in the present study). However, previous research has established that performance-based measures of irregular word reading are superior estimates of baseline (premorbid) function, and are moreover free from bias against individuals who may not have had the opportunity to pursue higher education (Rentz et al., 2004). Especially among older cohorts from developed countries, educational attainment is often confounded by gender and childhood/early adulthood socioeconomic status (White, Blane, Morris, & Mourouga, 1999). As such, the IQ-adjustment procedure was applied to scores corrected for age only (not age and education).

The premorbid IQ-adjustment method (method 2) was adapted from that introduced and described by Rentz et al. (2004). It is done to approximate within-person decline relative to hypothesized premorbid levels. According to this method, age-corrected standard scores (M = 100, SD = 15) from the WAIS-IV TOPF were used to adjust the norm-referenced scores for other neuropsychological test scores upward or downward. First, TOPF standard scores were converted to scaled scores (M = 10, SD = 3), which were then added/subtracted to the MOANS age-corrected scaled scores.

For example, consider the Trails B performance (raw score = 80 seconds) of a hypothetical 67-year-old individual with a premorbid IQ of 115. According to published MOANS norms accounting for age only (method 1), this Trails B performance corresponds to a scaled score of 10 (50th percentile) for his or her age range. However this individual's premorbid IQ of 115 represents performance that is about 1 standard deviation above the reference mean (*i.e.* TOPF scaled score = 13). As a result, for method 2, the individual's MOANS age-adjusted Trails B scaled score is adjusted downward by 1 unit of standard deviation (*i.e.* 3 scaled score units); in effect, this penalizes those with relatively higher premorbid IQ estimates; the result is that lower IQ-adjusted neuropsychological test scores reflect increasing impairment with respect to each individual's own estimated premorbid baseline. Thus, according to IQ-adjusted MOANS norms (method 2), this individual's Trails B performance

corresponds to a scaled score of 7 (20th percentile). In this way, the IQ-adjustment (method 2) is an attempt to increase the sensitivity to detection of within-person cognitive decline, based only on single-occasion data, by taking advantage of irregular word reading as a "hold skill". Summary statistics for all neuropsychological tests in the present assessment battery are printed in Table 4.

Once the number of impaired-range scores based on the two methods above was determined, diagnostic dementia-risk grouping was performed based on proposed criteria for subtle cognitive decline and MCI (Edmonds et al., 2015). First, 3 scores were selected to represent each of 3 neuropsychological domains (9 scores in total): language (Category Fluency, BNT total score, FAS phonemic fluency), attention/executive (Trails A, Trails B, CLOX Trial 1), and episodic memory (CVLT-II 30-minute delayed recall, CVLT-II recognition, WMS-R Visual Reproduction II). Impaired-range test scores were defined as those falling 1 or more standard deviations below the reference standard. Based on the presence of impaired-range scores, individuals were grouped as follows: normal (zero or one impaired scores), subtle cognitive decline (impaired score on two measures in different domains), or MCI (impaired score on two or more measures in same domain, *or* impaired score on one or more measures in all three domains). Every participant was grouped by dementia-risk status twice, according to each of the two impaired-score cutoff criteria (age-only and IQ-adjusted reference) discussed as methods 1 and 2 in the preceding paragraph.

Electroencephalographic recording and processing. Electroencephalographic (EEG) signals were recorded at 500 Hz sampling rate with online bandpass of 0.016 – 100 Hz using a 32-channel BrainAmp, Abralyt 2000 gel, and Ag/AgCl sensors mounted in a mesh cap (Electrocap International). Signals were recorded from frontal (F3, Fz, F4, FCz), central (C3, Cz, C4), and posterior (CPz, P3, Pz, P4) sites (Figure 3). Sensors were also affixed to left mastoid (M1), the outer canthi of both eyes (LO1 and LO2), and below the left eye (IO1). Right mastoid (M2) served as online reference. EEG activity was recorded during 4 alternating 2-minute blocks of rest with eyes open and rest with eyes closed. In

an effort to minimize contamination as a result of eye movement and blinks, only data from the eyes-closed recording condition is considered for the purposes of this study. Offline, EEGLAB (Delorme & Makeig, 2004) was used to re-reference to averaged mastoids, apply a bandpass filter of 1 – 40 Hz, and remove artifacts using an automated algorithm (Artifact Subspace Reconstruction). This algorithm (ASR) identifies epochs of artifact-free ("clean") data and epochs with high relative amplitude or variance; data from the latter epochs is then reconstructed based on data from the former (Mullen et al., 2013). This pre-processing method was selected to encourage reproduction/replication by reducing the demands on human perceptual expertise for manual epoch rejection (Cassani, Falk, Fraga, Kanda, & Anghinah, 2014). In light of continued advances in computational capability, this protocol will moreover make feasible the semi-automated derivation of clinically-relevant brain signal analytics in near real-time (Bhat, Rajendra, & Adeli, 2015; Kothe & Makeig, 2013). Finally, each participant's 4 minutes of resting, eyes-closed EEG data was segmented into 60, 4-second epochs (2000 data points within each epoch) which were subjected to multiscale entropy analysis. The full pre-processing script is included in Appendix 1.

For each 4-second epoch, multivariate multiscale sample entropy (multivariate MSE) was computed as a measure of brain signal variability using the *mvsampen_full.m* algorithm (Ahmed & Mandic, 2011), available at http://www.commsp.ee.ic.ac.uk/~mandic/research/Complexity_Stuff.htm (Appendix 2), implemented using a commercial software package (MATLAB version 7.10; The Mathworks Inc., 2000). Sample entropy is a method of quantifying the complexity or irregularity of a signal or time series. Formally, it is defined as the negative logarithm of the probability that subsets of the signal which are similar up to time t will also be similar at time t+1. By progressively "coarse-graining" or "down-sampling" a time series (partitioning it into equal-sized subintervals of increasing size, always taking the mean of each interval), signal entropy can be examined at different timescales (hence *multiscale* sample entropy). The multivariate version of MSE uses multiple inter-related time

series vectors as input: it has been especially developed for and validated with multi-channel physiological data, including EEG (Ahmed & Mandic, 2011).

The MSE algorithm hence proceeds in two stages (coarse-graining and entropy-computation). First, a series of progressively coarser-grained time series are computed from the pre-processed EEG epoch. This is done by averaging EEG data points across time within non-overlapping windows of increasing length (*i.e.* sliding windows of width 2, 3, 4...), akin to a moving average. In effect, each new time series represents the fluctuations (entropy) in the raw EEG signal at different timescales. For example – because the EEG records one sample every 2 ms (500 Hz sample rate) – the time series at the smallest timescale is the same as the raw signal (2 ms). The next time series is created by averaging adjacent 2-ms samples, yielding the second smallest timescale (4 ms). The next time series represents the average of 3 adjacent samples and has timescale 6 ms, and then 8 ms, 10 ms, and so on to a maximum timescale of 60 ms. Thus there were thirty time series derived from each EEG epoch, corresponding to timescales between 2 and 60 ms. In the second stage, the algorithm calculates the sample entropy for each time series (*i.e.* at each timescale). The entropy computation itself is a non-linear process of pattern recognition applied to each individual time series. The algorithm determines whether the pattern of data points within one portion of a time series differs from the pattern of data points in adjacent segments of the time series. Time series which show differences in the pattern of values from segment to segment are higher in entropy than those time series with repetitive patterns. Input parameters must be set to determine the pattern length (number of consecutive data points used for pattern matching) and the similarity criterion (threshold to determine whether or not amplitude values from adjacent subsegments are distinguishable). McIntosh et al. (2014) recommended using a pattern length of $m = 2$ and a similarity criterion of $r = 0.5$ (data points considered to have indistinguishable amplitude values if the absolute amplitude difference between them is ≤ 5% of the time series standard deviation). Prior to epoching, each individual's EEG epochs (measured in μV)

were unit-normalized (mean = 0 and variance = 1) to eliminate bias due to differences in mean or variance of the input signal (Ahmed & Mandic, 2011). MSE was then computed for each individual's 60 4-second epochs, with data from 3 sensors over the central region (C3, Cz, C4) forming the multivariate time series vector required as the algorithm's input. A script for computing multiscale sample entropy from pre-processed EEG data is included in Appendix 2.

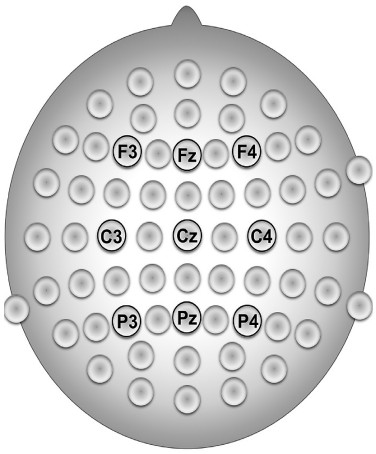

Figure 3. Sensor placement on scalp. View from above, participant facing up.

Procedures

The study procedures were approved by the University of Victoria Human Research Ethics Board and all participants provided free and informed consent consistent with the Declaration of Helsinki. Following the telephone screen, participants attended the laboratory with their informants for completion of the consent process and self-report questionnaires. At a subsequent 2-hour appointment participants underwent neuropsychological testing and resting EEG recording. Finally, each participant attended 4 to 6 burst measurement sessions (individual or group testing) to be completed within a period of no more than 6 consecutive weeks, with an interval of at least 24 hours between subsequent assessments. All study appointments were scheduled at the convenience of the participant. No single appointment lasted more than 90 minutes and participants were offered breaks to minimize fatigue.

Design and Planned Analyses

First, sample and diagnostic-group demographic and neuropsychological performance descriptives were computed, and univariate analysis of variance (ANOVA) was used to investigate diagnostic group differences on demographic variables. Because EEG entropy was measured at multiple timescales and for multiple data epochs per person, multilevel models were used to represent EEG entropy at 3 hierarchically-nested levels: timescale (level 1), epoch (level 2), and person (level 3). A null multilevel linear model allowed assessment of the reliability of the EEG entropy metric via estimation of its intra-class correlation (ICC) coefficient. Multilevel linear and nonlinear models were then used to examine performance-based dementia-risk group differences in resting-state EEG entropy as a function of timescale.

All data manipulation and analysis was performed in *R* (R Core Team, 2016). Descriptive statistics and analyses of variance (ANOVA) were performed using functions in the *stats* package. Multilevel linear models were estimated using the *lme4* package (Bates, Maechler, Bolker, & Walker, 2015) and multilevel nonlinear models were estimated using the *nlme* package (Pinheiro, Bates, DebRoy, Sarkar, & R Core Team, 2016).

Study 1 Results

Sample and diagnostic group descriptives

Applying dementia-risk diagnostic rules using MOANS age-based cutoff scores yielded group sizes of 39 (normal), 2 (subtle cognitive decline), and 3 (mild cognitive impairment, MCI). The small group sizes reflect the expected low frequency of impaired-range scores relative to age-based norms in this high-functioning community-based sample of healthy older adults (*i.e.* see education and premorbid IQ estimate). These numbers shifted drastically when applying the same diagnostic groupings criteria using cut-scores adjusted for each individual's own estimated premorbid IQ. The

premorbid IQ-adjusted method yielded group sizes of 14 (normal), 9 (subtle cognitive decline), and 21 (MCI). Thus, when diagnosis was based on scores adjusted for age only, 88.6% of the sample was classified as normal. The corresponding value for diagnosis based on scores adjusted for age and premorbid IQ was 31.8%. However, a chi-square test showed that the number of individuals classified as normal, subtle decline, or MCI were not significantly discordant across grouping methods (χ^2 (4) = 5.12, p = 0.28). Descriptive statistics for the whole sample, and for the individual dementia-risk groups, are visible in Table 2 and 3 for grouping based on conventional- and IQ-adjusted cut-scores, respectively.

One-way univariate ANOVA suggested that age-adjusted diagnostic groups did not differ in age (F(2,41) = 0.962, p = 0.39, η^2 = 0.04), education (F(2,41) = 0.90, p = 0.41, η^2 = 0.04), or premorbid function (F(2,41) = 0.21, p = 0.81, η^2 = 0.01), nor in the distribution of males and females (χ^2 (2) = 1.66, p = 0.44). However there was a significant group difference in MMSE (F(2,41) = 9.56, p < 0.01, η^2 = 0.32). *Post hoc* analysis (Tukey's HSD) revealed that the MCI group scored significantly lower on the MMSE than the normal group, and that all other pairwise group differences were non-significant.

Diagnostic groups based on IQ-adjusted cut-scores did not differ in terms of MMSE (F(2,41) = 0.36, p = 0.70, η^2 = 0.02), or in sex distribution (χ^2 (2) = 1.75, p = 0.42); however, there were small but significant differences in age (F(2,41) = 3.39, p = 0.04, η^2 = 0.14), education (F(2,41) = 7.33, p < 0.01, η^2 = 0.26), and premorbid function (F(2,41) = 5.66, p < 0.01, η^2 = 0.22). *Post hoc* investigation with Tukey's HSD revealed that (1) the subtle decline group was significantly older than the normal group, while all other pairwise group differences in age were non-significant, (2) both the subtle decline and MCI groups had significantly more education than the normal group, but did not differ from one another, and (3) the MCI group also had significantly higher premorbid function than the normal group, while neither the normal nor MCI groups differed significantly from the subtle decline group on this measure.

Table 2. Characteristics of participants (*n* = 44) enrolled in final study, grouped by dementia-risk status based on age-based normative cutoffs.

	Means (SD) for diagnostic groups defined by age-based cutoffs			
	Total	Normal	Subtle decline	MCI
Size (*n*)	44	39	2	3
Age (y)	71.6 (3.7)	71.4 (3.7)	70.5 (0.8)	74.4 (4.4)
Sex (M/F)	12/32	11/28	1/1	0/3
Education (y)	17.5 (3.4)	17.4 (3.3)	20.5 (6.4)	16.7 (1.5)
TOPF (*ss*)	118.6 (9.5)	118.9 (9.6)	117.0 (7.1)	115.3 (11.1)
MMSE	28.1 (2.2)	28.5 (1.7)	26.0 (0.0)	24.0 (3.6)

Table 3. Characteristics of participants (*n* = 44) enrolled in final study, grouped by dementia-risk status based on IQ-adjusted cutoffs.

	Means (SD) for diagnostic groups defined by IQ-adjusted cutoffs			
	Total	Normal	Subtle decline	MCI
Size (*n*)	44	14	9	21
Age (y)	71.6 (3.7)	70.1 (3.1)	74.0 (2.2)	71.5 (3.4)
Sex (M/F)	12/32	2/12	3/6	7/14
Education (y)	17.5 (3.4)	15.2 (2.8)	19.9 (3.4)	18.0 (2.9)
TOPF (*ss*)	118.6 (9.5)	112.3 (12.2)	119.9 (5.1)	122.1 (6.7)
MMSE	28.1 (2.2)	28.1 (2.1)	28.6 (1.7)	27.8 (2.4)

TOPF = Wechsler Adult Intelligence Scale – Fourth Edition, Test of Premorbid Function
MMSE = Mini-Mental Status Exam – Second Edition, total score

Sample summary statistics for neuropsychological measures used in the current study are reported in Table 4. Overall, the sample tended to perform within the higher end of the average range relative to their same-aged peers when age-based MOANS norms were used. When norms were adjusted based on individual differences in TOPF-estimated premorbid IQ, sample mean neuropsychological scores tended toward the lower end of the average range. The effect of this IQ-adjustment is also evident in the average number of impaired-range scores (those falling > 1 SD below the reference standard): for MOANS age-based cut-scores, the average number of impaired-range scores was at the level that would be expected for a healthy individual (0 to 2; *i.e.* see (Edmonds et al., 2015), while after IQ-adjustment the average number of impaired-range scores was notably higher than typical for healthy older individuals (Mistridis et al., 2015).

Table 4. Whole-sample descriptive statistics for neuropsychological variables scored using either conventional cut-scores or cut-scores with a TOPF-estimated IQ adjustment.

Measure	*Normative reference method*	
	Conventional	IQ-Adjusted
CVLT-II (*z*)	*z*	*z*
Trial 1	0.20 (1.27)	-1.05 (1.30)
Trial 5	0.38 (0.93)	-0.86 (1.01)
Trial B	0.36 (1.17)	-0.88 (1.24)
SDFR	0.56 (0.94)	-0.69 (1.10)
SDCR	0.40 (0.84)	-0.85 (0.88)
LDFR	0.52 (0.88)	-0.72 (0.97)
LDCR	0.36 (0.82)	-0.88 (0.86)
Recog. Hits	-0.27 (0.73)	-1.51 (0.95)
Recog. FP	-0.20 (1.01)	-1.44 (1.19)
WMS-R (*SS*)	*SS*	*SS*
VR I	12.70 (2.94)	8.96 (3.60)
VR II	12.09 (2.69)	8.36 (3.25)
LM I	11.44 (2.98)	7.71 (3.16)
LM II	11.42 (3.03)	7.68 (3.22)
Boston Naming Test (*SS*)	12.88 (3.49)	9.15 (3.41)
WAIS-IV Digit Span (*SS*)	13.00 (2.85)	9.27 (2.82)
Trail Making Test (*SS*)	*SS*	*SS*
Trails A	11.70 (2.76)	7.96 (3.65)
Trails B	12.53 (2.89)	8.80 (3.20)
COWAT (*SS*)	12.77 (2.66)	9.03 (2.61)
Category Fluency (*SS*)	12.96 (3.40)	9.20 (3.39)
CLOX (*z*)	*z*	*z*
CLOX 1	0.56 (1.23)	-0.69 (1.26)
CLOX 2	0.56 (0.93)	-0.68 (1.02)
Impaired-range scores (*count*)	2.16 (2.31)	6.95 (4.42)

Sample means (SD) are reported.
SS = scaled score
z = z-score
CVLT-II = California Verbal Learning Test – Second Edition
SDFR = short-delay free recall
SDCR = short-delay cued recall
LDFR = long-delay free recall
LDCR = long-delay cued recall
Recog. Hits = recognition hits
Recog. FP = recognition false positives
WMS-R = Wechsler Memory Scales – Revised
VR = Visual Reproduction subtest
LM = Logical Memory subtest
COWAT = Controlled Oral Word Association Test

Reliability and Unconditional Models

Linear model development. Determination of the reliability (represented by intra-class correlation coefficient) of the EEG entropy metric was made possible by the fact that, for each person, sample entropy was estimated at each of 30 timescales (between 2 and 60 ms) for 60 separate 4-second recording epochs. First, a null 3-level model (random intercept, no fixed effects) revealed a grand-mean (SE) EEG entropy score of 1.28 (0.02), and an intraclass correlation coefficient (ICC) of 0.22, suggesting that 22% of the overall variance in entropy was due to differences between individual participants. Of this, about half was due to person-level (level 3, 11%) and half due to epoch-level variance (level 2, 10%). However the greatest proportion of entropy variance was at level 1, the across-timescale (residual) level (78%).

The subsequent model included timescale centered at 14 ms. This centering value was selected based on previous empirical evidence of this as the approximate inflection point (e.g. McIntosh et al., 2014; Mizuno et al., 2010). This parameter represented the fixed linear effect of timescale. The second model showed that EEG entropy averaged 1.08 at the 14-ms timescale, and evidenced a significant linear increase with timescale at a rate of 0.01/ms. A random linear effect of timescale was included in the next model, as well as a term for its covariance with the random intercept. This significantly improved the model fit ($-2\Delta LL\ (\sim 2) = 1878.9$, $p < 0.001$, with smaller AIC and BIC), suggesting that there was individual variation in the linear change in entropy across timescale. Adding the fixed linear effect of timescale (centered at 14 ms) reduced the level-1 (residual) variance component by approximately 53%, and adding a random linear effect of timescale reduced the remaining level-1 variance by a further 3%. A fixed quadratic timescale term was included in the next model, and this revealed that the average EEG entropy curve was significantly concave (opening downward), as expected based on published evidence. A model that also included a random quadratic timescale effect failed to converge. Including a fixed quadratic timescale slope parameter reduced the remaining

residual (level-1) variance by 65% compared to the model including fixed and random linear timescale parameters. Relative to the random intercept only model, the fixed quadratic, random linear timescale model had 84% less residual variance. Residual entropy variance for this, the unconditional 3-level linear model, was 0.014. Coefficients for this empirically-derived unconditional linear model are available in Table 5 and Table 6.

Nonlinear model development. The nonlinear approach to analyzing group differences in multi-timescale EEG entropy involved approximating within-person, across-timescale differences in entropy via asymptotic regression. This meant estimating terms for the intercept (entropy at smallest scale), asymptote, and (natural log of) the rate of increase in entropy as a function of timescale. The null nonlinear model (including fixed and random effects for all three terms) revealed an average finest-scale (2-ms scale) entropy value of 0.31, an asymptotic EEG entropy value of 1.45, and a rate of increase in entropy across timescale of about 0.13/ms. Residual entropy variance for the unconditional 3-level nonlinear model was 0.00152, smaller by an order of magnitude than the residual variance for the unconditional linear model. Coefficients for this empirically-derived unconditional nonlinear model are available in Table 6.

Dementia-risk group differences in multiscale EEG entropy

The main objectives of this study pertained to an analysis of timescale-specific EEG entropy differences as a function of dementia-risk status (*i.e.* diagnostic group). Both linear and nonlinear approaches were thus used to model between-person differences in across-timescale EEG entropy as a function of dementia-risk. The linear approach employed linear and quadratic slope terms to approximate the across-timescale entropy curve. Including dementia-risk status based on conventional cut-scores in the fixed quadratic, random linear timescale model of EEG entropy revealed that increasing dementia-risk related to a significant flattening of the entropy curve; but the size of this effect was negligibly small (*pseudo-*$R^2 < 0.01$). Moreoever, conventionally-determined dementia-risk

did not relate to differences in overall level of entropy (*i.e.* intercept) or linear timescale slope. Using an identical model to test the effect of dementia-risk based on IQ-adjusted cut-scores revealed that increasing IQ-adjusted dementia-risk predicted both a reduction in the linear timescale slope (*pseudo-*R^2 = 0.04) and a significant but small flattening of the entropy curve (*pseudo-*R^2 < 0.01); the effect on the entropy intercept was non-significant (*pseudo-*R^2 = 0.05). Multilevel linear model results are reported in Table 5 and Table 6.

Dementia-risk was then used in a nonlinear model of EEG entropy as a between-person predictor of the entropy asymptote and rate of increase regression parameters. A model using conventional cut-scores to assign dementia-risk failed to converge, likely because of insufficient members in the subtle decline and MCI groups. The model employing IQ-adjusted dementia-risk as a predictor revealed that neither asymptotic EEG entropy nor the rate of increase in EEG entropy across timescale differed significantly according to dementia-risk group. Coefficients from this model are reported in Table 7.

Finally, follow-up graphical examination of across-timescale averages and confidence intervals (±SE) for groups defined by conventional cut-scores (Figure 4) seemed to suggest consistent group differences at nearly all timescales, with those in the subtle decline group having the highest group mean entropy, followed by those in the normal group, and those classified as MCI having the lowest EEG entropy. However this is of dubious value considering that group averages were based on extremely small MCI and subtle decline groups. Plotting group averages based on IQ-adjusted cut-scores (Figure 5) suggested effects of dementia-risk group membership that were isolated to the approximate ranges of fine- and coarse-grained entropy identified by (McIntosh et al., 2014). Thus, relative to the IQ-normal group, the IQ-MCI group had lower EEG entropy across all timescales. In contrast the EEG entropy for those in the IQ-subtle group appeared to be intermediate to the IQ-normal (higher) and IQ-MCI (lower) groups at fine-grained timescales (~10 to 30 ms), but did not differ from

the IQ-normal group at coarse-grained timescales (above ~36 ms).

Table 5. Summary of multilevel linear model coefficients illustrating the effects of age-adjusted cutoff-based dementia-risk status on resting-state EEG entropy.

	Unconditional Model			Age-Adjusted Dementia Risk		
Fixed Effect	*b*	SE	*P*	*b*	SE	*P*
Intercept						
Intercept	**1.08×10^{0}**	**1.49×10^{-2}**	**<0.01**	**1.09×10^{0}**	**1.58×10^{-2}**	**<0.01**
Dementia-risk	-	-	-	-2.16×10^{-2}	2.80×10^{-2}	0.44
Linear timescale						
Intercept	**3.23×10^{-2}**	**3.08×10^{-4}**	**<0.01**	**3.23×10^{-2}**	**3.08×10^{-4}**	**<0.01**
Dementia-risk	-	-	-	-1.09×10^{-3}	5.45×10^{-4}	0.05
Quadratic timescale						
Intercept	**-5.91×10^{-4}**	**1.64×10^{-6}**	**<0.01**	**-5.91×10^{-4}**	**1.64×10^{-6}**	**<0.01**
Dementia-risk	-	-	-	**2.11×10^{-5}**	**2.91×10^{-6}**	**<0.01**
Random Effect	Variance	SD		Variance	SD	
Person:Epoch						
Intercept	1.35×10^{-2}	0.12		1.35×10^{-2}	0.12	
Person						
Intercept	9.47×10^{-3}	0.10		9.56×10^{-3}	0.10	
Linear timescale	3.54×10^{-6}	<0.01		3.58×10^{-6}	<0.01	
Residual	1.37×10^{-2}	0.12		1.37×10^{-2}	0.12	
Model R^2	0.879			0.879		

b = unstandardized regression weight (slope)
SE = standard error
SD = standard deviation

Table 6. Summary of multilevel linear model coefficients illustrating the effects of IQ-adjusted dementia-risk status on resting-state EEG entropy.

	Unconditional Model			IQ-Adjusted Dementia Risk		
Fixed Effect	*b*	SE	*P*	*b*	SE	*P*
Intercept						
Intercept	**1.08×10^{0}**	**1.49×10^{-2}**	**<0.01**	**1.12×10^{0}**	**2.41×10^{-2}**	**<0.01**
Dementia-risk	-	-	-	-2.90×10^{-2}	1.66×10^{-2}	0.09
Linear timescale						
Intercept	**3.23×10^{-2}**	**3.08×10^{-4}**	**<0.01**	**3.39×10^{-2}**	**4.71×10^{-4}**	**<0.01**
Dementia-risk	-	-	-	**-1.57×10^{-3}**	**3.24×10^{-4}**	**<0.01**
Quadratic timescale						
Intercept	**-5.91×10^{-4}**	**1.64×10^{-6}**	**<0.01**	**-6.23×10^{-4}**	**2.57×10^{-6}**	**<0.01**
Dementia-risk	-	-	-	**3.08×10^{-5}**	**1.77×10^{-6}**	**<0.01**
Random Effect	Variance	SD		Variance	SD	
Person:Epoch						
Intercept	1.35×10^{-2}	0.12		1.35×10^{-2}	0.12	
Person						
Intercept	9.47×10^{-3}	0.10		9.04×10^{-3}	0.10	
Linear timescale	3.54×10^{-6}	<0.01		3.41×10^{-6}	<0.01	
Residual	1.37×10^{-2}	0.12		1.37×10^{-2}	0.12	
Model R^2	0.879			0.879		

b = unstandardized regression weight (slope)
SE = standard error
SD = standard deviation

Table 7. Summary of multilevel nonlinear model (asymptotic regression) coefficients illustrating the effects of IQ-adjusted dementia-risk status on resting-state EEG entropy.

	Unconditional Model			IQ-Adjusted Dementia Risk		
Fixed Effect	*b*	SE	*P*	*b*	SE	*P*
Intercept						
Intercept	**0.31**	**0.01**	**<0.01**	**0.32**	**0.01**	**<0.01**
Asymptote						
Intercept	**1.45**	**0.02**	**<0.01**	**1.48**	**0.03**	**<0.01**
Dementia-risk	-	-	-	-0.02	0.02	0.13
Rate of increase[*]						
Intercept	**-2.04**	**0.02**	**<0.01**	**-2.01**	**0.04**	**<0.01**
Dementia-risk	-	-	-	-0.03	0.02	0.28

Random Effect	Variance	SD	Variance	SD
Person:Epoch				
Intercept	2.77×10^{-3}	5.27×10^{-2}	6.71×10^{-3}	8.19×10^{-2}
Asymptote	1.73×10^{-2}	1.32×10^{-1}	1.82×10^{-2}	1.35×10^{-1}
Rate of increase	2.84×10^{-2}	1.69×10^{-1}	4.23×10^{-30}	2.06×10^{-15}
Person				
Intercept	3.26×10^{-3}	5.71×10^{-2}	3.20×10^{-3}	5.66×10^{-2}
Asymptote	1.55×10^{-2}	1.24×10^{-1}	1.43×10^{-2}	1.20×10^{-1}
Rate of increase	2.25×10^{-2}	1.50×10^{-1}	2.24×10^{-2}	1.50×10^{-1}
Residual	1.52×10^{-3}	3.89×10^{-2}	2.03×10^{-3}	4.51×10^{-2}
Model R^2	0.987		0.983	

[*]Coefficient is estimated as the natural logarithm of the rate of across-timescale entropy increase.
b = unstandardized regression weight (slope)
SE = standard error
SD = standard deviation

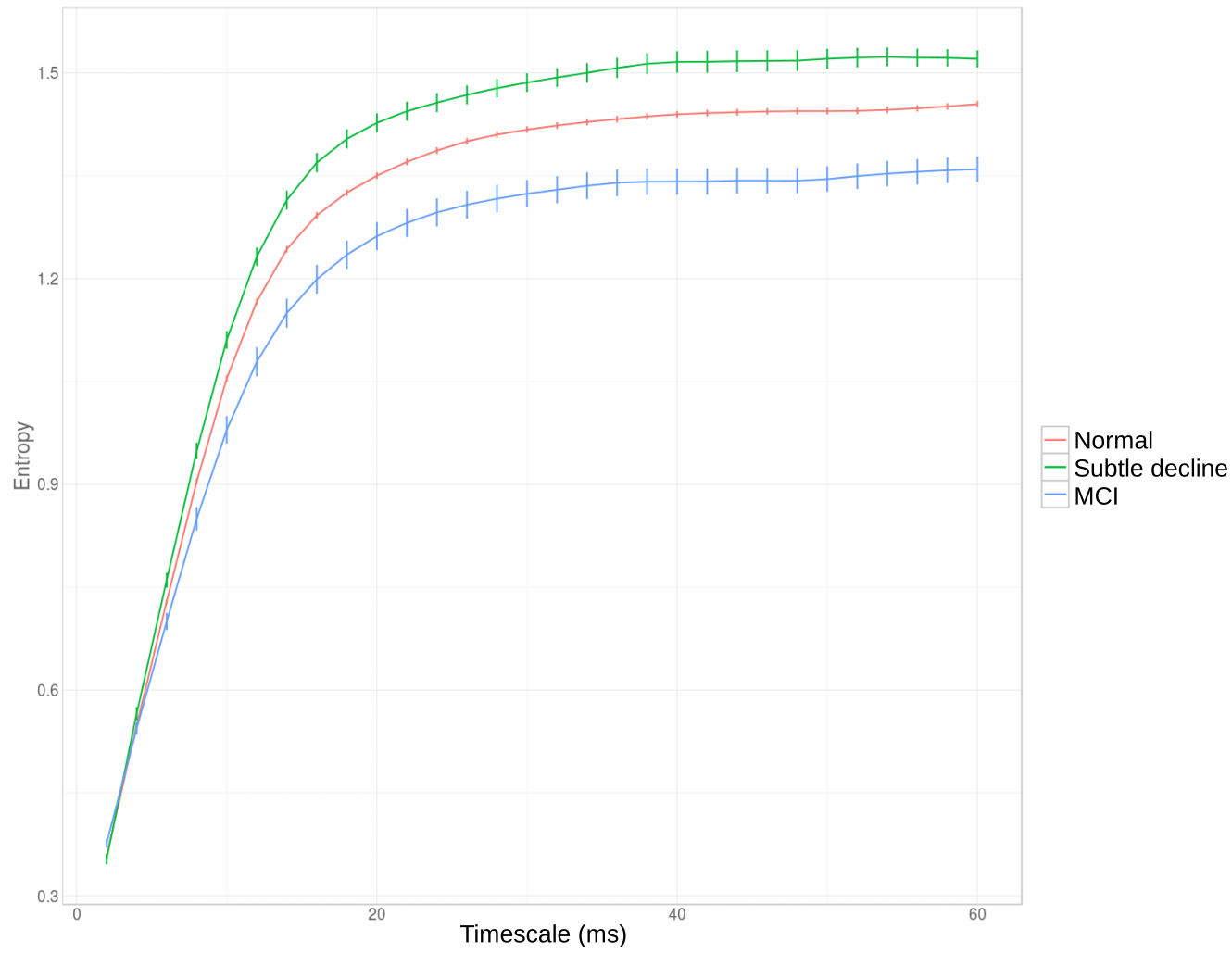

Figure 4. Average entropy (+/- SEM), plotted by timescale, as a function of conventional cut-score dementia-risk status.

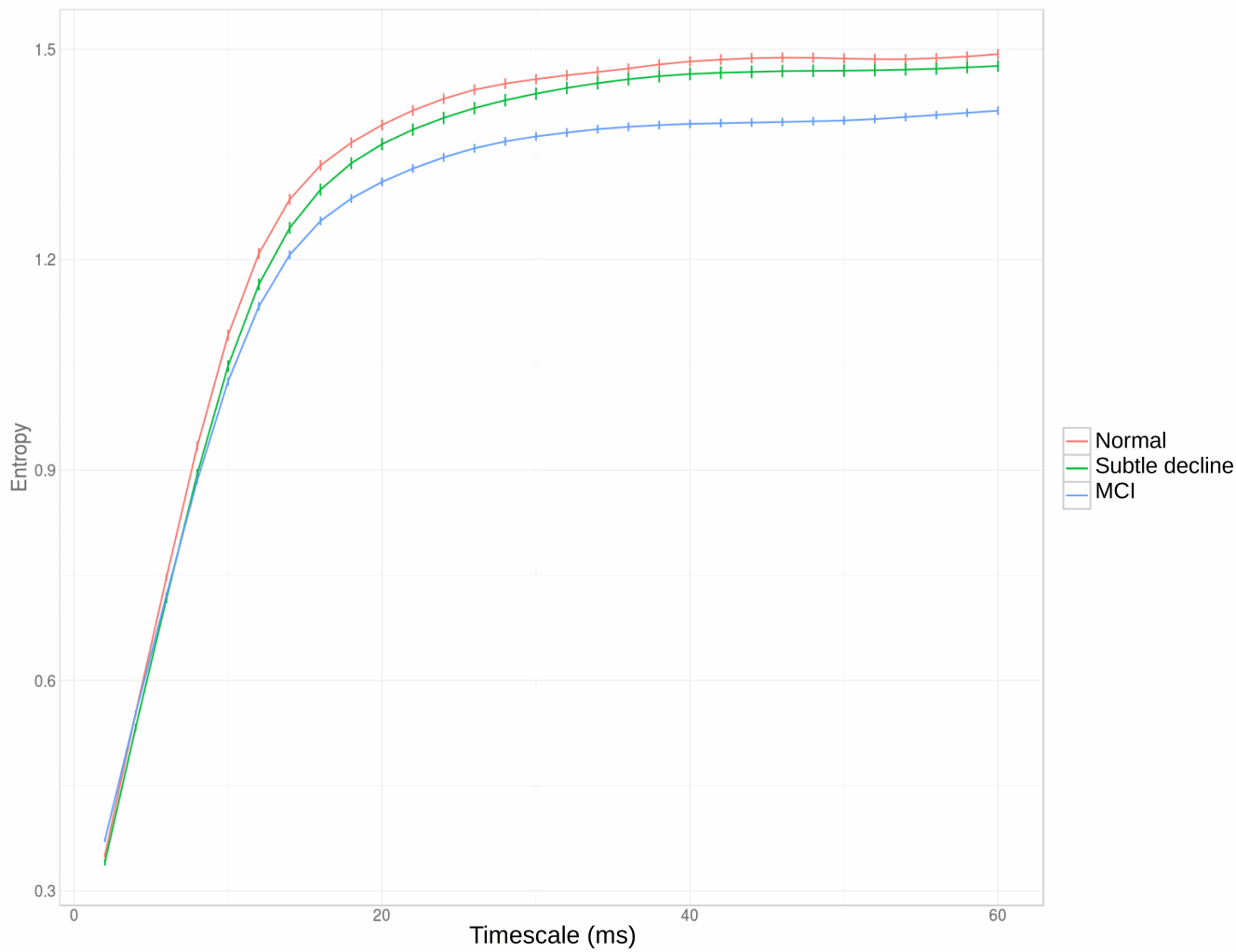

Figure 5. Average entropy (+/- SEM), plotted by timescale, as a function of IQ-adjusted cut-score dementia-risk status.

Study 1 Discussion

The present study sought to co-validate 2 cross-sectional proxies of within-person loss in neurocognitive adaptability. A major motive for this study was to improve early-dementia screening of apparently healthy (non-demented) older adults. Resting-state EEG and standardized neuropsychological performance data were gathered at the same 2-hour assessment occasion; this allowed for the investigation of performance-based diagnostic group differences in resting-state multiscale EEG entropy. As detailed above, the use of a premorbid IQ-based adjustment led to an increase in the number of healthy older adults in this sample that were classified as either “subtle decline” or MCI. Further, using the premorbid IQ-adjusted diagnostic grouping revealed potentially informative timescale-specific differences in resting-state multiscale EEG entropy profiles.

This sample of healthy older individuals was exceptional in terms of its high level of educational attainment and estimated premorbid function, as well as for the low and restricted number of impaired-range neuropsychological test scores. Differentiation of the group of study participants was greatly improved by considering current performance with reference to each individual's estimated premorbid function. This modification to the performance-based actuarial approach to designating dementia-risk status addressed an admitted limitation of the proposed diagnostic criteria. Namely, the criteria are insensitive to significant decline among individuals (like those in the present study) who may have originally performed at high- or above-average levels (Edmonds et al., 2015). This method of adjustment based on estimated “peak” function was adapted from one developed specifically for the assessment of high-functioning individuals who perform in the average range relative to same-aged peers despite significant decline relative to their own previous performance level (Rentz et al., 2006).

Although its practical utility has been illustrated herein as well as previously, the conceptual implications of diagnostic classification based on premorbid IQ-adjusted neuropsychological test scores

have yet to be elucidated. In effect the IQ-adjustment procedure is analogous to increasing the sensitivity or gain of an audio amplifier (the test), so that weaker input signals (relatively little between-person variance) can be differentiated by the listener in the output signal (presence of an impaired-range score). This IQ-adjustment also analogously amplifies the input noise: since those higher in premorbid function are penalized to a greater extent, there may be an increased risk of false-positive impaired-range scores. This would be of particular concern in the case of an individual whose premorbid IQ estimate greatly over-estimated his or her actual premorbid level, which would lead to inappropriate over-penalization. Premorbid estimates based on irregular word reading are thought to be most prone to bias at extreme ends of the distribution (Lezak et al., 2012).

Adjusting current performance for estimated premorbid function may thus be a matter of "tuning" the tests to the right sensitivity for each individual. In this respect it is important to highlight that individuals who score high on proxies of "premorbid" function (such as TOPF or years of education) are not necessarily "more intelligent" or “more healthy”. As always, there is a danger of identifying the construct with its indicator. Educational achievement is in large part a reflection of circumstances of birth and early life (White, 1982). TOPF-estimated premorbid function, based on the reading of English words with irregular spellings, is also correlated with educational attainment (Apolinario et al., 2013). Education and irregular word reading might both be considered measures of degree of acculturation, or “test-wiseness”; neuropsychological tasks are known to underestimate the performance of individuals who are lower in education as well as acculturation (Gasquoine, 1999; J. J. Manly, Byrd, Touradji, & Stern, 2004). Thus the IQ-adjustment procedure used herein may be more parsimoniously explained as a method for correcting a bias in the tests as opposed to equalizing groups of individuals that are fundamentally different in terms of some inherent biological trait (Gould, 1996). With that said, there is longitudinal evidence that post-secondary (university) education actually causes an increase in fluid intelligence even after accounting for adolescent cognition, gender, and parental

social class (Clouston et al., 2012). Whatever the causal mechanism, it is clear that higher education or premorbid IQ predict a reduced risk of cognitive decline and dementia (Amieva et al., 2014; Hall et al., 2007; Rentz et al., 2010; Valenzuela & Sachdev, 2006). Some have even found evidence that the dementia-protective benefits of education vary according to the "dose" (Brayne et al., 2010).

At first glance, resting EEG entropy appeared to be less reliable than typically considered adequate for clinical tools. However the estimate of its reliability is limited by the model used to approximate the dimensions of the entropy curve across timescales. Since timescales are nested in epochs, and in turn within persons, entropy estimates at individual timescales cannot be considered to be independent measurements. Multi-level linear models were thus used to accommodate this nested structure. These revealed that the within-person variance in entropy could be reduced substantially (by about 84%) by including fixed linear and quadratic effects of timescale as well as a random effect of linear timescale. The resultant model allowed for person-, epoch-, and (unexplained) timescale-level variation in entropy, accounting for roughly 25%, 37%, and 37%, respectively, of total entropy variance. Using a nonlinear (asymptotic) regression approach, within-person, across-timescale variation in entropy was approximated with fixed and random terms denoting intercept, asymptote and rate of entropy increase across timescale. Variance components from this model showed that about 45%, 53%, and 2% of EEG entropy variance occurred at the person-, epoch-, and timescale-level, respectively.

Diagnostic grouping based on performance during the 90-minute neuropsychological battery revealed differences in EEG entropy recorded during 4 minutes of rest with the eyes closed occurring immediately afterward. These findings suggest that resting EEG may be a useful neurocognitive health screening tool, especially since remote and under-served clientèle may be assessed with increasingly available mobile EEG technology (Bhat et al., 2015; Casson, Smith, Duncan, & Rodriguez-villegas, 2008; Mcdowell et al., 2013; Anderson S Oliveira, Schlink, Hairston, König, & Ferris, 2016; Anderson Souza Oliveira, Schlink, Hairston, König, & Ferris, 2016; Ries, Touryan, Vettel, Mcdowell, & Hairston,

2014).

As predicted, after accounting for differences in premorbid IQ, individuals classified as higher in dementia risk tended to show a generalized suppression of resting EEG entropy. This difference was most pronounced between the normal and MCI groups, where differences appeared to occur across almost all timescales between 2 and 60 ms. However the timescale-specificity of the entropy differences between the normal and intermediate risk (subtle cognitive decline) groups was opposite in direction to that hypothesized. Based on an "accelerated aging" model, it was predicted *a priori* that the earliest stages of pathological decline would involve greater than expected losses in entropy at coarser-grained timescales. In fact, relative to the normal group, the subtle decline group showed a relative preservation of coarse-grained entropy and selective loss in fine-grained entropy. This mirrors previous findings of lower fine-grained EEG entropy among people with Alzheimer type dementia relative to healthy older persons (Yang et al., 2013). Perhaps fine-grained entropy tracks the progression of disease from its very earliest stages to relatively advanced stages. In that case, it may be a very useful quantitative risk index. The finding also suggests that individuals at the earliest detectable stage of cognitive performance decline may have compromised local (within-neuronal population) processing. In healthy aging, a relative increase in local processing is hypothesized to compensate for losses in long-range (inter-population) processing (McIntosh et al., 2014).

Relative preservation of or gain in finer-grained entropy that occurs with healthy aging may thus reflect an adaptive shift in response to or anticipation of fundamental biological change with age (Baltes, 1997). The present results suggest that dementia-risk is elevated for some individuals because they never develop adequate compensatory mechanisms, not because of "accelerated aging". In a sense, the finding suggests that their brains do not show optimal adaptation to expected changes related to biological age. Future research will be needed to determine whether or not age- and dementia-resistant adaptive traits develop consequent to or in anticipation of declines in biological viability. In particular,

longitudinal studies should consider the possibility that a failure to show expected anticipatory gains in timescale-specific EEG entropy could identify those individuals who may be more susceptible to later declines in cognitive performance or functional status.

Both the multilevel linear and multilevel asymptotic regressions proved inadequate to capture the nuanced, timescale-specific nature of the dementia-risk effect that is plain upon examination of group means and confidence intervals (see Figure 5). Although the linear/quadratic model seemed a poor representation of the across-timescale entropy curve, increasing dementia-risk was detected in this model as a reduction in both the linear slope and in the typical concave curvature of entropy across timescale. On the other hand the asymptotic regression model seemed to capture the general features of the entropy curves quite well (*i.e.* very small proportion of residual relative to total variance), but lacked the flexibility to detect group differences at isolated timescales. Examination of plotted curves suggests that a refined mathematical model is required. Until that time, across-timescale differences in entropy might best be appreciated as qualitative differences in across-timescale curves between individuals or groups. Alternatively, they might be expressed as differences in entropy at a timescale of particular empirical or theoretical interest. The present results hint that fine-grained (12 to 20 ms) resting EEG entropy might reflect an adaptive shift characteristic of healthy aging. For this reason 12-20 ms EEG entropy might be useful for the discrimination of healthy older individuals from those with subtle decline or frank MCI. This is within the same timescale-band identified by others as showing across-group gains in healthy older relative to young and middle-aged adults (McIntosh et al., 2014), and across-group losses with progressing dementia (Mizuno et al., 2010). On the other hand, development from childhood through to adulthood is marked by progressive increases in entropy at this timescale (McIntosh, Kovacevic, & Itier, 2008).

Unlike some previous studies of EEG entropy, the current study relied on EEG signals defined by sensors and not intra-cranial sources. This study was focused on deriving a clinically useful metric

of EEG entropy, and thus used central sites to capture para-vertex EEG activity from scalp sites over both hemispheres as well as the midline. Follow-up analysis revealed a similar pattern of findings for regions defined by other multivariate vectors (*i.e.* parietal sites, midline sites). The present results suggest that multivariate multiscale entropy of resting EEG signals recorded with a relatively low-density montage can detect differences between older adults with differences in neuropsychological performance. Further research with data from a higher-density montage will be necessary to disentangle the many distributed, semi-independent cortical and subcortical sources of the resting-state EEG signal.

In summary, the current study demonstrated that timescale-specific differences in resting-state EEG entropy existed between groups of healthy older adults who differed in performance-based dementia-risk status. This basic finding lends further validity to the concept of subtle cognitive decline as a useful diagnostic entity. It also illuminates the comparably subtle character of neural changes potentially underlying very-early dementia. Finally, the present results suggest that older individuals who show more neuropsychological performance “decline” relative to their own estimated premorbid level (a performance indicator suggestive of lost cognitive adaptability) also show evidence of reduced neural adaptability. Future research is required to further elucidate the construct validity and clinical utility of EEG entropy at particular timescales.

Study 2: Performance-based measures of neurocognitive flexibility and plasticity

The initial study demonstrated the relationship between two measures of neurocognitive adaptability (decline in neuropsychological performance relative to estimated premorbid level, and a multiscale metric of resting-state EEG entropy). Participants completed both of these measures within the same 3-hour assessment occasion; as such, there was no opportunity to observe neurocognitive adaptations that required longer time intervals. For that reason, the following study employs *intensive cognitive assessment*: each participant also completed computerized cognitive assessments on 4 to 6 separate days within about a month. This closely-spaced "burst" of assessment was designed to directly capture neurocognitive adaptation in real-time, as across-occasion learning effects in response to a novel cognitive challenge.

Adaptability in response to dynamic and unpredictable environmental demands is a hallmark of brain and cognitive health that enables the ultimate survival of the individual. In healthy development and aging, ongoing adaptation of neural and cognitive processes allows individuals to first develop and then maintain functional independence, often well in to old age. While some neurocognitive changes are seen as normative aging, many individuals show additional losses in neurocognitive adaptability with age presumed to reflect pathology (Steinerman, Hall, Sliwinski, & Lipton, 2010). The earliest detectable harbingers of prospective pathological neurocognitive aging are subtle changes in neural and cognitive function that undermine adaptability (Edmonds et al., 2015). With continued decline the demands of the environment can outstrip the adaptive potential of the individual (Baltes et al., 1992; Charles & Carstensen, 2010; Lövdén et al., 2010; Raz, 2009). This person-environment mismatch impinges on functional independence and creates a greater need for family and professional in-home or institutional care.

Neurocognitive adaptability manifests within one individual at multiple timescales. The

timescales are hierarchically organized within a person, and span from the scale of subseconds to the scale of decades (Lövdén et al., 2010). At shorter timescales, rapid physical and chemical neural responses support *flexibility*; a capacity for short-term, in-the-moment adaptation to a relatively limited range of environmental or task conditions. Flexible adaptations are rapid, reversible responses to transient environmental changes. *Plasticity* is on the longer end of the timescale continuum. It denotes a capacity for adapting the range of possible in-the-moment responses to relatively enduring changes in environmental demand. Thus plastic neurocognitive adaptations are slower to evolve, and once established are more persistent. Plastic adaptations are underlain by neurocognitive processes (*e.g.* dendritic remodeling) distinct from those serving flexibility (*e.g.* transient disinhibition). The distinctness is also inherent in their respective cognitive or behavioural descriptors; flexibility may be referred to as "processing efficiency" whereas plasticity may be referred to as "alteration of representations" (Lövdén et al., 2010).

Despite its importance to healthy aging, the clinical assessment of neurocognitive adaptability tends to be limited in scope. This is due in part to the inconvenience of measuring neurocognitive adaptability at certain timescales. Neurocognitive flexibility (adaptability at shorter timescales) is often assessed within a single occasion. When clinicians observe an individual alternate between sets in a sequencing task, shift across categories in a sorting task, or learn across repeated trials of a list-learning task they are a real-time witness to a manifest behavioural result of neurocognitive adaptability (Lezak et al., 2012). Because, in contrast, neurocognitive plasticity evolves at the scale of days to weeks (rather than subseconds to minutes in the case of flexibility), behavioural manifestations correspondingly take multiple assessment occasions to capture.

Intensive cognitive assessment – repeated testing of a single individual at multiple occasions spanning a short period of time (Rast, MacDonald, & Hofer, 2012) – has the potential to help fill this niche in adaptability assessment. Intensive measurement can serve as a "direct-observation method" for

the assessment of neurocognitive adaptability at multiple timescales. That said, there are measures already in common use which could also contribute to the clinical characterization of adaptability. Unlike direct-observation methods, “proxy methods” assess neurocognitive adaptability indirectly. For example, clinical neuropsychologists might consider estimated premorbid function or self-report measures of certain personality dimensions (*e.g.* conscientiousness). These dimensions provide another perspective on neurocognitive adaptability. Next, we consider the theory and evidence for premorbid function and conscientiousness as individual differences that moderate the expression of other forms of neurocognitive adaptability (*e.g.* practice effects). Following that is a closer examination of intensive cognitive measurement: a direct-observation method of adaptability assessment.

Premorbid function as a cross-sectional indicator of neurocognitive adaptability

Premorbid function is routinely used in clinical practice as a standard against which to ascertain within-person decline relative to estimated peak functioning (*e.g.* in cases of suspected neurodegenerative disease, or following a discreet neural insult). Further, a higher level of premorbid function is itself associated with delayed onset of dementia. The concept of premorbid function is closely allied with that of “cognitive reserve” or “reserve capacity” (Stern, 2009), which is essentially a capacity for neurocognitive adaptability (Baltes et al., 1992; Lövdén et al., 2010). In fact, premorbid function and reserve are both most often quantified in proxy terms: as educational level or irregular word reading performance (Rentz et al., 2010). The difference between premorbid function and reserve lies principally in how they are conceived: while premorbid function is presumed to reflect some peak of function in the past, reserve is conceived of as malleable, to some extent, throughout the lifespan.

Questions of mechanism notwithstanding, markers of premorbid function or reserve (represented as years of education or as scores on standardized irregular word reading tasks) undoubtedly moderate the longitudinal trajectory of neurocognitive aging. Reserve buffers cognitive performance against the disruptive effects of neuropathology (Bennett et al., 2003; Rentz et al., 2010).

Higher reserve delays the onset of accelerated cognitive decline, but also predicts a more precipitous rate of terminal decline (Hall et al., 2007). Older adults with greater reserve appear to temporarily adapt to early age- or disease-related changes in brain and cognitive function before ultimately succumbing near the end of life (Bäckman & MacDonald, 2006). Those higher in reserve may also be more likely to endorse symptoms of depression and cognitive dysfunction at the onset of accelerated "terminal declines" (those accelerated periods of decline 3 to 5 years before dementia onset) (Amieva et al., 2014). Depression and subjective impairment may be psychological indicators of the point at which adaptive capacity is no longer sufficient to meet functional demands. Indeed, self-reported symptoms of cognitive decline among healthy older adults seem to have greater predictive value among individuals who are highly-educated (Jonker et al., 2000; van Oijen, de Jong, Hofman, Koudstaal, & Breteler, 2007).

Thus, considering a given individual's estimated reserve or premorbid function is useful for understanding their history and predicting their neurocognitive aging trajectory as it emerges through the interaction of normative and non-normative influences (Steinerman et al., 2010). Moreover, considering reserve can help to tailor psychoeducational interventions for older adults at risk for decline and their families. The present study will help to refine the construct validity of reserve by showing its relation to manifest behavioural evidence of adaptation.

Conscientiousness as a cross-sectional indicator of neurocognitive adaptability

Reserve thus seems to predict a delayed onset but an accelerated rate of terminal cognitive decline. The emergence of psychological symptoms at the onset of terminal decline suggests that those higher in reserve might also be more likely to use explicit meta-cognitive strategies to circumvent the constraints on neurocognitive adaptability imposed by age and/or disease processes (Stern, 2012). It so happens that the use of deliberate strategies to achieve functional goals is common among individuals high in conscientiousness, a dimension of personality. Conscientiousness might similarly confer

protection against the onset of cognitive decline. For example, in performing laboratory and clinical cognitive tasks, older adults have often been observed to demonstrate an apparent reticence to make mistakes. This sometimes results in a sacrifice, relative to younger adults, of speed in favour of more accurate performance (Ratcliff, 2006). “Conservative” approaches such as this often prove strategic in that they frequently result in a slower rate of skill acquisition but ultimately higher asymptotic level of performance (Yeo & Neal, 2004). Conservative, deliberate, and considered strategy use (*e.g.* elaboration, repetition, rehearsal, refinement) is not only more common in older than younger adults, it is also characteristic of individuals high in conscientiousness (Tett, 1998; Tett et al., 1999).

Conscientiousness denotes a “propensity to be self-controlled, responsible to others, hardworking, orderly, and rule abiding” (Roberts, Lejuez, Krueger, Richards, & Hill, 2014, p. 1). Conscientiousness has been associated with a delayed onset of cognitive decline, and with reductions in the rate of cognitive decline (Chapman, 2013; Wilson et al., 2015). Moreover, conscientiousness dampens the negative impact of both advanced age and neuropathology on cognitive function (Wilson et al., 2015; Wilson, Schneider, Arnold, Bienias, & Bennett, 2007). In short, conscientiousness may be a self-reported proxy for an older adult's capacity and/or motivation to adapt in the face of age- and disease-related changes to brain and cognition in order to meet functional needs.

Retest effects as a manifestation of neurocognitive adaptability

Performance improvement as a result of retest practice is considered a basic form of neurocognitive plasticity (Yang et al., 2006). The magnitude and impact of retest-related gains in performance (practice effects) among older adults are now increasingly appreciated in both clinical-neuropsychological (Attix et al., 2009; Calamia, Markon, & Tranel, 2012) and aging-research circles (Jones, 2015). In clinical application, serial neuropsychological assessment data are routinely adjusted for practice effects. Most often, this is achieved through empirically-derived reliable change indices (RCI) or standardized regression-based (SRB) corrections (Duff, 2012). These procedures correct for

expected retest-related improvements in order to increase sensitivity for detecting true serial declines that characterize the onset of dementia. Likewise, in cognitive aging research, failure to account for improvements due to prior test exposure is known to bias the empirical estimates of longitudinal cognitive decline that inform the development of clinical cutoff scores (Hoffman, Hofer, & Sliwinski, 2011). Despite the acknowledged existence of practice effects on clinical measures of cognitive function they have until recently seldom been conceptualized as indices of neurocognitive plasticity.

This oversight is in part an artifact of psychometric history. According to classical test theory, adjusting for "error" due to practice effects is a means to ascertain the "true" rate of decline or improvement in cognitive performance over time. However practice effects on cognitive performance measures need not be conceptualized as a source of nuisance variance in laboratory and clinical data. In fact, practice gains are a direct manifestation of neurocognitive adaptability (Baltes, Kühl, & Sowarka, 1992), a capacity typically preserved among healthy older adults (Yang et al., 2006). Relative preservation of practice effect size accordingly distinguishes healthy older adults from individuals with mild cognitive impairment (MCI; Darby, Maruff, Collie, & McStephen, 2002) and dementia (Fernández-Ballesteros et al., 2012).

Retest effects in intensive measurement designs. Many studies have quantified practice effects as a difference score across two repeated administrations of a standardized neuropsychological task separated by hours, days, months, or years. In contrast to these studies, so-called intensive measurement designs (Rast et al., 2012) have focused on patterns of shorter-term variation in cognitive performance across more than two (up to 100) testing occasions, with inter-occasion intervals of days to weeks (*e.g.* Beglinger et al., 2005; Shing, Schmiedek, Lövdén, & Lindenberger, 2012). Intensive computerized cognitive assessment with tasks that include tens or hundreds of repeated trials within each measurement occasion moreover span multiple hierarchical timescales. This type of approach has been used to illustrate older adult performance differences between persons, across testing occasions,

and across the trials within an occasion (Rast et al., 2012; Schmiedek, Lövdén, & Lindenberger, 2013).

A major benefit of intensive measurement (*i.e.* inclusion of more than two assessment occasions) is that individual-specific changes in performance as a result of practice can subsequently be modeled with a variety of hierarchical linear and nonlinear functions. The choice of model for a particular dataset is typically based on empirical comparisons of relative fit, with candidate models dictated by the number of data points available and the theorized patterns of change and fluctuation (Hoffman, 2015). Though not common in current neuropsychological practice, intensive computerized cognitive assessment has potential to complement existing approaches to assessment and treatment-monitoring (Gates & Kochan, 2015).

Some intensive measurement studies have examined patterns and sources of individual difference in retest-related change in older adult cognitive performance at the scale of days to weeks. Yang et al. (2009) found that older adults improved across 8 sessions of retest on measures of perceptual speed, inductive reasoning, and visual attention. This group also reported that retest gains were maintained – even among the "oldest old" (80 to 90 year-olds) – at about 50% of their original level after an 8-month delay (Yang & Krampe, 2009). This speaks to the persistence of retest-induced plastic change in older adult cognitive function. Along the same lines, Kurtz et al. (2013) modeled within-person performance changes using a hyperbolic model. They found that baseline performance on standardized clinical-neuropsychological measures of processing speed and working memory predicted (1) higher initial levels of performance, (2) increased rate of learning, and (3) higher asymptotic performance across 7 occasions of a computerized memory task. This latter study illustrates the potential connection between neurocognitive adaptability at various timescales, in that baseline flexibility (reflected by processing speed and working memory measures) predicted subsequent plasticity-related improvement across several days of practice.

Computerized assessment of neurocognitive adaptability at multiple timescales

Flexible (transient) and plastic (enduring) adaptation to a novel cognitive task unfolds simultaneously at trial-to-trial and across-session timescales, respectively (Newell, Liu, & Mayer-Kress, 2001). Flexibility and plasticity are driven by distinct neural mechanisms operating at hierarchical timescales. As such, features of the within-occasion performance profile can be observed to change across occasions, as illustrated in Figure 6. Indeed, for some paradigms, parameters derived from the within-occasion trajectory may anticipate across-occasion performance trends. For example, at least one study has found that initial, within-session performance variability predicted later, across-occasion practice benefit among older adults (Strobach, Gerstorf, Maquestiaux, & Schubert, 2015). Measurement and analysis methodologies that accommodate within-session as well as across-session performance change and fluctuation (Boker, Molenaar, & Nesselroade, 2009; Newell et al., 2001; Newell, Mayer-Kress, & Liu, 2009; Rast & Zimprich, 2011) may therefore aid in depicting individual neurocognitive adaptability at multiple hierarchical timescales during an ongoing cognitive challenge.

As basic psychometric issues related to computerized testing are addressed, remote computerized cognitive testing via the internet and mobile devices will become commonplace (Gates & Kochan, 2015). As a result, clinicians can expect to gain valuable additional insight into older adult neurocognitive adaptability. Such methods will expose the essence of neurocognitive adaptability: fluctuation and change in parallel with shifts in day-to-day ecological context (Hertzog et al., 2009; Oishi & Graham, 2010).

The current study focused on one particular computerized set-shifting task (Rogers & Monsell, 1995). Set-shifting underlies efficient transition between multiple tasks, operations, or mental sets (Miyake et al., 2000). Set-shifting is often characterized as an indicator of cognitive flexibility. The shift between response sets or rules is thought to be a dissociable neurocognitive process that is instrumental for learning and adapting to changing demands (Cunillera et al., 2012). Laboratory

measurement has revealed that shifts from one response rule to another are associated with a reliable increase in response latency (RT), known as the “switch cost”. Switch cost is independent of global slowing (Verhaeghen & Cerella, 2002) and said to be robust to extensive practice, even when the occurrence of the switches is unsurprising (Rogers & Monsell, 1995). In the everyday life of an older adult, difficulty with set-shifting may be experienced as problems “multi-tasking” (transitioning back and forth between multiple distinct tasks, *e.g.* cooking while also engaging in conversation). Set-shifting paradigms have a long history in the assessment of cognitive flexibility; well-known clinical tasks that use set-shifting to assess flexibility include the Wisconsin Card Sorting Test and Trails B (Lezak et al., 2012).

Objectives and predictions

Intensive computerized cognitive assessment provides a unique opportunity to directly quantify within- and across-occasion performance features that reflect multiple distinct mechanisms of neurocognitive adaptability. The switch cost and the within-occasion performance improvement provide a window on neurocognitive flexibility (adaptability at the scale of trials/seconds). In contrast, across-occasion improvement in performance tracks neurocognitive plasticity (adaptability at the scale of days/weeks).

This, the second of three studies in this dissertation, examines individual differences in switch cost, within-occasion performance improvement, and across-occasion performance improvement as a function of two well-validated covariates (reserve and conscientiousness). A multilevel modeling framework is used to account for the hierarchically nested nature of the data (*i.e.* trials nested within occasions, nested in turn within individuals) in examining the effects of interest.

It was hypothesized that those individuals with greater reserve and higher self-rated conscientiousness would also show within- and across-occasion evidence of greater retest-related

performance improvement (practice effects), including reduced switch cost. In particular, those higher in reserve and conscientiousness were predicted to show:

(1) greater within-occasion increase in response speed (especially on switch relative to stay trials); and

(2) steeper linear increase in response speed across the 4 to 6 occasions of testing (especially on switch relative to stay trials).

Findings are discussed in terms of the utility and feasibility of self-report and intensive computerized testing to accentuate existing clinical neuropsychological practice and support population-scale screening of older adult neurocognitive health.

Study 2 Methods

Participants

See Study 1 Methods: Participants. Due to a change in availability, one participant from study 1 did not complete computerized testing after participating in baseline testing. This left data from 43 participants for the analyses in this study.

Measures

The 43 study participants underwent a telephone screen, completed self-report scales, underwent neuropsychological testing (Table 4), and attended multiple “measurement burst” appointments comprised of self-report and computer tasks. Resting electroencephalographic (EEG) recordings were also obtained from each participant, immediately following the neuropsychological assessment. EEG and neuropsychological measures were the focus of the first chapter of this dissertation and are not considered in the present study.

Conscientiousness. The Big Five Inventory (BFI; John, Donahue, and Kentle, 1991) is a validated self-report instrument for the assessment of the Big Five personality dimensions. The BFI has

been shown to have adequate test-retest reliability (John and Srivastava, 1999). For the purposes of this study the total raw conscientiousness score from the BFI was used.

Reserve. Age-corrected standard scores (M = 100, SD = 15) from the WAIS-IV Test of Premorbid Function (TOPF) were used as the measure of reserve for this study. This measure is based on reading a list of words with irregular pronunciation and is routinely used to estimate premorbid IQ in clinical neuropsychological assessment.

Repeated computerized testing. Each of the computer assessment appointments lasted about 40 minutes, and began with completion of a brief self-report form (not considered here). Following self-report, participants completed a battery of 3 computerized tasks. The battery included go/no-go (inhibitory control), letter-number (switching), and *n*-back (working memory) tasks, presented in this sequence, at each visit. All participants attended between 4 and 6 visits.

Only performance on the switch task is considered in this study. The switch task was selected because it required a response to every single trial (unlike *n*-back or go/no-go), providing a continued demand on the participant to respond and also a continual, trial-by-trial behavioural record of their neurocognitive performance at the timescale of seconds (*i.e.* single trial-level).

The switch task, a variant of that described in Rogers & Monsell (1995), required participants to make stimulus-categorization decisions based on 2 distinct response rules alternated in a predictable succession (similar, in this respect, to the commonly used neuropsychological test, Trails B). In brief, the task involved the display of a string of letter-number pairs (about once per second) on a computer screen. The stimuli remained on the screen until a response was made. Participants responded with a left/right index finger keyboard press based on a response rule that varied according to the location of the stimulus on the screen. Stimuli appearing in the *top* half of the screen denoted a *letter* response rule (left/right = vowel/consonant) and those appearing in the *bottom* half a *number* rule (left/right = odd/even). Number-letter pairs appeared in a *predictable sequence* (top-left, top-right, bottom-left,

bottom-right, top-left....) such that the response rule (based on the stimulus being in the top or bottom half of the screen) switched every second trial. Thus participants responded to a string of alternating "stay" (no rule change relative to previous trial) and "switch" (rule change relative to previous trial) trials, with 96 total trials. Instructions emphasized accuracy as well as speed. Response latency and accuracy on the individual trials of the switch task served as cognitive performance indices.

Based on distributions, responses with latencies greater than 4 seconds and less than 0.4 seconds were excluded as invalid (suggestive of disengagement and guessing, respectively). In order to better approximate a normal distribution, response speed (RS), the inverse of response time (*i.e.* 1/RT), was used as the main model outcome. Mean response speed and response accuracy (proportion of correct responses) were computed separately for the first 20 and the last 76 trials at each occasion. This approach allowed for the capture of changes in performance occurring within-session (*i.e.* due to learning), rather than contaminating the occasion-mean with response variance due to early-trial learning. Often, performances on early trials are called "practice" or "warm-up" trials and are excluded from analyses (e.g. McEvoy, Smith, & Gevins, 2000; Vallesi, 2011).

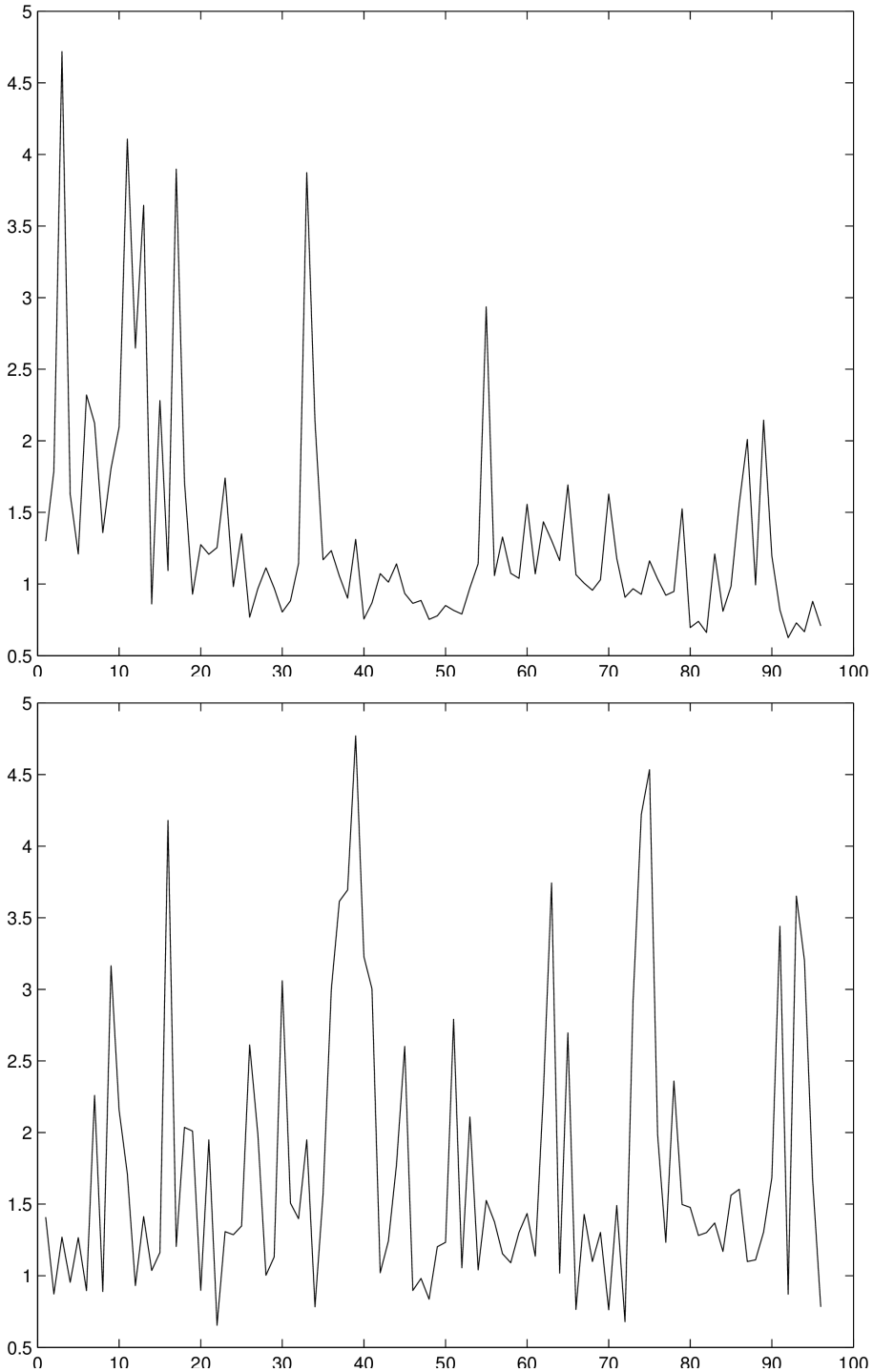

Figure 6. Example plots depicting response time (RT, in seconds, *y*-axis; higher value corresponds to slower response) across trial number (*x*-axis) on the switching task. The top panel shows data from a person's first assessment occasion, and the bottom panel shows data from this same person's final (6^{th}) assessment, 3 weeks later. Note the asymptotic performance speeding trend in the early trials of the first occasion, perhaps reflecting initial novelty adaptation, absent at the final assessment. Pronounced trial-to-trial variability is present across trials within both occasions, reflecting the rule-switches that occur on every second trial of the task, and illustrating the robustness of the switch cost effect to practice.

Procedures

See Study 1 Methods: Procedures.

Design and Planned Analyses

The present study design, involving variables in 3 hierarchically nested levels (condition, occasion, and person; Table 8), was accommodated with multilevel modeling. Response speed (RS) served as the outcome measure. RS varied within occasions as a function of condition (stay or switch): the condition factor was nested within occasions. Occasion was coded using a balanced design, in terms of the numerical sequence of occurrence. Participant computer testing sessions were scheduled according to participant preferences and availability. Thus the intervals (in days) between subsequent testing sessions were not equivalent between or within-persons. An average re-test interval (in days) was therefore computed for each participant (person-mean retest interval) for use as a model covariate. Finally, testing occasions were, in turn, nested within persons; person-level (cross-section) indicators are at the peak of the hierarchy and construed as time-invariant within the multilevel framework of this study.

Initial analyses required the development of baseline models that were conditional on only time (occasion) and task condition in order to describe the patterns of change in RS using fixed and random effects of time. Determination of the best baseline model of change was based on model deviance difference tests (likelihood ratio test, or -2**Δ**LL). The statistical significance of fixed effects was based on a Wald test of $p < 0.05$. Both of these practices are in accordance with the method of model development outlined by Hoffman (2015).

Once the best-fitting baseline models were established, additional parameters were added to the various levels of the model to represent main and interaction effects of the study predictors (see Table 8). Namely, person-level effects of reserve and conscientiousness were used to predict changes in response speed and switch cost within and across occasions. If individual differences in reserve and

conscientiousness reflect variation in neurocognitive adaptability, then across occasions higher scores on these measures should have a significant promotional effect on overall response speed and on the attenuation of switch cost. Reserve and conscientiousness should also predict more within-session improvement in performance. Beyond mere speed, it was important that models accommodate between- and within-person differences in response accuracy. As such, the proportion of correct responses per occasion/condition was itself initially modeled as a univariate outcome to determine the best means of representing response accuracy in the models of mean RS and within-occasion change in RS.

All data manipulation and analysis was performed in *R* (R Core Team, 2016). Multilevel linear models were estimated using the *lme4* package (Bates, Maechler, Bolker, & Walker, 2015).

Table 8. Study variables and their associated levels in the analysis model.

Level of analysis	**Metric**	**Variable(s) in analysis**
Person (level 3)	WAIS-IV TOPF standard score	Reserve
	Raw BFI Conscientiousness score	Conscientiousness
Occasion (level 2)	Time	Occasion number (first occasion = 0)
Condition (level 1)	Switch (letter-number) task	Trial condition (stay =0, switch = 1)
		Response accuracy
Outcome	Switch (letter-number) task	Occasion-mean response speed (RS)
		Change in RS from early to late trials

Study 2 Results

Intra-class correlation and the effect of task condition

First, in order to estimate intraclass correlations (ICC; proportion of between-person relative to total variance), univariate empty means, random intercept models were used to estimate response accuracy and each of the two RS outcomes. There were data from 222 individual testing occasions (and

scores from 2 task conditions, stay and switch, within each occasion) and 43 unique participants for these analyses. Each participant completed between 4 and 6 occasions of testing (M = 5.16, SD = 1.04). The average time to complete these assessments, scheduled at each participant's convenience, was about 3 weeks from baseline to final assessment (M = 22.53 days, SD = 10.31).

Response accuracy. Task instructions emphasized accuracy as well as speed, and this was reflected in the grand average occasion-wise percentage of accurate responses. Across all 222 testing occasions response accuracy approached ceiling (100%) for both stay (M = 94.9, SD = 12.6, observed range = 29.0 to 100%) and switch trials (M = 93.2, SD = 12.5, observed range = 26.3 to 100%). Accuracy scores from both conditions had pronounced negative skew despite the wide range of observed occasion-wise response accuracies, suggesting possible low-accuracy outliers. However, removal of potential outlier accuracy scores had no bearing on the results. This is likely in part because of the multiple occasions per person, the adjustment for person-mean accuracy, and the low occurrence of exceptionally low accuracy scores within any one individual.

The univariate empty means, random intercept model revealed an ICC of 0.19, reflecting that about 19% of the variance in response accuracy was attributable to differences between persons. The majority of the variance in accuracy was at the occasion-to-occasion level (level 2; about 75%), with relatively little variance (about 5%) at level-1 (residual level). Adding a fixed effect for task condition (stay/switch) in the model reduced the residual (level-1) variance by about 17%; this value represents the *pseudo-*R^2, a multilevel regression effect size estimate, for the switch cost effect on accuracy. This model indicated a grand average (across all individuals and occasions) response accuracy of 94.7% for stay trials, with a statistically significant reduction in accuracy of 1.7 units, to 93.0%, for switch trials.

Occasion-mean RS and within-occasion change in RS. Next, univariate empty means, random intercept models were used to estimate the RS outcomes: occasion-mean RS (M = 0.98, SD = 0.29, observed range = 0.34 to 1.82 s^{-1}, with higher value meaning faster response), and within-

occasion ("late-minus-early") change in RS (M = 0.10, SD = 0.15, observed range = -0.28 to 0.64 s^{-1}, with higher positive score meaning more speeding up in latter 80% of trials compared to initial 20% of trials). This partitioning of variance yielded an ICC of 0.29 for occasion-mean RS and 0.39 for within-occasion change in RS. This suggests that a considerable portion of the variance in both outcomes (71% and 61%, respectively) was at the within-person/-occasion level. Including a fixed effect for task condition (stay or switch) at the within-occasion level (level 1) further reduced the unexplained (residual) outcome variance by 76% and 3%, respectively. This model estimated a grand-average occasion-mean RS of 1.14 s^{-1} (RT ~ 877 ms) for stay trials, and an expected slowing to 0.79 s^{-1} (RT ~ 1266 ms) for switch trials. The average within-occasion (early-to-late trial) increase in RS was also greater for stay trials (0.12 s^{-1}) relative to switch trials (0.09 s^{-1}).

Raw data plots for accuracy, occasion-mean RS, and within-occasion RS change are plotted across occasion and by condition in Figures 7, 8, and 9, respectively.

Longitudinal change in performance across occasion

Next, a parameter for the fixed linear time slope was added to the accuracy, occasion-mean RS, and within-occasion RS change models. Each person's first computer testing occasion served as their baseline (occasion = 0), and successive occasions were coded in sequence as increasing integers.

Response accuracy. A model of linear change including only task condition, testing occasion, and their interaction as predictors showed that average response accuracy at baseline (first testing occasion) was 92.5% for stay trials and 91.2% for switch trials. There was a small but statistically significant increase of 1.0 percentage-accuracy units per occasion. This rate of improvement did not differ across task conditions (*i.e.* the occasion by condition interaction effect on accuracy was not statistically significant). Inclusion of a random linear effect of occasion and a term for its covariance with the random intercept significantly improved model fit ($-2\Delta LL$ (~2) = 23.23, $p < 0.001$, with smaller AIC and BIC). This suggests that there was significant person-level variation in the slope of

across-occasion changes in response accuracy. Including this random effect also revealed that the vast majority of the variance in response accuracy was due to differences between persons (55%) and across occasions (37%).

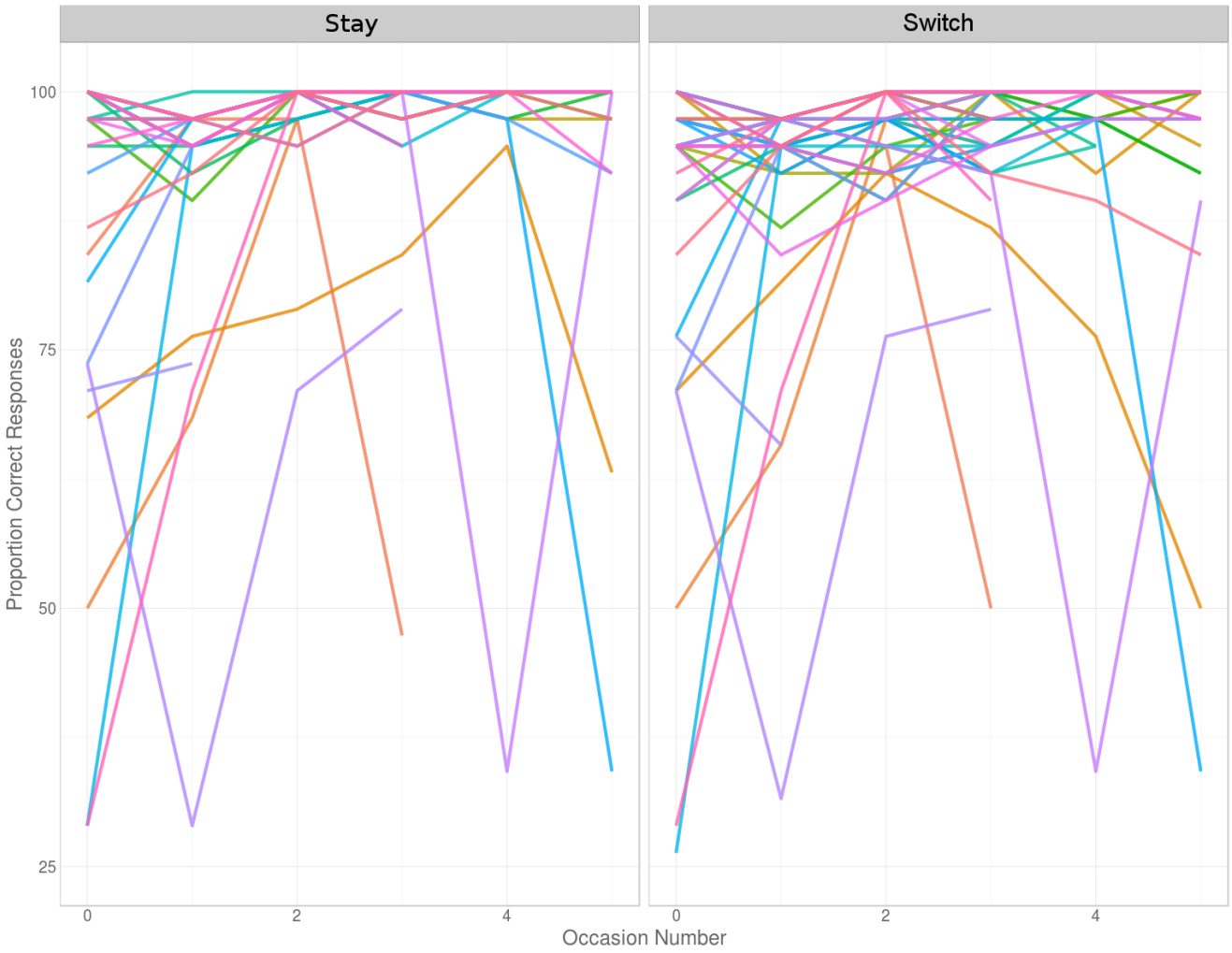

Figure 7. Raw accuracy scores (proportion correct responses) across occasion for stay trials (left panel, 0) and switch trials (right panel, 1); each participant's data are represented by a separate line.

Figure 8a. Raw occasion-mean response speeds across occasion for stay trials (left panel, 0) and switch trials (right panel, 1); each participant's data are represented by a separate line.

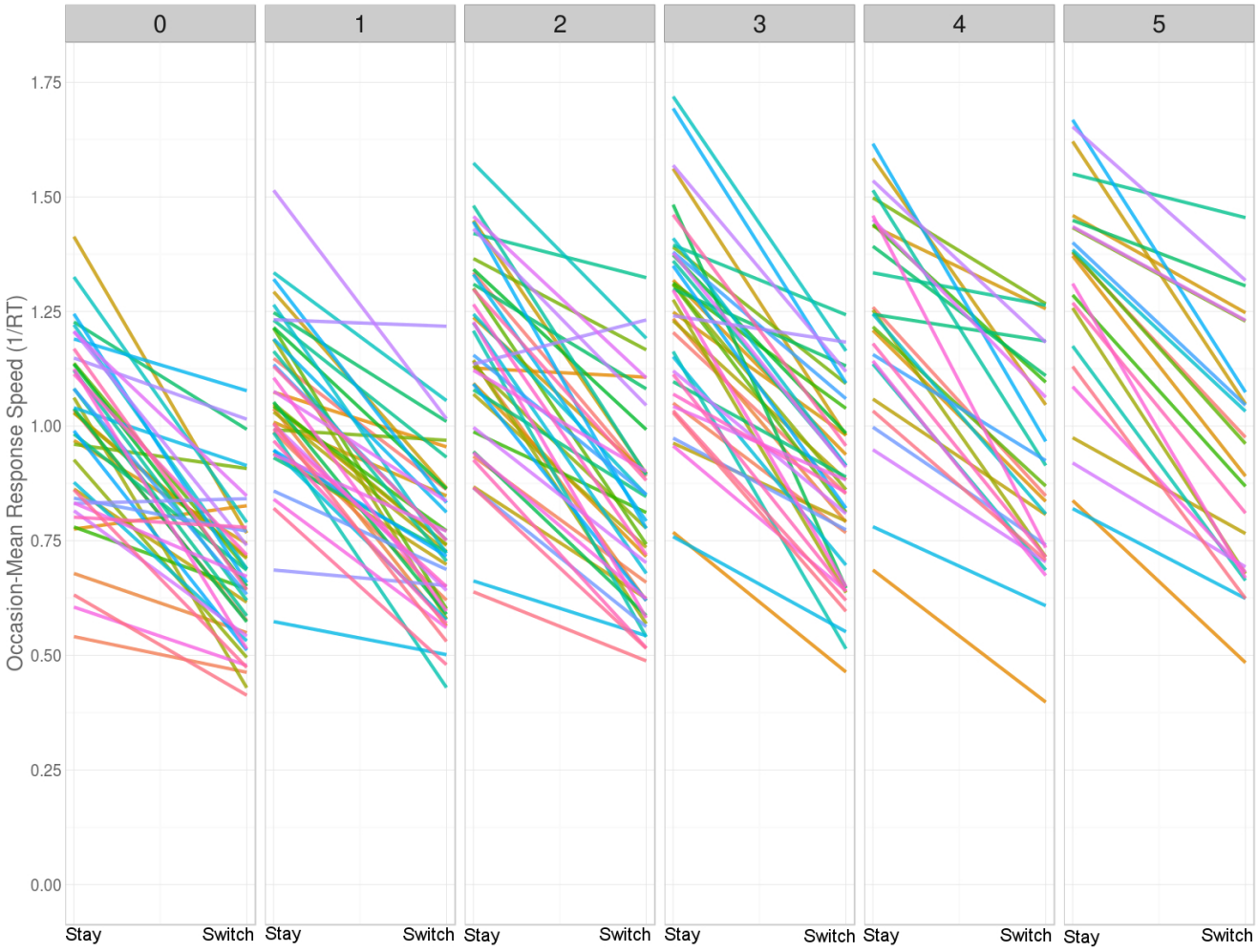

Figure 8b. The same data as in 8a but with task condition (stay or switch) on the *x*-axis and occasions across panels, from left (baseline = 0) to right. Note the rightward negative slope of the lines, highlighting individual differences in switch cost at each occasion.

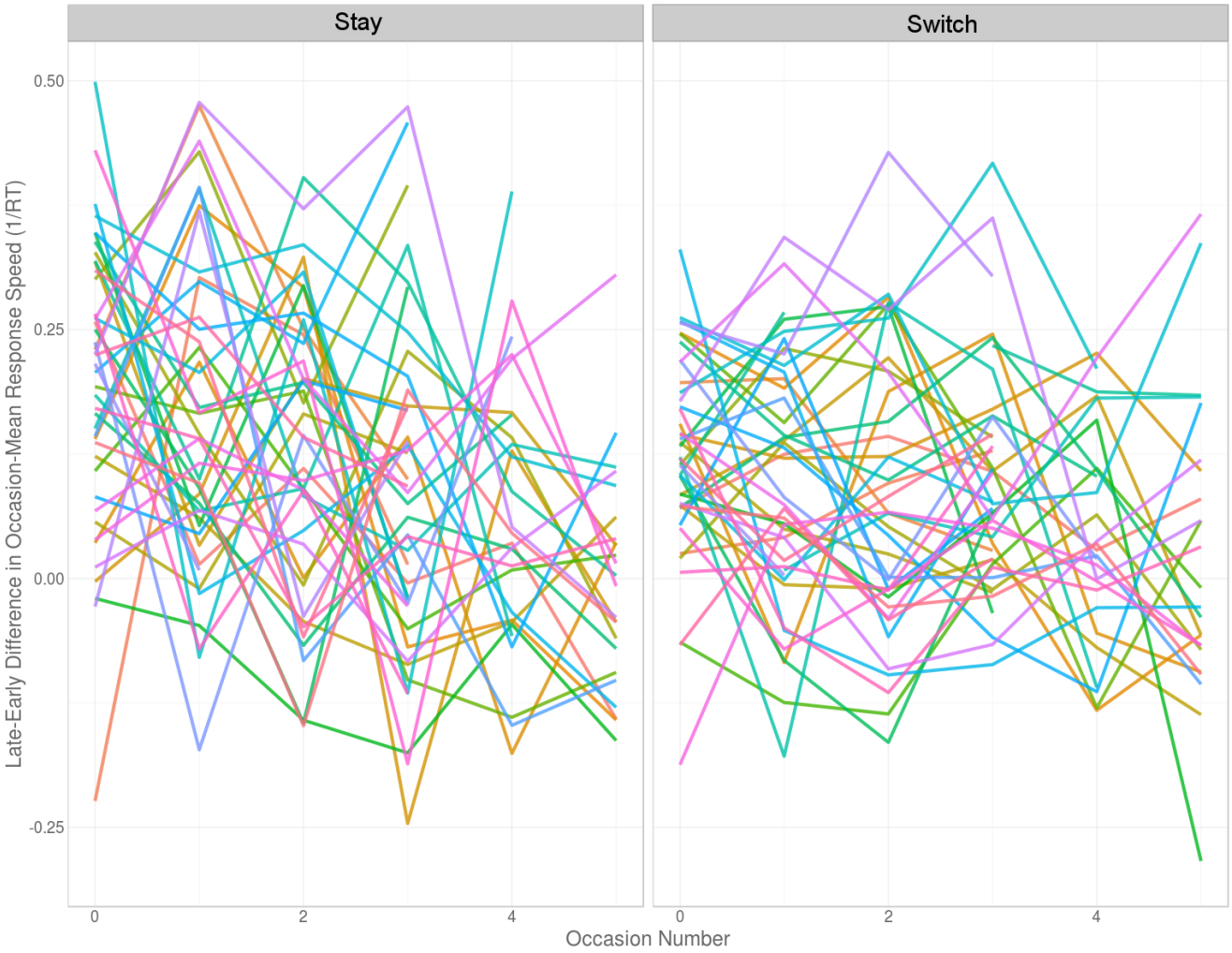

Figure 9a. Raw within-occasion response speeding (difference of latter 80% minus initial 20% of trials at each occasion) across occasions for stay trials (left panel, 0) and switch trials (right panel, 1); each participant's data are represented by a separate line.

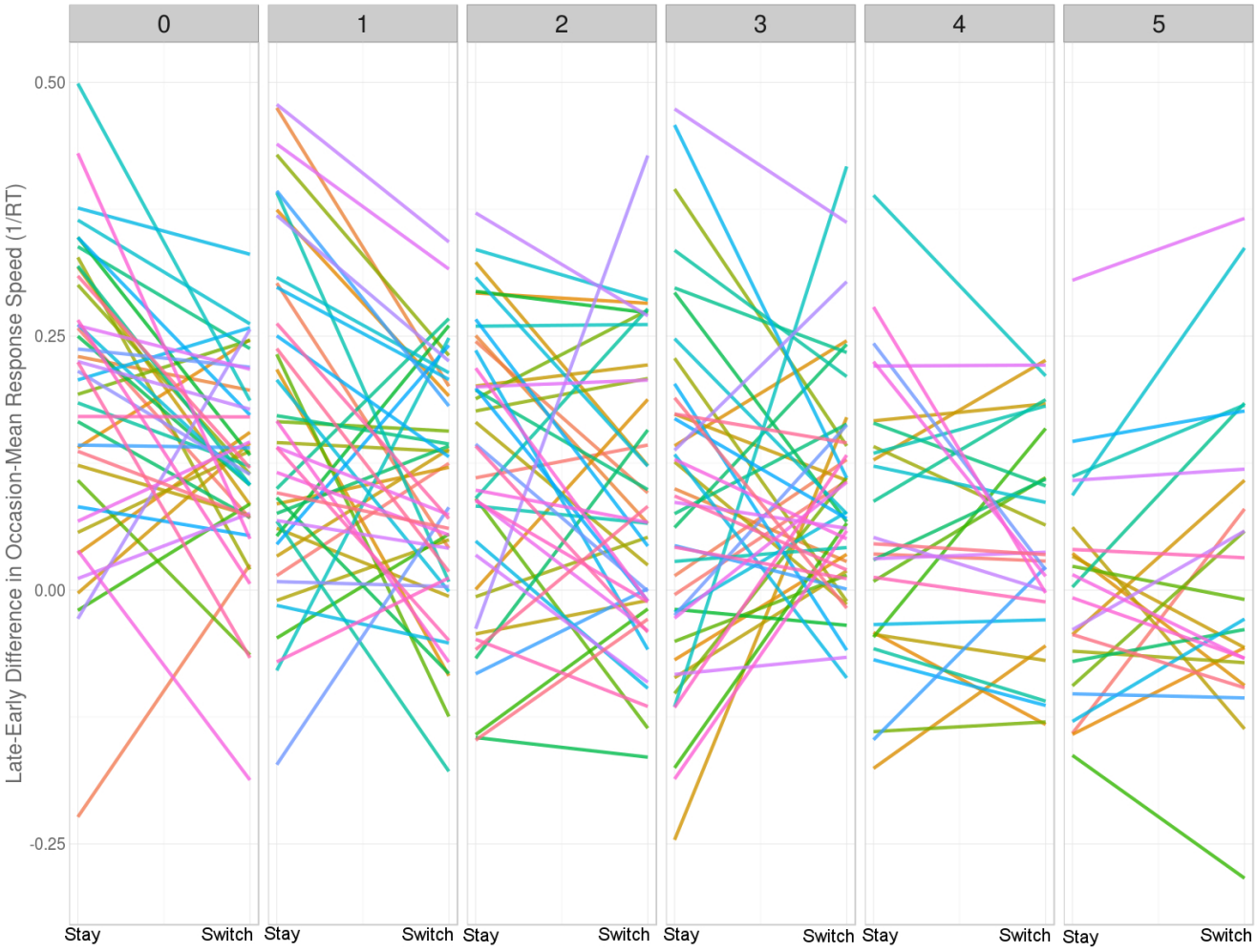

Figure 9b. The same data as in 9a but with task condition on the *x*-axis and occasions across panels, from left (baseline = 0) to right. Note the pronounced individual differences in slope magnitude and direction, indicative of switch cost effects on within-occasion response speeding.

In light of these findings, response accuracy was represented as a predictor in the RS models below at both the person and occasion levels (level 3 and level 2) using two related variables: (1) within-person, across-occasion mean (person-mean) response accuracy (expressed as a percentage), and (2) occasion-level deviations from the person-mean (person-centred accuracy). Terms were included to represent the main effect of each accuracy variable, as well as their two- and three-way interactions with occasion and condition, on RS outcomes.

Occasion-mean RS. At baseline, RS for stay trials was 1.00 s^{-1}, and slowed by 0.32 s^{-1} on switch trials. There was a statistically significant estimated linear increase in mean RS of 0.07 s^{-1} per occasion. The interaction effect of condition and occasion on mean RS was of marginal significance, suggesting that the speeding up across occasions may have been slightly dampened for switch relative to stay trials. Including a random linear effect of time and a term for its covariance with the random intercept significantly improved model fit (-2ΔLL (~2) = 33.69, $p < 0.001$, with smaller AIC and BIC). This suggests the presence of significant individual differences in the linear rate of change in occasion-mean RS across testing occasions.

Within-occasion RS change. There was also a statistically significant estimated linear effect of occasion on within-occasion change in RS. Thus, at baseline, the average early-to-late RS difference score was 0.20 s^{-1} for stay trials; there was significantly less within-occasion speeding for switch trials (0.13 s^{-1}). For stay trials, the within-occasion RS change decreased by 0.04 s^{-1} per occasion. The interaction between the fixed linear time parameter (occasion) and task condition was also statistically significant. This latter effect revealed that the relative dampening of within-occasion RS speeding due to the switch condition was lessened at each successive testing occasion. Thus within-occasion RS speeding decreased for both stay and switch trials across occasion. However reductions in RS speeding were relatively more pronounced on switch trials. Including a random linear effect of time and a term for its covariance with the random intercept did not significantly improve the fit of this model (-2ΔLL

(~2) = 0.01, $p > 0.99$, with larger AIC and BIC).

Table 9. Summary of multilevel model fixed effect coefficients for baseline models of RS.

	Response Accuracy			Occasion-Mean RS			Within-Occasion RS Change		
Fixed Effect	*b*	SE	*P*	*b*	SE	*P*	*b*	SE	*P*
Intercept									
Intercept	**92.45**	**1.50**	**<0.01**	**1.00**	**0.02**	**<0.01**	**0.20**	**0.02**	**<0.01**
Condition	**-1.24**	**0.42**	**<0.01**	**-0.32**	**0.02**	**<0.01**	**-0.07**	**0.02**	**<0.01**
Occasion									
Intercept	**1.04**	**0.47**	**0.03**	**0.07**	**0.01**	**<0.01**	**-0.04**	**0.01**	**<0.01**
Condition	-0.20	0.16	0.20	-0.01	0.01	0.06	**0.02**	**0.01**	**<0.01**
Model Deviance	2953.5			-459.2			-563.7		

b = unstandardized regression weight (slope)
SE = standard error
RS = Response speed

Effects of response accuracy on RS outcomes

The empirical model development process described above led to a baseline model (equation 1) that was used in the ascertainment of effects of (person- and occasion-level) response accuracy on the two response speed (RS) outcomes. Note that the random effect of occasion (U_{01}) was not estimated for models of within-occasion RS change as it did not significantly improve model fit.

$$\text{Level 1: } \text{RS} = b_{0j} + b_{1j}(\text{Switch}) + e_j \quad (1)$$

$$\text{Level 2: } b_{0j} = \beta_{00} + \beta_{01}(\text{Occasion}) + r_{0j}$$

$$b_{1j} = \beta_{10} + \beta_{11}(\text{Occasion})$$

$$\text{Level 3: } \beta_{00} = \gamma_{00} + U_{00}$$

$$\beta_{01} = \gamma_{10} + U_{01}$$

$$\beta_{10} = \gamma_{20}$$

$$\beta_{11} = \gamma_{30}$$

Including terms to represent accuracy at both the between-person (PM-Acc; person-mean accuracy) as well as the within-person (PC-Acc; person-centred accuracy) level showed that both had statistically significant effects on occasion-mean RS but not on the magnitude of within-occasion RS change. The direction of the effects was in the expected direction for speed-accuracy tradeoff: as response accuracy increased (between or within-persons) response speed decreased. In fact, both PM-Acc and PC-Acc interacted with task condition, indicating that the increase in accuracy associated with response slowing was disproportionately magnified in the switch relative to stay condition (Table 10).

Each participant's average occasion-to-occasion retest interval, measured in days (PM-Interval; M = 5.93, SD = 4.56, observed range of retest intervals = 1 to 31 days), was also added to the model at this stage as a grand-mean centred covariate. This was done in order to adjust estimates (especially learning slopes) for possible confound as a result of between-person differences in retest interval. This showed that the rate of across-occasion RS increase was dampened among individuals with longer average inter-occasion (retest) intervals, and had a particular deleterious impact on performance under the switch condition. Average retest interval had no discernible effect on within-occasion changes in RS. Given these empirical findings and the theoretical relevance of test-retest interval to learning, intercepts and occasion slopes of the final models for both occasion-mean RS and within-occasion RS change were adjusted for between-person differences in average retest interval. Models including both accuracy and retest interval parameters are represented in equation 2:

$$\text{Level 1: RS} = b_{0j} + b_{1j}(\text{Switch}) + e_j \qquad (2)$$

$$\text{Level 2: } b_{0j} = \beta_{00} + \beta_{01}(\text{Occasion}) + \beta_{02}(\text{PC-Acc}) + \beta_{03}(\text{Occasion*PC-Acc}) + r_{0j}$$

$$b_{1j} = \beta_{10} + \beta_{11}(\text{Occasion}) + \beta_{12}(\text{PC-Acc}) + \beta_{13}(\text{Occasion*PC-Acc})$$

$$\text{Level 3: } \beta_{00} = \gamma_{00} + \gamma_{01}(\text{PM-Acc}) + \gamma_{02}(\text{PM-Interval}) + U_{00}$$

$$\beta_{01} = \gamma_{10} + \gamma_{11}(\text{PM-Acc}) + \gamma_{12}(\text{PM-Interval}) + U_{01}$$

$$\beta_{02} = \gamma_{20}$$

$\beta_{03} = \gamma_{30}$

$\beta_{10} = \gamma_{40} + \gamma_{41}$(PM-Acc) + γ_{42}(PM-Interval)

$\beta_{11} = \gamma_{50} + \gamma_{51}$(PM-Interval)

$\beta_{12} = \gamma_{60}$

$\beta_{13} = \gamma_{70}$

Effects of person-level predictors: conscientiousness and reserve

The following random linear time model (equation 3) was thus used as the basis for a predictive analysis of change in occasion-mean RS and within-occasion RS change outcomes as a function of the previously-discussed person-level covariates of interest (conscientiousness and TOPF-estimated reserve). Grand-mean-centered BFI conscientiousness and median-split TOPF-estimated reserve scores were thus entered as model covariates allowed to interact with occasion, task condition, and accuracy (*i.e.* main effects, and 2-, 3-, and 4-way interaction effects for each person-level covariate were estimated).

Level 1: RS = $b_{0j} + b_{1j}$(Switch) + e_j (3)

Level 2: $b_{0j} = \beta_{00} + \beta_{01}$(Occasion) + β_{02}(PC-Acc) + β_{03}(Occasion*PC-Acc) + r_{0j}

$b_{1j} = \beta_{10} + \beta_{11}$(Occasion) + β_{12}(PC-Acc) + β_{13}(Occasion*PC-Acc)

Level 3: $\beta_{00} = \gamma_{00} + \gamma_{01}$(PM-Acc) + γ_{02}(PM-Interval) + γ_{03}(Consci) + γ_{04}(Reserve) + γ_{05}(PM-Acc*Consci) + γ_{06}(PM-Acc*Reserve) + U_{00}

$\beta_{01} = \gamma_{10} + \gamma_{11}$(PM-Acc) + γ_{12}(PM-Interval) + γ_{13}(Consci) + γ_{14}(Reserve) + γ_{15}(PM-Acc*Consci) + γ_{16}(PM-Acc*Reserve) + U_{01}

$\beta_{02} = \gamma_{20} + \gamma_{21}$(Consci) + γ_{22}(Reserve)

$\beta_{03} = \gamma_{30} + \gamma_{31}$(Consci) + γ_{32}(Reserve)

$\beta_{10} = \gamma_{40} + \gamma_{41}$(PM-Acc) + γ_{42}(Consci) + γ_{43}(Reserve) +

$$\gamma_{44}(\text{PM-Acc*Consci}) + \gamma_{45}(\text{PM-Acc*Reserve})$$

$$\beta_{11} = \gamma_{50} + \gamma_{21}(\text{Consci}) + \gamma_{22}(\text{Reserve})$$

$$\beta_{12} = \gamma_{60} + \gamma_{21}(\text{Consci}) + \gamma_{22}(\text{Reserve})$$

$$\beta_{13} = \gamma_{70} + \gamma_{71}(\text{Consci}) + \gamma_{72}(\text{Reserve})$$

Table 10. Summary of multilevel model fixed effect coefficients for models of RS including accuracy and person-mean retest interval.

	Occasion-Mean RS			Within-Occasion RS Change		
Fixed Effect	*b*	SE	*P*	*b*	SE	*P*
Intercept						
Intercept	**1.01×10^{0}**	**2.42×10^{-2}**	**<0.01**	**1.98×10^{-1}**	**1.69×10^{-2}**	**<0.01**
PC-Accuracy	-2.63×10^{-4}	1.24×10^{-3}	0.83	-1.41×10^{-3}	1.27×10^{-3}	0.27
PM-Accuracy	4.18×10^{-3}	2.71×10^{-3}	0.13	-2.36×10^{-4}	1.61×10^{-3}	0.88
PM-Interval	-4.87×10^{-3}	5.73×10^{-3}	0.40	-3.87×10^{-3}	4.05×10^{-3}	0.34
Condition						
Intercept	**3.46×10^{-1}**	**1.79×10^{-2}**	**<0.01**	**-7.83×10^{-2}**	**1.78×10^{-2}**	**<0.01**
PC-Accuracy	**-5.14×10^{-3}**	**1.55×10^{-3}**	**<0.01**	-9.29×10^{-4}	1.54×10^{-3}	0.55
PM-Accuracy	**-5.44×10^{-3}**	**1.45×10^{-3}**	**<0.01**	-1.12×10^{-3}	1.44×10^{-3}	0.44
PM-Interval	**1.01×10^{-2}**	**4.34×10^{-3}**	**0.02**	3.24×10^{-3}	4.31×10^{-3}	0.45
Occasion						
Intercept	**6.60×10^{-2}**	**6.60×10^{-3}**	**<0.01**	**-3.68×10^{-2}**	**5.29×10^{-3}**	**<0.01**
Condition	-5.10×10^{-3}	6.62×10^{-3}	0.44	**2.17×10^{-2}**	**6.58×10^{-3}**	**<0.01**
PC-Accuracy	1.47×10^{-4}	4.33×10^{-4}	0.74	5.30×10^{-4}	4.47×10^{-4}	0.24
PM-Interval	**-7.20×10^{-3}**	**2.48×10^{-3}**	**<0.01**	7.41×10^{-5}	1.98×10^{-3}	0.97
Condition*PC-Accuracy	**1.58×10^{-3}**	**5.36×10^{-4}**	**<0.01**	1.01×10^{-4}	5.32×10^{-4}	0.85
Condition*PM-Interval	-2.36×10^{-4}	2.31×10^{-3}	0.92	-1.85×10^{-3}	2.29×10^{-3}	0.42
Model Deviance	-522.0			-569.0		

b = unstandardized regression weight (slope)
SE = standard error
RS = Response speed
PC = Person-mean-centred
PM = Person-mean

Occasion-mean RS. Both predictors exhibited significant cross-level interaction effects on occasion-mean RS, suggesting that they reflected between-person differences in task performance (see coefficients in Table 11). There was a significant interaction of conscientiousness with occasion. This effect indicated that, adjusting for response accuracy, participants higher in conscientiousness showed steeper across-occasion linear increases in occasion-mean RS. There was also a trend-level interaction of conscientiousness with occasion and condition. This suggests that the steeper across-occasion speed increase in those higher in conscientiousness may have been relatively exaggerated in the switch relative to stay condition. In other words those higher in conscientiousness tended to show an enhancement of retest-related switch-cost attenuation (see Figure 10 and 11). The interaction between task condition and reserve (not including occasion) was also significant, even after adjustment for person-mean differences in response accuracy. Thus at baseline, those higher in reserve showed a greater switch cost (*i.e.* greater slowing on switch relative to stay trials at the first testing occasion). To reiterate, reserve (TOPF score) did not predict significant differences in across-occasion slope (practice effect).

Within-occasion RS change. Similar to findings for occasion-mean RS, both conscientiousness and TOPF-estimated reserve interacted with task condition to predict differences in within-occasion RS change. These differences persisted even after adjusting the interaction term for response accuracy. Neither person-level predictor interacted significantly with occasion, and thus all effects on within-occasion RS speeding were related to performance at the baseline (first) testing occasion (see coefficients in Table 11). Interpretation of these effects showed that, at baseline and adjusting for individual differences in response accuracy, within-occasion response speeding was disproportionately greater on switch relative to stay trials for individuals higher in either conscientiousness or reserve (Figure 12). These interactions with task condition represent the effects of person-level covariates on the within-occasion reduction in switch cost. In essence, those higher in reserve or conscientiousness

showed a greater within-occasion reduction in switch cost at the first assessment occasion.

A summary of the effects of interest are presented in Table 12.

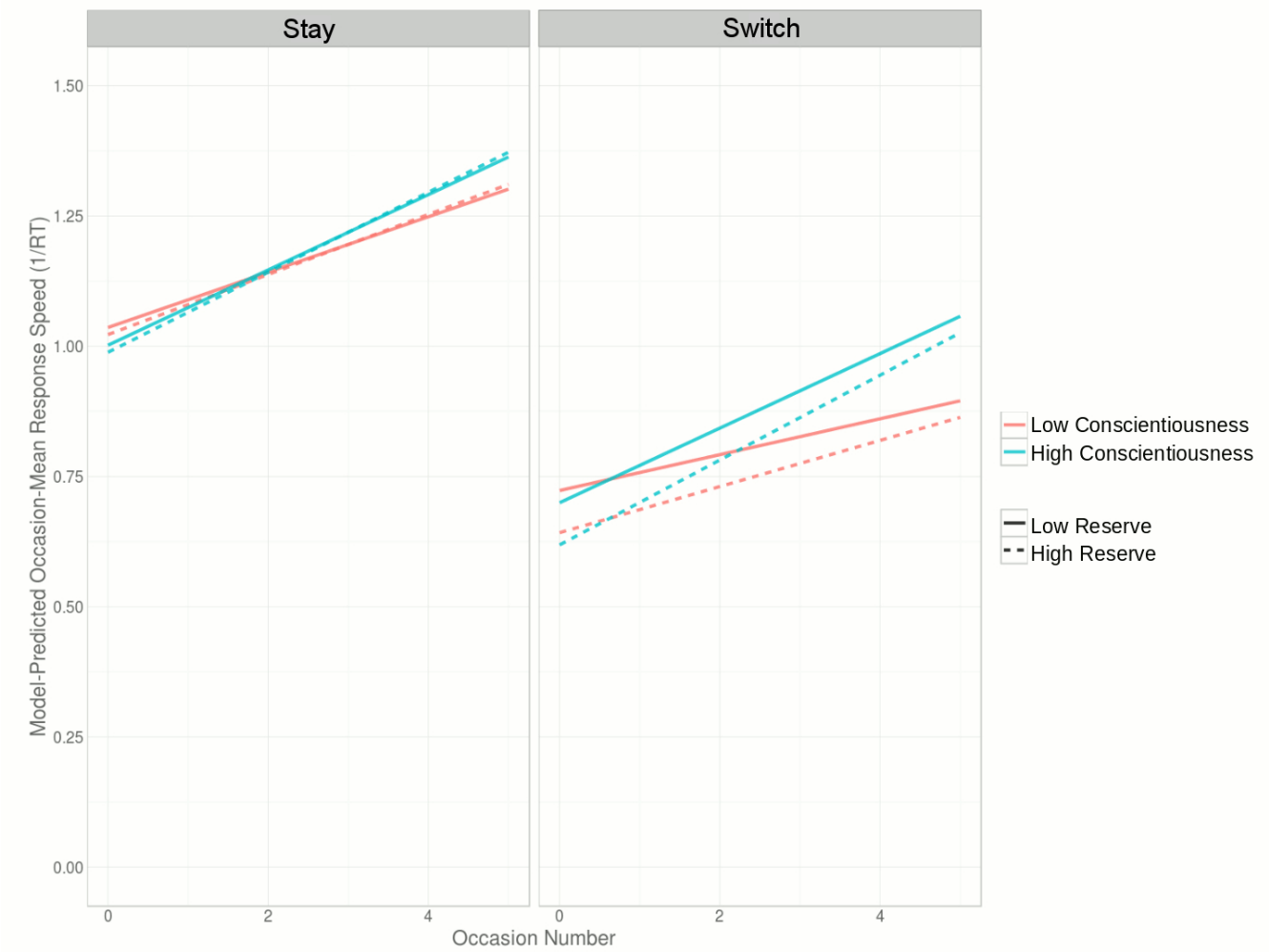

Figure 10. Model-predicted trajectories of occasion-mean RS across testing occasion for counterfactual (hypothetical) participants above and below the sample median score for TOPF, and at the 25th and 75th sample percentiles for conscientiousness. Plot panels represent stay (left) and switch (right) task conditions.

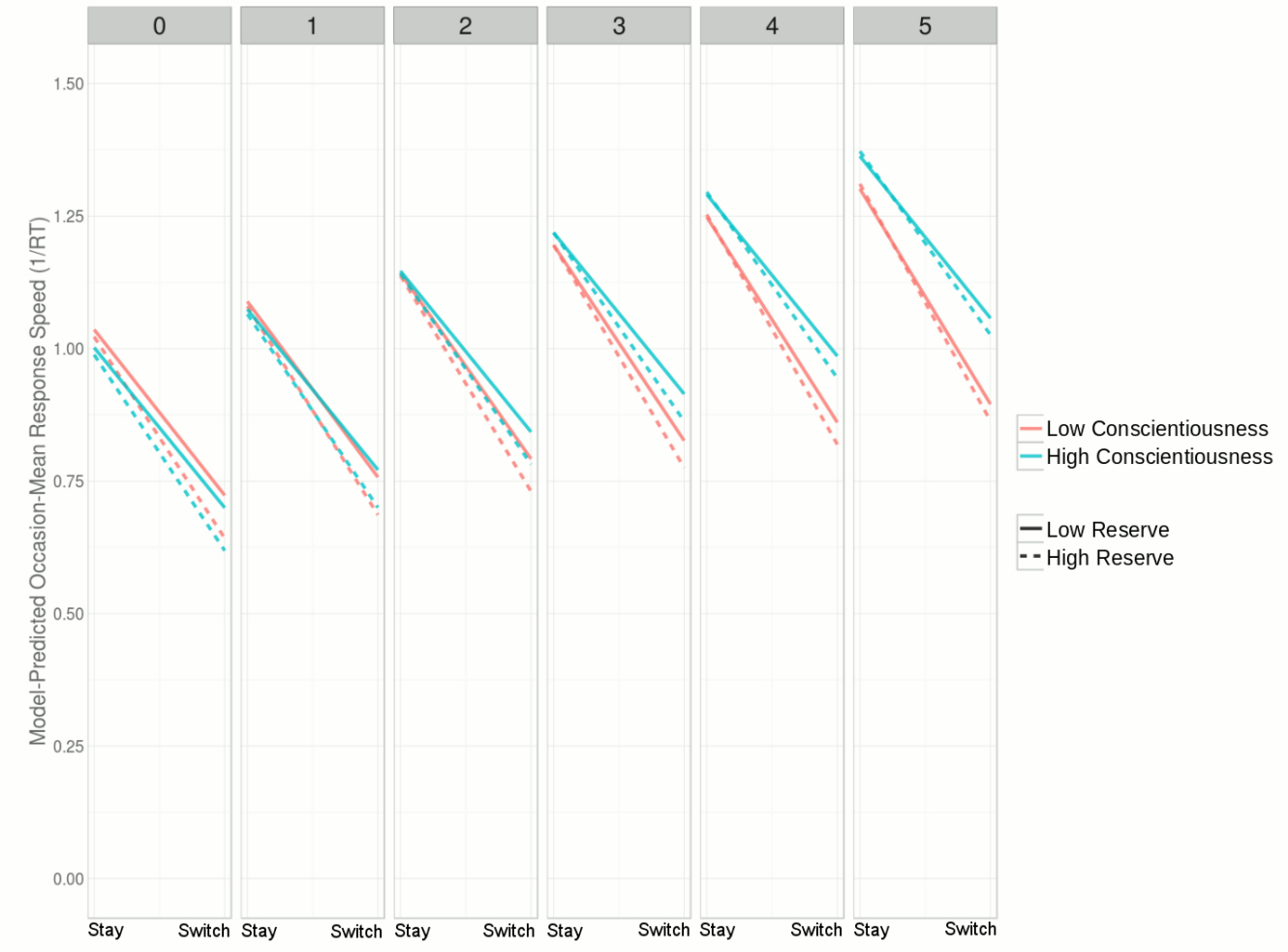

Figure 11. The interaction effect of conscientiousness with occasion can be seen as the relative gains of the blue relative to red lines across occasions (panels proceeding from baseline, left to right). The further interaction trend between conscientiousness, occasion, and task condition is evident in the relative attenuation of switch cost (downward slope) for blue relative to red across occasions. Also note the significant difference in switch cost between the lower (solid lines) and upper (dotted lines) halves of the reserve estimate (TOPF) median-split.

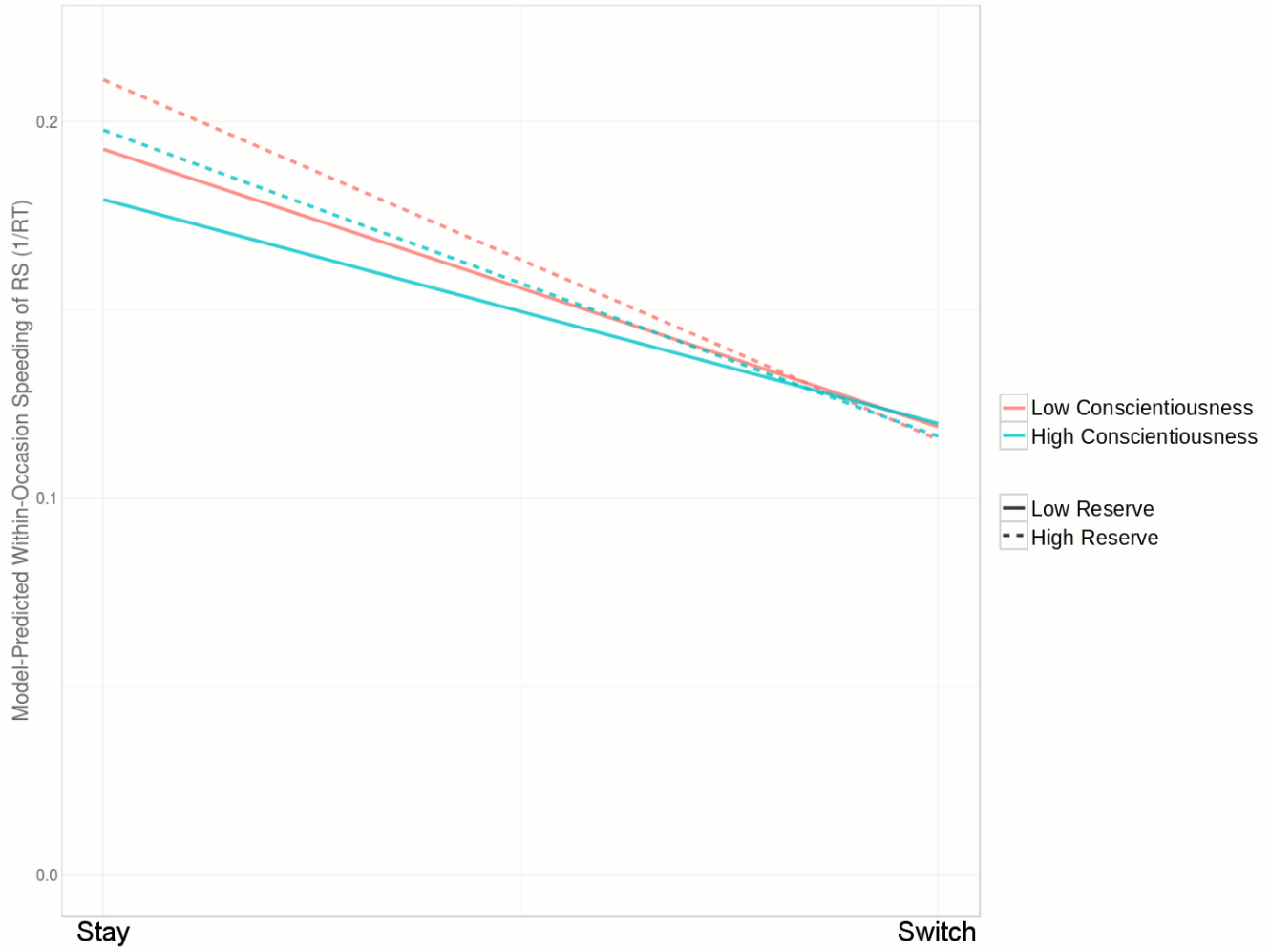

Figure 12. Interaction plot illustrating effect of person-level covariates (conscientiousness and reserve) on the within-occasion reduction in switch cost (left-to-right slope across conditions) at the baseline assessment. Counterfactual (hypothetical) participant trajectories are plotted for above and below median sample TOPF score, and at the 25th and 75th sample percentiles for conscientiousness.

Table 11. Summary of multilevel model fixed effect coefficients for predictive models of RS change.

	Occasion-Mean RS			Within-Occasion RS Change		
Fixed Effect	*b*	SE	*P*	*b*	SE	*P*
Intercept						
Intercept	**1.02×10^{0}**	**3.21×10^{-2}**	**<0.01**	**1.87×10^{-1}**	**2.40×10^{-2}**	**<0.01**
PC-Accuracy	-3.20×10^{-3}	1.78×10^{-3}	0.07	**-4.76×10^{-3}**	**1.93×10^{-3}**	**0.01**
PM-Accuracy	2.27×10^{-3}	3.11×10^{-3}	0.49	2.00×10^{-3}	2.19×10^{-3}	0.36
PM-Interval	-6.58×10^{-4}	5.19×10^{-3}	0.90	-2.75×10^{-3}	3.61×10^{-3}	0.45
Condition						
Intercept	**3.08×10^{-1}**	**2.48×10^{-2}**	**<0.01**	**-6.75×10^{-2}**	**2.52×10^{-2}**	**<0.01**
PC-Accuracy	-3.00×10^{-3}	2.25×10^{-3}	0.18	1.57×10^{-3}	2.29×10^{-3}	0.49
PM-Accuracy	**-7.23×10^{-3}**	**2.13×10^{-3}**	**<0.01**	-3.08×10^{-3}	2.14×10^{-3}	0.15
Occasion						
Intercept	**6.15×10^{-2}**	**8.05×10^{-3}**	**<0.01**	**-3.79×10^{-2}**	**7.59×10^{-3}**	**<0.01**
Condition	-1.08×10^{-2}	9.12×10^{-3}	0.24	**1.97×10^{-2}**	**9.26×10^{-3}**	**0.03**
PC-Accuracy	6.83×10^{-4}	8.71×10^{-4}	0.43	**1.99×10^{-3}**	**9.09×10^{-4}**	**0.03**
PM-Interval	**-5.52×10^{-3}**	**1.84×10^{-3}**	**<0.01**	-9.57×10^{-4}	1.64×10^{-3}	0.55
Condition*PC-Accuracy	**2.05×10^{-3}**	**1.01×10^{-3}**	**0.04**	-1.13×10^{-3}	1.03×10^{-3}	0.27
Conscientiousness						
Intercept	-3.77×10^{-3}	3.73×10^{-3}	0.32	-1.48×10^{-3}	2.82×10^{-3}	0.60
Condition	1.18×10^{-3}	2.91×10^{-3}	0.68	1.59×10^{-3}	2.96×10^{-3}	0.59
Occasion	**2.12×10^{-3}**	**1.06×10^{-3}**	**0.05**	-8.22×10^{-4}	1.02×10^{-3}	0.42
PC-Accuracy	-4.37×10^{-4}	2.55×10^{-4}	0.09	3.27×10^{-4}	2.76×10^{-4}	0.24
PM-Accuracy	5.92×10^{-4}	4.36×10^{-4}	0.18	1.14×10^{-4}	2.93×10^{-4}	0.70
Condition*Occasion	2.00×10^{-3}	1.21×10^{-3}	0.10	9.58×10^{-4}	1.23×10^{-3}	0.44
PC-Accuracy*Occasion	1.23×10^{-4}	9.83×10^{-5}	0.21	-1.41×10^{-4}	1.04×10^{-4}	0.18
Condition*PC-Accuracy	5.45×10^{-5}	3.22×10^{-4}	0.87	-3.08×10^{-4}	3.27×10^{-4}	0.35
Condition*PM-Accuracy	**7.73×10^{-4}**	**2.78×10^{-4}**	**<0.01**	**5.89×10^{-4}**	**2.80×10^{-4}**	**0.04**
Condition*Occasion*PC-Accuracy	-7.53×10^{-6}	1.19×10^{-4}	0.95	1.18×10^{-5}	1.21×10^{-4}	0.92
Reserve						
Intercept	-1.36×10^{-2}	4.39×10^{-2}	0.76	1.84×10^{-2}	3.28×10^{-2}	0.58
Condition	**-6.73×10^{-2}**	**3.38×10^{-2}**	**0.05**	-2.18×10^{-2}	3.43×10^{-2}	0.53
Occasion	4.56×10^{-3}	1.11×10^{-2}	0.68	2.23×10^{-3}	1.04×10^{-2}	0.83

PC-Accuracy	**7.84×10^{-3}**	**2.35×10^{-3}**	**<0.01**	4.83×10^{-3}	2.53×10^{-3}	0.06
PM-Accuracy	1.69×10^{-3}	5.33×10^{-3}	0.75	-4.49×10^{-3}	3.41×10^{-3}	0.19
Condition*Occasion	5.30×10^{-3}	1.26×10^{-2}	0.67	2.87×10^{-3}	1.28×10^{-2}	0.82
PC-Accuracy*Occasion	-1.59×10^{-3}	1.08×10^{-3}	0.14	-1.67×10^{-3}	1.12×10^{-3}	0.14
Condition*PC-Accuracy	-4.82×10^{-3}	2.96×10^{-3}	0.10	-3.47×10^{-3}	3.00×10^{-3}	0.25
Condition*PM-Accuracy	**7.19×10^{-3}**	**3.02×10^{-3}**	**0.02**	**7.37×10^{-3}**	**3.04×10^{-3}**	**0.02**
Condition*Occasion*PC-Accuracy	-1.20×10^{-4}	1.26×10^{-3}	0.92	1.82×10^{-3}	1.28×10^{-3}	0.16
Model R^2	0.898			0.639		
Model Deviance	-585.2			-598.8		

b = unstandardized regression weight (slope)
SE = standard error
RS = response speed
PC = person-mean-centred
PM = person-mean

Table 12. Narrative summary of effects of interest, adjusting for performance accuracy, in the context of the multi-level design.

Outcome	Highest level	Covariate(s)	Interpretation
Occasion-mean response speed	Person (level 3)	WAIS-IV TOPF standard score	No differences in across-occasion change as a function of reserve. At baseline, higher reserve predicted greater switch cost.
		Raw BFI Conscientiousness score	Higher conscientiousness predicted steeper across-occasion linear increases. Trend level interaction with task condition: higher conscientiousness marginally predictive of enhanced retest-related switch-cost attenuation.
	Occasion (level 2)	Occasion number	At baseline, was 1.00 s^{-1} for stay trials and 0.68 s^{-1} for switch trials. Across occasion increases did not vary as a function of task condition.
	Within-occasion (level 1)	Task condition (stay/switch)	Difference between stay (1.14 s^{-1}, RT ~ 877 ms) and switch trials (0.79 s^{-1}, RT ~ 1266 ms).
Within-occasion response speed increase	Person (level 3)	WAIS-IV TOPF standard score	No differences in across-occasion change as a function of reserve. At baseline, higher reserve predicted greater within-occasion reduction in switch cost.
		Raw BFI Conscientiousness score	No differences in across-occasion change as a function of conscientiousness. At baseline, higher conscientiousness predicted greater within-occasion reduction in switch cost.
	Occasion (level 2)	Occasion number	At baseline, was 0.20 s^{-1} for stay trials and 0.13 s^{-1} for switch trials. Across occasion reductions were greater for stay than switch trials.
	Within-occasion (level 1)	Task condition (stay/switch)	Difference between stay (0.12 s^{-1}) and switch trials (0.09 s^{-1}).

Study 2 Discussion

The present study was undertaken to capture behavioural manifestations of neurocognitive adaptation: switch cost and retest learning (practice effects) on a cognitive task. Because the assessment was computerized and intensive, it provided precise measures of response speed across multiple trials (timescale of seconds) and across multiple occasions (timescale of days): the study captured

neurocognitive adaptation at multiple hierarchically nested timescales (Lövdén et al., 2010). In order to advance and refine the assessment of older adult neurocognitive adaptability, the present study explored the relationship of retest learning effects – a direct-observation method of adaptability assessment – to two potential moderators of retest learning: conscientiousness and reserve. The latter were based on standardized measures (self-report and irregular word reading, respectively). Many *a priori* predictions were borne out in this study, and the pattern of findings provides novel insight into the nature and clinical assessment of older adult neurocognitive adaptability.

The present results demonstrated that higher conscientiousness, but not reserve, anticipated more plasticity-related (across-occasion) neurocognitive adaptation. However both higher reserve and higher conscientiousness predicted more adaptation to immediate task demands (*i.e.* flexibility). At the first testing occasion, those higher in reserve or conscientiousness had a greater within-occasion reduction in switch cost relative to their lower-reserve peers: evidence of reserve and conscientiousness as reflective of a greater propensity for short-timescale (flexible) adaptation. If performance at the first session is indeed reflective of flexibility-supportive neurocognitive processes, it might also be closely allied with neural metrics of subsecond-timescale flexibility such as multiscale brain signal entropy (see Chapter 1 of this dissertation). The final chapter of this dissertation will consider this possibility explicitly.

In general, mean response speed increased and within-occasion speeding decreased across occasions; both of these trends would be expected as individuals adapted their performance to the task demands over repeated exposures. Although speed-accuracy trade-offs were not a focus of this study, interactions with response accuracy were crucial in isolating and interpreting the major findings discussed below. For example, many of the effects of task condition on response speed emerged only after adjustment for response accuracy. This suggests that differences in response accuracy (perhaps in part related to differences in effort or strategy), if omitted from the models, would have obscured

switch-cost-related differences in response speed. Moreover, the effects of conscientiousness and reserve helped to highlight important sources of individual difference in older adult neurocognitive adaptability.

Occasion-mean response speed

Changes in occasion-mean response speed were used to index neurocognitive adaptability at the timescale of days to weeks, in other words as an index of plasticity. Above and beyond individual- and occasion-level differences in response accuracy it was found that those higher in conscientiousness showed a steeper across-occasion increase in overall performance speed (occasion-mean RS), with a trend toward greater practice-related reduction in switch cost (trend-level interaction with task condition). This is in line with previous research suggesting that individuals higher in conscientiousness tend to benefit more from practice across occasions (Yeo & Neal, 2004). This also aligns with *a priori* predictions. In particular, the present finding supports the supposition that between-person differences in conscientiousness and in the tendency to optimize performance on novel cognitive challenges both reflect a common underlying capacity for neurocognitive adaptability.

Conscientiousness is of particular relevance to “direct-observation” methods of adaptability assessment, such as intensive cognitive assessment, insofar is it relates to differences in approach, priority, motivation, response to time pressure, and skill acquisition (Yeo & Neal, 2004, and refs therein). For example, on computerized cognitive tasks, older adults higher in conscientiousness have been shown to have greater across-trial performance consistency (Tse, Balota, Yap, Duchek, & McCabe, 2010). Use of conservative, considered approaches to cognitive testing by older individuals has also been hypothesized to underlie qualitative age-group differences in across-occasion, practice-related improvements (Whitson, Karayanidis, & Michie, 2012) and to discriminate different patterns of learning and asymptotic performance among groups of healthy older adults (Shing et al., 2012).

A relatively conscientious orientation has the potential to impact late-life neurocognitive

function in a variety of ways. The benefits of conscientiousness have most often been ascribed to health behaviours that may be protective of late-life cognitive well-being; higher conscientiousness is related to longevity, is positively related to beneficial health behaviours, and negatively related to risky health behaviours (Bogg & Roberts, 2004). Some researchers (Wilson et al., 2015) have suggested that conscientiousness may also contribute to preserved cognitive function in older adulthood through mechanisms of "motivational reserve" such as will and goal-directedness (Forstmeier & Maercker, 2008). This perspective is complemented by findings that conscientiousness relates to structural and functional characteristics of the orbitofrontal/prefrontal cortices implicated in motivational/reward circuitry (Jackson, Balota, & Head, 2011).

Conscientiousness shares a conceptual relation to constructs such as self-regulation, impulse control (Roberts et al., 2014), and executive functioning (Tse et al., 2010). Thus those higher in conscientiousness may also be more likely to exert the effort required to adapt to the limitations imposed by advancing age- or disease-associated neuropathology. This, in turn, would help maintain performance on laboratory or clinical "cognitive training" tasks, as well as to meet the demands of daily life (*e.g.* conscientiousness is predictive of academic achievement; Busato, Prins, Elshout, & Hamaker, 2000). Indeed, the cognitive performance of older adults higher in conscientiousness is less impacted by genetic risk of Alzheimer disease (Caselli et al., 2016; Wilson et al., 2015). Perhaps those older adults who are higher in conscientiousness benefit twice: the tendency to persevere and meet functional goals that supports efficient adaptation to daily, clinical, and laboratory cognitive demands is also expressed as a more general propensity to avoid risky and seek protective health behaviours.

What is more, though conscientiousness in particular, and personality in general, have the classical connotation of "trait" (time-invariant), updated theories accommodate for change in personality traits over developmental time (Srivastava, John, Gosling, & Potter, 2003). Declines in performance on executive functioning tests are among the earliest and most prominent indicators of

early pathological cognitive aging (Rabbitt, Diggle, Holland, & McInnes, 2004), perhaps even in the context of Alzheimer disease (Saunders & Summers, 2011). Within-person declines in conscientiousness may predict declines in older adult dementia status (Donati et al., 2013). It is possible that certain self-reported personality dimensions may track trends in the capacity for neurocognitive adaptation at the scale of years to decades (*i.e.* at the plastic end of the adaptability continuum). Indeed, conscientiousness may be a valid self-rating of executive function (Smart, Koudys, & Mulligan, 2015).

Unlike conscientiousness, TOPF-estimated reserve was associated with switch cost at baseline, but did not relate to across-occasion changes in speed or switch cost. The influence of reserve was therefore predominantly expressed as differences in performance at the first testing occasion. This finding is consistent with previous research on the effects of factors such as race, acculturation, and educational experience on neuropsychological test performance (Manly, Byrd, Touradji, & Stern, 2004; Manly, Jacobs, Touradji, Small, & Stern, 2002). Research in this area suggests that those lower in such domains tend to underperform at the initial assessment occasion, such that retest gains are often most prominent between the first and second testing occasion (Gross et al., 2015). This is thought to be due to a relative advantage in "test-wiseness" – familiarity and proficiency with the context as opposed to the content of testing – on the part of those higher in acculturation or educational experience (Borrello & Thompson, 1985; Suchy, Kraybill, & Franchow, 2011). While "computer-wiseness" may be expected to complicate the interpretation of older adult computerized cognitive task performance (*i.e.* due to erroneous inflation of scores), physically active older adults who use computers have actually been found to have a reduced risk of MCI (Geda et al., 2012).

Somewhat surprisingly, those individuals with higher reserve actually showed a greater switch cost at baseline than those individuals lower in reserve. Follow-up analysis revealed that the increased switch cost at baseline among those higher in reserve was not a result of slower performance on switch

trials; in fact, participants higher in reserve performed as quickly as their lower-reserve counterparts on switch trials at the baseline occasion. The greater switch cost among individuals higher in reserve was driven by faster performance on stay trials compared to participants lower in reserve. This could reflect that older adults share a common "ceiling" in terms of responding under rule-switch conditions, but those higher in reserve perform better than their low-reserve peers on the stimulus-classification aspect of the task (*i.e.* under rule-stay conditions). This is consistent with the fact that reading-test-based estimates of reserve such as the TOPF are not necessarily strong predictors of functioning in executive domains. Evidence suggests that estimates of reserve based on reading tests show strong correlation with indices of overall and verbal intelligence, but medium-strength association with perceptual reasoning, working memory, and processing speed indices (Bright, Hale, Gooch, Myhill, & van der Linde, 2016; Willshire, Kinsella, & Prior, 1991).

Within-occasion RS change

In this study, within-occasion RS speeding was used as an index of cognitive flexibility – adaptability at the scale of seconds/trials. Neither person-level predictor of interest (reserve or conscientiousness) predicted across-occasion differences in within-occasion RS change. However both predicted differences in within-occasion switch cost reduction at baseline. Overall, the switch-cost effect resulted in less within-occasion speeding on switch relative to stay trials at baseline. However, higher TOPF-estimated reserve or conscientiousness mitigated the switch-cost effect.

It is notable that there was very little systematic variance (variance explained by study variables) in the index of within-occasion RS change, save for at the baseline (first) assessment occasion. This may reflect the fact that unique neurocognitive events, occurring only during one's first exposure to the switch task, were indexed by this within-occasion change metric. That is, within-occasion RS change at the baseline testing session reflects rapid neurocognitive adaptation to a novel situation (Cunillera et al., 2012; Kopp & Lange, 2013; Nessler, Friedman, & Johnson, 2012). On the

other hand, the same metric derived from later testing sessions might be more reflective of episodic and procedural memory processes, strategy (speed/accuracy tradeoffs), sustained attention, and/or interest/motivation (Shing et al., 2012; Strobach et al., 2015; Whitson et al., 2012).

Implications for future research and clinical practice

This study's multi-method approach illuminates the nature of older adult neurocognitive adaptability, in part by avoiding the pitfalls of shared common method variance (Avolio, 1991; Brannick, Chan, Conway, Lance, & Spector, 2010; Doty & Glick, 1998; Podsakoff, MacKenzie, Lee, & Podsakoff, 2003; Podsakoff, MacKenzie, & Podsakoff, 2011). It is also innovative insofar as it combines metrics of neurocognitive flexibility and plasticity within the same design. The use of intensive measurement in particular allowed the direct observation of within- and across-occasion performance improvement, and speaks to the wider need for timescale considerations in modern psychometric research (Molenaar, 2004). Intensive measurement can be done with “pencil-and-paper” testing (Darby et al., 2002; Duff, 2014; Duff, Callister, Dennett, & Tometich, 2012; Duff, Chelune, & Dennett, 2012; Reeves, Winter, Bleiberg, & Kane, 2007), although it is more cumbersome to administer and less precise in some aspects of measurement than computerized testing. Calls to meet standards of psychometric rigor should be heeded, but computerized testing is likely to become a mainstay of neuropsychological assessment (Gates & Kochan, 2015; Matarazzo, 1986).

As baby-boomers approach the old-age horizon, it is imperative that neuropsychologists contribute to the development of an economically viable system of early-dementia diagnosis, monitoring, and treatment-delivery that is accessible to all individuals, regardless of geographical constraint. With minimal economic and infrastructural support a battery of self-reported and performance-based assessment activities such as that presented herein could be deployed remotely, via the internet and mobile devices, for population-level screening and longitudinal follow-up of at-risk older adults (Cella et al., 2015). In Canada in particular, rural- and remote-dwelling residents will rely

increasingly on e-health/tele-health schemes to access screening and long-term follow-up services (Muttitt, Vigneault, & Loewen, 2004). Some internet-based cognitive screening platforms have already been piloted and show promise (Zakzanis & Azarbehi, 2013).

A recent review (Zygouris & Tsolaki, 2014) of computerized cognitive testing in older adults identified 17 distinct batteries which varied in terms of the breadth and number of tests included. Of those identified, some of the more well-known included CANTAB, CNS Vital Signs, CogState, and CAMCOG-CAT. The review highlighted common strengths: rigorous standardization; accurate measurement of many performance indices; automated scoring, record-keeping, and reporting (including comparisons relative to self and normative sample); and economic efficiencies. It also noted a lack of coherence in the field due to across-battery variety in the modality of delivery and composition of the batteries, and in the quality/availability of psychometric data.

It has been pointed out that many of the challenges often ascribed to the adoption of computerized cognitive testing are not unique to computerized tests (Bauer et al., 2012; Katherine Wild, Howieson, Webbe, Seelye, & Kaye, 2008; Zygouris & Tsolaki, 2014). Among clinical neuropsychologists, test selection has remained relatively stable over the last 10 years (Rabin, Paolillo, & Barr, 2016). Computing and telecommunications technologies are transforming human culture, and the next generation of neuropsychological practice is likely to increasingly involve computerized testing and scoring procedures. Among other things, technology affords opportunities for desperately needed economies of scale in health care. Older adult attitudes toward use of technology in health care are generally positive; researchers have begun to develop e-health hardware and software that addresses older adults' unique needs and preferences (O’Hanlon, Bourke, & Power, 2013).

However there are ethical and psychometric problems to be solved that are more pronounced with the reliance on a computer in cognitive testing (Gates & Kochan, 2015). For one, clear policies are needed to maintain test and patient data security. Though beyond the technical expertise of many, issues

related to electronic health data security are not beyond the ethical expertise of neuropsychologists. Innovative solutions are likewise needed to monitor and encourage effort/engagement to ensure performance validity. Unlike face-to-face testing with a clinician, computerized testing lacks the performance-facilitating context of implicit social demand (Lezak et al., 2012). Along related lines, more sophisticated methods must be developed to flag signs of potential malingering. In this regard, remote computer assessment (*e.g.* in a rural medical clinic) done under the supervision of a trained healthcare professional poses less of a challenge relative to at-home, unsupervised testing.

Indeed, the detection of malingering on computerized cognitive testing has proven difficult in some groups of individuals who are motivated or instructed to under-perform (Gaudet & Weyandt, 2016). A number of solutions to this quandary deserve exploration. For one, further validation studies should employ intensive measurement of individuals who are instructed or otherwise motivated to underperform. The increased power and within-person resolution afforded by intensive measurement will help to refine embedded performance validity indicators. Furthermore, easily-acquired self-report measures (*e.g.* of demographics, personality) may be informative for identifying individuals at heightened risk of suboptimal effort. For this reason, it would be helpful for basic demographic and medical history information to be verified by a qualified professional. Finally, high-tech solutions might involve directly assessing engagement, for example by monitoring activity, eye movements, or physiology.

Widespread adoption of computerized cognitive testing is therefore contingent upon addressing potential threats to construct validity, ethical integrity (*e.g.* confidentiality, test security), and professional purview. Neuropsychologists are well-positioned to address the weaknesses and capitalize on the strengths of including computerized cognitive screening tools in their assessment repertoires (Wild, Howieson, Webbe, Seelye, & Kaye, 2008; Zygouris & Tsolaki, 2014). The judicious, flexible deployment of computerized tests on a case-by-case basis alongside other informal and standardized

techniques such as interview, self-report, and in-person (“pencil-and-paper”) performance-based assessments would undoubtedly augment current practice (Bauer et al., 2012).

If intensive computerized cognitive assessment is to be used as part of a comprehensive multi-method neuropsychological evaluation, then studies such as the present one are important for reducing confound and refining interpretations of performance metrics. For instance, an older adult who self-reports a high-level of conscientiousness would be expected to show steeper across-occasion cognitive performance gains relative to low-conscientiousness peers (independent, presumably, of the degree of aging or disease burden). On the other hand, performance differences due to reserve might be most obvious at the baseline testing occasion, and negligible thereafter. Identification of important additional sources of individual difference, beyond age and education, in intensively-measured cognitive performance will aid in the development of clinically useful standardized scores for direct-observation methods of adaptability assessment. This, in turn, would support more efficient screening and diagnosis and allow for real-time treatment outcome monitoring.

Finally, the implication of individual differences in premorbid function and conscientiousness as moderators of retest learning is also relevant to rapid growth in the field of computerized cognitive training interventions for older adults (Kueider, Parisi, Gross, & Rebok, 2012). Some training packages that are currently commercially available may be effective (Shah, Weinborn, Verdile, Sohrabi, & Martins, 2017), and could in principle be used remotely. Though data are still in short supply, there is some indication that computerized and virtual reality cognitive training can improve cognitive and psychological functioning among individuals with MCI and dementia (Coyle, Traynor, & Solowij, 2014). However the generalizability or transfer of cognitive skills that are “strengthened” through computerized training is still a matter of debate (Simons et al., 2016). Perhaps inconsistent findings in the field of “brain training” in part reflect a failure to account for crucial individual differences due to personality and educational/cultural experience.

In the following chapter, a final empirical study is presented that builds on and integrates the first two studies in this dissertation. In particular, it answers the outstanding question of whether the performance-based indices of neurocognitive adaptability introduced in the present study vary as a function of the dementia-risk diagnostic grouping or neural adaptability metrics introduced in the preceding study.

Study 3: Laboratory and clinical standards of neurocognitive adaptability predict distinct features of computerized cognitive task performance

Worldwide, there are an estimated 9.9 million new cases of dementia each year, and this incidence rate appears to be accelerating (Prince et al., 2015). Dementia is associated with pronounced neural and cognitive deterioration, now known to develop over several years to decades, eventually resulting in loss of functional independence (Tuokko & Smart, 2014; Tuokko & Ritchie, 2009). There is a need to identify at-risk individuals as soon as possible and to develop novel preventative interventions designed to slow the progression of dementia-related declines in neural and cognitive health.

Many researchers have been working to develop tools for reliable and efficient early identification of those older adults who are at increased risk for pathological cognitive decline (Edmonds et al., 2015; Jessen, 2013). Recent research has confirmed the utility of various biomarkers (Jack et al., 2011) and standardized cognitive performance measures (Rentz et al., 2013) in tracking dementia from its subtle/preclinical to its manifest clinical stages. However multiple interacting processes involved with normative and nonnormative development and aging yield individual cognitive trajectories. These are highly heterogeneous in their fluctuations and change over time (Bäckman & MacDonald, 2006; Sliwinski, Hofer, & Hall, 2003). Many individuals who eventually develop dementia show evidence of multiple etiologies (Schneider et al., 2009; Wilson et al., 2013). “Mean trajectories” of groups of people over time, including at preclinical dementia stages, may be misleading due to significant between-person variation.

There are standardized cognitive performance and neuroimaging measures that can track within-person declines in the context of dementia. But over half (58%) of the 46.8 million people with dementia in 2015 lived in developing countries such as China and India where access to such expert

neuropsychological and neuroimaging services may be limited (Prince et al., 2015). Similar issues with access arise in rural and remote regions of Canada, with disproportionate impact on First Nations persons (Muttitt et al., 2004). Even in developed regions, most older individuals do not undergo formal neurocognitive evaluation unless there is a specific complaint or concern regarding a perceived change on the part of the patient, their family, or their clinician (Kryscio et al., 2014).

Thus while useful and valid tools for the early detection of dementia exist, there are insufficient and heterogeneously-distributed resources to provide assessments to all adults over age 65. Instead, the burden falls on clinicians and family members to notice and respond to troublesome signs that manifest in the course of routine clinical examination or day-to-day life, respectively. Once dementia-related neurocognitive decline *relative to a person's own typical level of function* is obvious upon informal observation (*e.g.* the individual begins getting lost in familiar places), opportunities to intervene are limited. Dementia pathology may have progressed to a point where treatment options such as lifestyle change, pharmacological intervention, or compensatory strategy are less likely to be effective (Prince et al., 2015).

What is needed is a validated, economically-viable method for screening large numbers of individuals who are at risk for dementia. An ideal “first-pass” protocol would identify individuals over 65 years of age who are in need of comprehensive assessment with standardized clinical measures of neural and cognitive function. The protocol should also allow for repeated measurement in order to facilitate tracking of single individuals. It would also facilitate the detection of significant within-person changes over time that are characteristic of neurodegenerative disease. In the realm of dementia and neurocognitive health, computerized cognitive assessment shows promise in fulfilling such a population-scale screening role (Bauer et al., 2012; Darby et al., 2012; Hammers et al., 2012; Wild, Howieson, Webbe, Seelye, & Kaye, 2008; Zygouris & Tsolaki, 2014) even for historically underserved populations (Doniger, Jo, Simon, & Crystal, 2009; Muttitt et al., 2004). Computerized testing can also

facilitate at-home dementia self-assessments that can be monitored remotely by clinicians (Kim, Hsiao, & Do, 2012; Zakzanis & Azarbehi, 2013); this could remove geographic and wait-time barriers and reduce infrastructure burden.

The present study builds on the findings of the prior two studies, and was undertaken to assess the feasibility of using computerized cognitive testing to screen neurocognitive health among older adults. In particular, it addressed the question of whether performance on computerized cognitive testing related to meaningful between-person differences in neural function or standardized neuropsychological performance. This question was considered in the context of other factors (premorbid/reserve function, personality) that have the potential to confound the relationship between computerized cognitive performance and the neural processes that support it.

Computerized testing provides a time-varying view of cognition

Among the major strengths of some forms of computerized cognitive testing is the quantitative, time-varying perspective on cognitive function that it affords. Reliable, high-precision measurement of response latency across multiple repeated trials of a typical computerized cognitive task allows examination of within- and between-occasion performance variation within single persons. Split-second accuracy in the measurement of response latencies is simply not possible for a human with their thumb on the button of a stopwatch, as is common practice in standard neuropsychological evaluations.

Since its inception in the 20th century, insights gained through computerized measurement of cognitive performance have transformed both expert and lay views of real-time brain function. It is now known that recondite features of response latency distributions reflect meaningful differences in underlying neural processes (Monto, Palva, Voipio, & Palva, 2008; Palva et al., 2013a; Palva & Palva, 2012). Previously dismissed as noise and eliminated through averaging, cognitive performance variability at the trial-level can differentiate between older individuals who differ in terms of cognitive status or dementia risk (Tse, Balota, Yap, Duchek, & McCabe, 2010; Mulligan, Smart, & Ali, 2016).

Beyond within-session, trial-to-trial variations (*i.e.* variation at the timescale of seconds) in cognitive performance, computerized cognitive testing can also facilitate investigation of cognitive function over time at longer retest intervals (Boker et al., 2009; Newell et al., 2009; Rast et al., 2012). Though not always explicitly understood as such, repeated exposures to a particular test paradigm provide an opportunity to study neurocognitive adaptability. Clinicians sometimes target across-occasion differences to assess neurocognitive adaptability (plasticity) with serial learning tasks, or by repeating assessments at intervals of minutes/hours (within the same occasion), days/weeks, or years (different occasions) (Lezak et al., 2012). Various quantitative/qualitative shifts in performance can be expected depending on the duration of the retest interval, the particular paradigm in question, and the individual's intervening activities (e.g. rehearsal, opportunities for interference). Practice gains in performance with repeated exposure to a particular paradigm are a reflection of the nervous system's essential capacity for adaptation. Though some forms are lost with age, neurocognitive adaptability is preserved in healthy relative to pathological neurocognitive aging (Baltes & Carstensen, 1996; Ram, Gerstorf, Lindenberger, & Smith, 2011).

Retest-related performance improvement is sensitive to dementia

Recently, the existence of retest-related performance gains has emerged as a confounding barrier to reliable repeat cognitive assessment (Attix et al., 2009; Goldberg, Harvey, Wesnes, Snyder, & Schneider, 2015; Heilbronner et al., 2010; Hoffman et al., 2011; Jones, 2015; Lemay, Bédard, Rouleau, & Tremblay, 2004). Practice effect size is also a dementia-risk index that explains unique variance above and beyond performance level at any single measurement occasion: practice effects are lost with increasing dementia severity (Duff, Chelune, & Dennett, 2012); individuals diagnosed with mild cognitive impairment (MCI) show attenuated retest-learning relative to their healthy peers (Darby, Maruff, Collie, & McStephen, 2002); and older adults who benefit less from practice are more likely to experience prospective cognitive decline (Duff et al., 2010).

Improvements in cognitive performance as a result of exposure are a direct behavioural manifestation of neurocognitive adaptability (Yang et al., 2006). As such retest-related improvement can be used to infer the integrity of the nervous system underlying this capacity for neurocognitive adaptation. Neurocognitive adaptability is lost in the course of primary biological decline as a result of aging, and may be accelerated or qualitatively different in the presence of worsening dementia pathology. For instance a relative lack of retest/practice gains has been found to predict increased *in vivo* amyloid burden (Duff, Foster, & Hoffman, 2014) and brain hypometabolism as measured by FDG PET (Duff, Horn, Foster, & Hoffman, 2015).

Confounding factors complicate the clinical application of practice effects

Though a useful index of dementia-related neuropathology, there is evidence that retest-related performance improvement can be influenced by confounding factors such as age, education/reserve, and personality/motivation. The effects of individual differences in reserve on retest-related performance improvement have been inconsistent. Some studies have shown significant positive effects of reserve on practice-related improvement (Kurtz et al., 2013; Lemay et al., 2004) while others have found no effect (Duff et al., 2010; Yang, Krampe, & Baltes, 2006; previous chapter in this dissertation). Beneficial effects of education on cognitive performance in particular have sometimes been attributed to factors such as anxiety-reduction (Yang et al., 2009) and “test-wiseness” that come with knowledge of a specific test or acculturation to the context of testing (Borrello & Thompson, 1985). For these reasons practice effects on neuropsychological tests tend to be most pronounced between the first and second testing occasion (Gross et al., 2015).

As for personality, conscientiousness in particular seems to predict steeper rates of improvement across cognitive testing occasions as well as higher asymptotic performance (Yeo & Neal, 2004; previous chapter in this dissertation). Conscientiousness-related influences on cognitive retest effects might sometimes alter or obscure trajectories of pathological cognitive decline (Wilson et

al., 2015). The previous chapter in this dissertation found that reserve (premorbid IQ) related to differences in switch cost and within-occasion response speeding at the first testing occasion. In contrast, conscientiousness related to differences at baseline and predicted a steeper rate of across-occasion gains.

Retest-related improvement in cognitive performance may indeed be a useful and easily-acquired marker of underlying neural function among older adults. However its interpretation is confounded by other individual differences, for example in reserve and conscientiousness. Corrections for age and education are routinely used to reduce their confounding influence on raw neuropsychological test scores. In the same way, the present study sought to clarify the unique relationship between across-occasion practice effects and (1) neural adaptability or (2) actuarial dementia risk above and beyond the effects of reserve and conscientiousness.

Multiscale EEG sample entropy is an electrophysiological measure of neural adaptability introduced in the first empirical study in this body of work. It has previously been used to discriminate between younger and older adults (McIntosh et al., 2014). It can also differentiate between older adults who vary in terms of dementia status (Mizuno et al., 2010) or dementia-risk status (Chapter 1 of this dissertation). In all cases, group differences emerge as timescale-specific between-person gains and losses in brain signal entropy. In some populations (*e.g.* traumatic brain injury), brain signal entropy has been used to predict features of across-trial changes in response time (McIntosh et al., 2008).

Actuarial dementia risk was determined according to the criteria laid out by Edmonds and colleagues (2015), and specifically according to the method introduced in Study 1 of this dissertation. Based on standardized neuropsychological test cutoff-scores that were adjusted for individual differences in reserve (TOPF-estimated premorbid function), individual older adults were classified as normal, subtle cognitive decline, or mild cognitive decline. In the present study, this diagnostic grouping was used as a predictor of across-occasion practice effects on the computerized cognitive

task.

The first empirical study in this dissertation revealed that older adults differing in actuarially-determined dementia risk status showed the expected timescale-specific differences in EEG entropy. The second empirical study examined differences in within- and across-occasion cognitive performance as a result of individual differences in reserve (premorbid function) and conscientiousness. The present study examined whether EEG entropy or actuarial dementia-risk status predicted differences in retest-related performance improvement, above and beyond individual differences in premorbid function and conscientiousness.

Objectives and predictions

Existing neuropsychological and neuroimaging practices are rigorous in their diagnosis and long-term tracking of neurocognitive health and disease. But in the face of increasing demand for early-dementia screening, computerized cognitive testing is emerging as a viable option. Within-person indices – such as switch cost and retest-related improvement in computerized cognitive test performance – may be particularly sensitive to losses of neurocognitive adaptability in early-pathological aging. However the relationship between these cognitive performance measures and neurocognitive adaptability is potentially obscured by personality- and reserve-related differences.

First, parameters describing each individual's resting-state EEG entropy profile were extracted. These, along with each individual's actuarial dementia-risk status, were then employed to predict retest-related performance improvement across 4 to 6 repeated computerized cognitive assessments. Then, analysis models were adjusted for individual differences in performance accuracy, premorbid IQ, and conscientiousness. This final step was done in order to determine if across-occasion practice effects relate to neural adaptability above and beyond differences in confounding demographic dimensions like reserve and conscientiousness.

For the present study, specific hypotheses were that:

(1) switch cost on a computerized rule-shifting task would be lower and across-occasion performance gains would be greater among those older adults with “younger” EEG entropy profiles (*i.e.* lower entropy intercept and more positive across-timescale entropy slope); and

(2) between-person differences in EEG entropy parameters would explain unique variance in across-occasion performance improvement, above and beyond individual differences in conscientiousness or reserve.

Study 3 Methods

Participants

See Study 1 Methods: Participants. One participant from study 1 did not complete computerized testing, leaving data from 43 participants for the analyses in this study.

Measures

Self-report, computerized testing, neuropsychological testing, and EEG measures. *See Study 1 Methods: Measures, and Study 2 Methods: Measures*.

Extraction of EEG entropy parameters for use as covariates. The first study of this sample, presented in Study 1, compared multilevel linear and nonlinear parameterizations of each individual's resting-state EEG multiscale entropy curve. The linear-timescale entropy model, which included fixed effects for intercept, linear timescale slope, and quadratic timescale slope, explained an estimated 88% of the overall variance in the entropy estimates. The linear model was selected to quantify EEG entropy for the current study because of the ease of coefficient interpretation (see Chapter 1 of this dissertation for a discussion of issues with low-dimensional quantification of multiscale EEG entropy). As such, coefficients from the linear entropy model were extracted and saved for each person; these served as level-3 (person-level) covariates in the present study. In order to simplify the analysis and interpretations, only two entropy parameters were extracted for each individual: entropy intercept

(centered at timescale = 14 ms) and linear timescale slope (increase in entropy as a function of timescale). The quadratic timescale slope was not used as a covariate in the present study. The intercept and linear slope parameters are graphically depicted in Figure 13. The average (SD) entropy intercept (centered at 14-ms timescale) was 1.083 (0.096) and the average entropy timescale slope was 0.032 (0.002) units/ms. Following extraction, values for each parameter were grand-mean centred in preparation for their use as covariates in the multilevel model.

Procedures

See Study 1 Methods: Procedures.

Design and Planned Analyses

The present study employed two person-level metrics of neurocognitive adaptability that were derived in Study 1: resting-state EEG entropy and actuarially-determined, premorbid IQ-adjusted dementia-risk status (normal = 0, subtle decline = 1, MCI = 2). The present study employed the multi-level analysis framework developed in Study 2 (3-level linear regression). As in Study 2, mean response speed at each occasion of computerized cognitive testing on the switch (number-letter) task served as the outcome of interest. The outcome was nested at 3 hierarchical levels: (1) condition (stay or switch), (2) occasion, and (3) person. There were two primary analyses. The first considered whether characteristics (intercept or slope) of individual entropy curves explained unique variance in across-occasion retest improvement on the switch task. The second posed the same question using premorbid IQ-adjusted dementia-risk status as the predictor of practice gains. In the multilevel modeling framework these are represented as cross-level interaction effects of the EEG entropy or diagnostic group covariates with testing occasion.

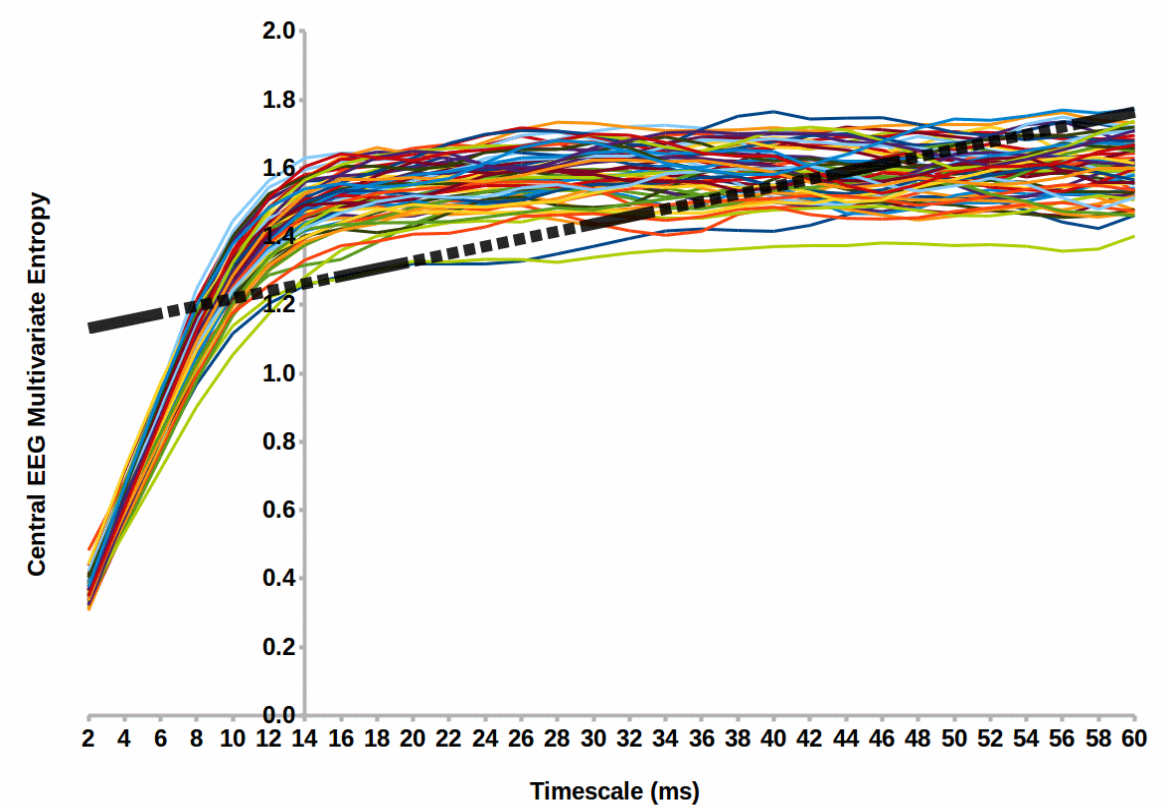

Figure 13. An example entropy plot showing the multiscale entropy curves for 60 4-second segments of resting-state EEG data (individual coloured lines) recorded over the central scalp locations (C3, Cz, C4) of a single participant. Entropy covariates were created by modeling the data (coloured lines) in terms of an intercept (timescale centred at 14 ms, the approximate inflection point) and a linear across-timescale slope (black dotted line); the quadratic timescale slope (not shown) was also included in the entropy model but not extracted for use as a covariate in the present study.

In a subsequent step, the model estimates were adjusted for individual differences in response accuracy by including interaction terms of person-mean accuracy by occasion and task condition (as in Study 2). Finally, to determine whether EEG entropy or diagnostic group covariates could explain unique variance in across-occasion performance changes, models were adjusted for differences in premorbid function and conscientiousness; the relationship between retest-related performance improvement and the covariates was compared to that for models lacking these latter covariates. Models in the present study accounted *a priori* for findings from Study 2 of this dissertation. In particular, the effect of reserve (TOPF-estimated premorbid function) was estimated for the intercept

(baseline occasion) only. However, conscientiousness was allowed to exert an effect on baseline performance as well as to interact with occasion number.

All data manipulation and analysis was performed in *R* (R Core Team, 2016). Multilevel linear models were estimated using the *lme4* package (Bates, Maechler, Bolker, & Walker, 2015).

Study 3 Results

Coefficients for unconditional models (including only occasion and task condition terms) developed in Chapter 2 are presented in Table 13 for convenience. These models served as the baseline framework against which to judge the effects of resting-state EEG entropy on across-occasion cognitive performance.

Table 13. Summary of multilevel model fixed effect coefficients for baseline models of response accuracy and speed.

	Response Accuracy			Occasion-Mean RS		
Fixed Effect	*b*	SE	*P*	*b*	SE	*P*
Intercept						
Intercept	**92.45**	**1.50**	**<0.01**	**1.00**	**0.02**	**<0.01**
Switch cost	**-1.24**	**0.42**	**<0.01**	**-0.32**	**0.02**	**<0.01**
Occasion						
Intercept	**1.04**	**0.47**	**0.03**	**0.07**	**0.01**	**<0.01**
Switch cost	-0.20	0.16	0.20	-0.01	0.01	0.06
Model Deviance	2953.5			-459.2		

b = unstandardized regression weight (slope)
SE = standard error
RS = Response speed

Effects of response accuracy

With person-mean response accuracy included as a level-3 covariate, the response speed model intercept was 1.04 s^{-1} (RT = 962 ms). There was a significant main effect of occasion, where response speed tended to improve by about 0.06 units per occasion. Response speed was significantly slowed on

switch relative to stay trials (the switch cost) by 0.33 s^{-1} at baseline, but the occasion by condition interaction effect was only marginally significant (*i.e.* the occasion-wise linear increase in response speed did not differ for switch relative to stay trials). There were also significant interactions with person-mean response accuracy. Both the task condition by response accuracy and condition by accuracy by occasion interaction terms were significant. The 2-way interaction (accuracy by condition) suggested that individuals higher in (person-mean) response accuracy had a reduced switch cost at baseline. In addition, the 3-way interaction (accuracy by condition by occasion) suggested that higher person-mean response accuracy was associated with disproportionately greater across-occasion switch cost reduction.

Effects of resting-state EEG entropy covariates

Model coefficients are summarized in Table 14. Neither of the EEG entropy parameters (entropy intercept at 14-ms timescale or across-timescale entropy slope) predicted any difference in response speed (no significant main or interaction effects). Although, there were marginally significant 2- and 3-way interactions of entropy intercept: with accuracy, and with accuracy by occasion. The 2-way interaction trend suggested that those with the fastest performance at baseline tended to have both higher response accuracy and higher EEG entropy intercepts. The 3-way interaction trend suggested an attenuation of the this accuracy-entropy interaction across subsequent occasions (*i.e.* 2-way effect most prominent at first testing session).

The model intercept and linear occasion terms were then adjusted for conscientiousness and premorbid function and for conscientiousness, respectively. Neither of these covariates predicted significant difference in response speed at baseline; however, conscientiousness predicted a unique increase in the across-occasion rate of response speed increase (expected because of findings in Chapter 2).

After this adjustment with conscientiousness and premorbid function, a significant interaction

emerged involving the across-timescale increase in EEG entropy (across-timescale slope). Between-person elevations in the slope of across-timescale EEG entropy predicted greater across-occasion increases in response speed, especially among individuals who were higher in response accuracy (Figure 14). Contrary to predictions, this effect did not differ systematically as a function of task condition. Thus, with respect to their own baseline performance, individuals higher in conscientiousness or with a steeper across-timescale EEG entropy slope showed more retest-related global response speeding, especially those individuals with better response accuracy.

Effects of actuarial diagnostic group covariate

Model coefficients are reported in Table 15. The only significant effect involving the actuarial dementia-risk group covariate was an interaction with task condition and response accuracy. This effect suggested that, adjusting for differences in response accuracy, individuals at higher actuarial risk for dementia showed an exaggerated switch cost at the baseline testing session. There was no interaction of actuarial diagnostic group with occasion (*i.e.* group did not predict the linear practice effect).

As with the model including EEG entropy covariates, the model intercept and linear occasion terms were then adjusted for conscientiousness and premorbid function and for conscientiousness, respectively. And, as with the EEG covariate model, neither of these covariates predicted significant difference in response speed at baseline. Again, conscientiousness predicted a unique increase in the across-occasion rate of response speed increase. However after this adjustment the results – specifically the interaction effect involving diagnostic group – were essentially unchanged.

Table 14. Summary of multilevel model fixed effect coefficients for predictive models of RS change.

	EEG Predictors Only			EEG Predictors + TOPF and Conscientiousness		
Fixed Effect	*b*	SE	*P*	*b*	SE	*P*
Intercept						
Intercept	**1.013**	**0.023**	**<0.01**	**1.040**	**0.032**	**<0.01**
PM-Accuracy	0.006	0.003	0.09	0.005	0.003	0.11
Condition						
Intercept	**-0.332**	**0.018**	**<0.01**	**-0.332**	**0.018**	**<0.01**
PM-Accuracy	**-0.010**	**0.003**	**<0.01**	**-0.010**	**0.003**	**<0.01**
Occasion						
Intercept	**0.067**	**0.007**	**<0.01**	**0.063**	**0.006**	**<0.01**
Condition	-0.012	0.007	0.07	-0.013	0.007	0.06
PM-Accuracy	0.001	0.001	0.36	0.002	0.001	0.14
Condition*PM-Accuracy	**0.003**	**0.001**	**<0.01**	**0.003**	**0.001**	**<0.01**
Premorbid function						
Intercept	-	-	-	-0.045	0.042	0.30
Conscientiousness						
Intercept	-	-	-	-0.004	0.004	0.34
Occasion	-	-	-	**0.004**	**0.001**	**<0.01**
EEG Entropy: 14-ms Intercept						
Intercept	0.034	0.270	0.90	0.030	0.276	0.91
Condition	0.161	0.219	0.46	0.159	0.219	0.47
Occasion	0.039	0.076	0.61	-0.003	0.071	0.96
PM-Accuracy	**0.052**	**0.027**	**0.06**	0.041	0.028	0.14
Condition*Occasion	-0.005	0.080	0.95	-0.002	0.080	0.97
Condition*PM-Accuracy	0.015	0.024	0.54	0.016	0.024	0.51
Occasion*PM-Accuracy	**-0.016**	**0.009**	**0.07**	-0.012	0.008	0.13
Condition*Occasion*Accuracy	0.001	0.009	0.88	<0.001	0.009	0.92
EEG Entropy: Timescale Slope						
Intercept	1.851	13.288	0.89	2.083	0.137	0.88
Condition	-9.588	10.592	0.37	-9.395	0.106	0.38
Occasion	-2.132	3.681	0.56	-0.158	3.416	0.96
PM-Accuracy	-1.509	2.292	0.51	-1.766	2.237	0.45
Condition*Occasion	-3.325	3.798	0.38	-3.503	3.797	0.36
Condition*PM-Accuracy	-0.161	1.949	0.93	-0.190	1.949	0.92
Occasion*PM-Accuracy	0.862	0.672	0.20	**1.338**	**0.641**	**0.04**
Condition*Occasion*Accuracy	0.231	0.716	0.75	0.234	0.715	0.74

b = unstandardized regression weight (slope)
SE = standard error
RS = response speed
PC = person-mean-centred
PM = person-mean

Table 15. Summary of multilevel model fixed effect coefficients for predictive models of RS change.

	Dementia-Risk Only			Dementia-Rick + TOPF and Conscientiousness		
Fixed Effect	*b*	SE	*P*	*b*	SE	*P*
Intercept						
Intercept	**1.054**	**0.036**	**<0.01**	**1.071**	**0.037**	**<0.01**
PM-Accuracy	0.009	0.006	0.12	0.006	0.006	0.27
Condition						
Intercept	**-0.320**	**0.028**	**<0.01**	**-0.320**	**0.028**	**<0.01**
PM-Accuracy	-0.001	0.005	0.80	-0.001	0.005	0.80
Occasion						
Intercept	**0.069**	**0.010**	**<0.01**	**0.063**	**0.009**	**<0.01**
Condition	-0.004	0.010	0.67	-0.004	0.010	0.68
PM-Accuracy	<0.001	0.002	0.65	<0.001	0.002	0.73
Condition*PM-Accuracy	0.003	0.002	0.16	0.003	0.002	0.16
Premorbid function						
Intercept	-	-	-	-0.040	0.044	0.37
Conscientiousness						
Intercept	-	-	-	-0.004	0.004	0.32
Occasion	-	-	-	**0.003**	**<0.001**	**<0.01**
IQ-Adjusted Dementia-Risk Grouping						
Intercept	-0.038	0.025	0.13	0.030	0.027	0.25
Condition	-0.012	0.020	0.53	0.012	0.020	0.53
Occasion	-0.001	0.007	0.87	0.002	0.007	0.76
PM-Accuracy	-0.003	0.003	0.39	<0.001	0.003	0.78
Condition*Occasion	-0.006	0.007	0.35	-0.007	0.007	0.35
Condition*PM-Accuracy	**-0.006**	**0.003**	**0.04**	**-0.006**	**0.003**	**0.03**
Occasion*PM-Accuracy	0.001	0.001	0.20	<0.001	0.001	0.67
Condition*Occasion*Accuracy	<0.001	0.001	0.82	<0.001	0.001	0.86

b = unstandardized regression weight (slope)
SE = standard error
RS = response speed
PC = person-mean-centred
PM = person-mean

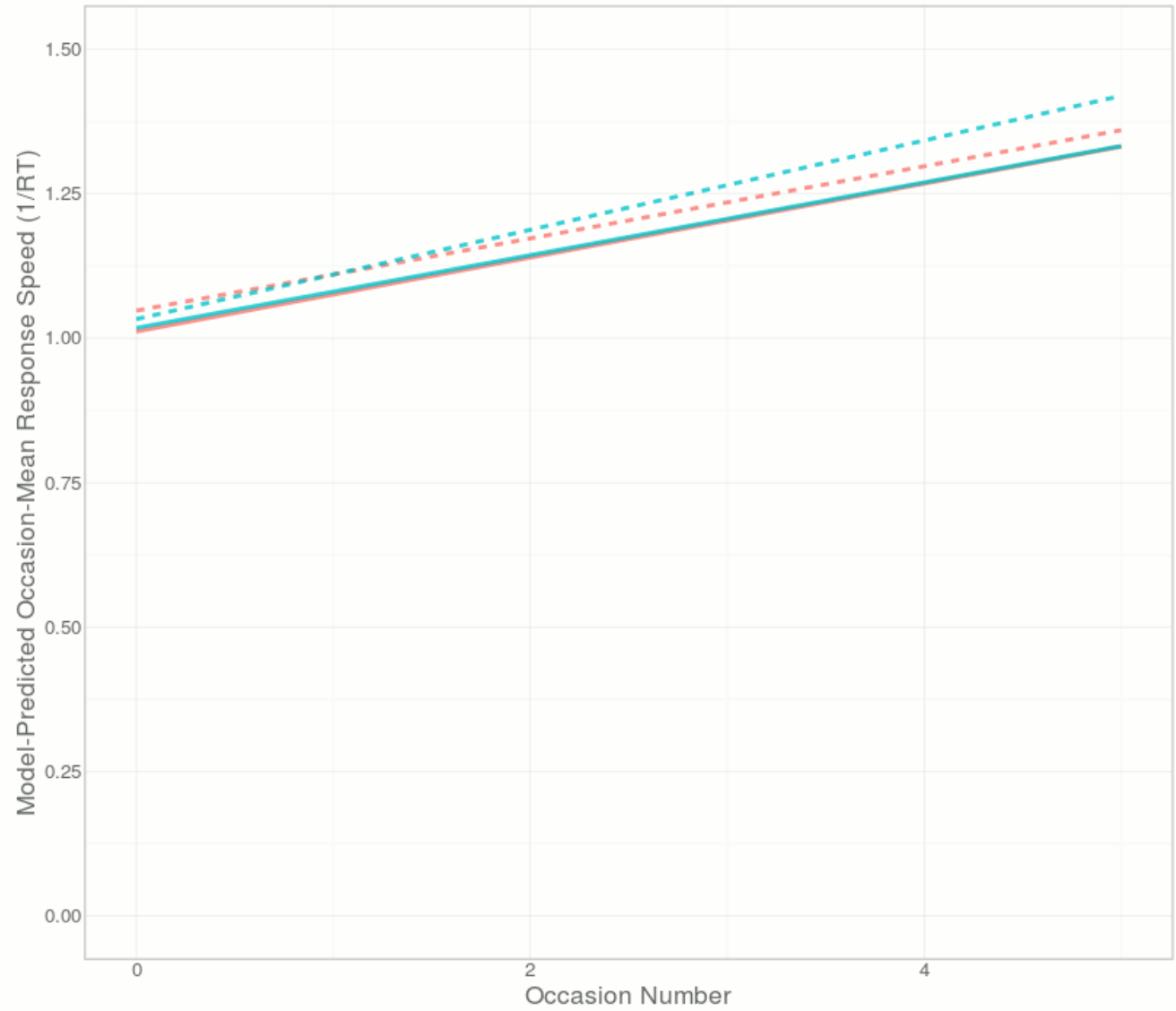

Figure 14. Across-occasion response speed trajectories demonstrating 3-way interaction effect for hypothetical individuals at the 25th and 75th percentiles for person-mean response accuracy (25th = solid; 75th = dotted) and the linear across-timescale EEG entropy slope (25th = red; 75th = blue).

Study 3 Discussion

This final empirical study was undertaken to demonstrate the potential for intensive computerized cognitive testing protocols to address a growing worldwide need for early-dementia screening. To recapitulate, the present study illustrated the relationship of cognitive performance characteristics on a computerized switching task with clinical and laboratory measures of

neurocognitive adaptability. In the first case, actuarial dementia-risk group (normal, subtle decline, MCI) as determined by premorbid IQ-adjusted performance on standardized neuropsychological tasks predicted a difference in switch cost at the baseline testing session. In the latter, EEG entropy profiles predicted individual differences in the slope of across-occasion cognitive practice effects.

This final of three studies emphasizes again the multi-dimensional, multi-timescale nature of neurocognitive adaptability. It showed that a dementia-risk diagnosis based on performance on a 2-hour battery of standardized neuropsychological tasks predicted individual differences in baseline switch cost, a component of executive function (Kiesel et al., 2010). Both global neuropsychological performance and switch cost can be conceptualized as cognitive flexibility, or adaptability at the timescale of seconds to minutes. Actuarial dementia-risk did not relate to across-occasion differences in computerized cognitive task performance that are reflective of neurocognitive plasticity: adaptability at the timescale of days to weeks (Lövdén et al., 2010). However, the direct measure of neural adaptability – EEG entropy – did predict differences in retest-related performance improvement. Thus, resting-state EEG entropy (subsecond-scale adaptability) may index a latent capacity for neurocognitive plasticity that is difficult to detect using performance-based tests administered at a single occasion.

Cognitive *screening* has neither the scope, detail, or integration of a fell-fledged neuropsychological *assessment*; nor does it serve the same purpose (Block et al., 2017). Use of computers for cognitive screening or testing in clinical neuropsychological practice remains controversial, but few of the barriers to its adoption are unique to computerized testing (Gates & Kochan, 2015). In fact, many of these issues have contributed to a generalized, decade-long stability in the selection of neuropsychological tests (Rabin et al., 2016). It behooves the field of neuropsychology to overcome feasibility- and validity-related barriers to the incorporation of computerized testing in routine clinical practice. The utility of computerized testing as a population-wide dementia screener

depends on its relation to neural adaptability above and beyond other factors that are expected to vary in the wider older adult population. The current study thus considered the following question: are switch cost and retest-related gains in performance on a computerized attention-shifting task related to individual differences in resting-state EEG entropy (a metric of neural adaptability) or actuarial dementia risk-status (based on standardized clinical measures of cognition), above and beyond differences in reserve (premorbid function) and conscientiousness?

Breakthroughs driven by laboratory computerized cognitive assessment have driven refinements in the conceptualization of neurocognitive function as a time-varying construct (Monto, Palva, Voipio, & Palva, 2008; Palva et al., 2013; Palva & Palva, 2012; Tse, Balota, Yap, Duchek, & McCabe, 2010; Mulligan, Smart, & Ali, 2016). Recently, a relative attenuation of retest-related performance gains (practice effects) has been shown to reflect the losses in neurocognitive adaptability that accompany aging and dementia (Darby, Maruff, Collie, & McStephen, 2002; Duff, Horn, Foster, & Hoffman, 2015; Duff, Beglinger, Moser, Schultz, & Paulsen, 2010; Duff, Foster, & Hoffman, 2014; Duff, Callister, Dennett, & Tometich, 2012; Duff, Chelune, & Dennett, 2012). However, factors beyond neural adaptability *per se*, such as personality and reserve, can also impact retest-related performance gains (Duff, Beglinger, Moser, Paulsen, et al., 2010; Kurtz, Mogle, Sliwinski, & Hofer, 2013; Lemay, Bédard, Rouleau, & Tremblay, 2004; Wilson et al., 2015; Yang, Krampe, & Baltes, 2006; Yang, Reed, Russo, & Wilkinson, 2009; Yeo & Neal, 2004).

Current conceptualizations of preclinical dementia are based on interpretation of metrics of cognitive performance summed across trials and administered at a single occasion of testing (Edmonds et al., 2015). As a result, many standardized neuropsychological test scores are both very reliable and insensitive to processes of adaptability that unfold at timescales greater than a few minutes. Consequently, in the current study, actuarial diagnostic group related to differences in cognitive flexibility (switch cost) at the initial testing occasion but failed to predict differences in across-occasion

improvement. However, one of the two EEG entropy metrics (across-timescale increase in entropy) did indeed show a positive association with retest-learning. After adjusting for differences in response accuracy, those individuals higher in across-timescale EEG entropy tended to show a generalized increase in response speed across occasions. Including the linear across-timescale increase in EEG entropy reduced the residual response speed variance by about 4% (*pseudo-*R^2 = 0.039). This suggests that resting-state EEG entropy may be a useful proxy for neurocognitive plasticity that can be acquired within minutes rather than days or weeks; however, a more refined quantification of EEG entropy may yield a stronger association with cognitive plasticity and hence be of greater clinical value.

In general, this finding corroborates and complements findings derived from previous research related to practice effects in the context of aging and dementia. In brief, improvements in cognitive performance across multiple occasions are dampened and qualitatively different in older relative to younger adults (Brose, Schmiedek, Lövdén, & Lindenberger, 2012; Whitson et al., 2012). Nonetheless healthy aging is characterized by a relative preservation of neurocognitive adaptability (*i.e.* an individual's capacity to learn and demonstrate performance improvement with retest) that is lost with increasing dementia pathology. Gains in cognitive performance with practice are proportionately attenuated among individuals with MCI (Darby et al., 2002) or AD (Fernández-Ballesteros et al., 2012). Practice effects moreover reflect resting global brain metabolism (Duff et al., 2015), *in vivo* amyloid burden (Duff et al., 2014), and differences in hippocampal subfield volumes (Engvig et al., 2012). In the context of prior research, the results of the current series of studies compel a reconceptualization of preclinical dementia to include measures sensitive to a wider spectrum of adaptability mechanisms. If retest learning and neural metrics of adaptability provide unique diagnostic information, then they should be considered in routine screening protocols for early dementia risk.

The present study suggests that older adults with relative losses in retest-related cognitive performance gain also show losses in resting-state brain signal entropy. In particular, practice effects

were greater for individuals with a greater across-timescale entropy slope. This is consistent with previous research suggesting that brain signal entropy at coarser (longer) timescales is selectively prone to decay with age (McIntosh et al., 2014; Sleimen-malkoun et al., 2015) and dementia (Mizuno et al., 2010; J.-H. Park et al., 2007). Study 1 of this dissertation revealed that, relative to normal participants, those with subtle decline had reductions in fine-grained EEG entropy; those with MCI had reduced entropy in both fine- and coarse-grained timescale bands. The mechanisms for timescale-specific losses in brain signal entropy have yet to be conclusively identified. Brain signal entropy at specific timescales has been hypothesized to reflect changes in structural and functional interactions between neuronal populations (Honey et al., 2007; Sporns et al., 2009). In aging, it may be related to a shift in the balance between long-range and local processing (McIntosh et al., 2014).

Thus, resting-state multiscale EEG entropy shows promise as an easily-acquired adjunct to current best practices in the clinical assessment of older individuals at risk for dementia. The link between neural adaptability and retest-learning was evident in the present study despite the relatively crude approach to the quantification of multiscale EEG entropy that was employed. In brief, this involved modeling each person's EEG entropy curve in terms of an intercept and linear across-timescale slope. Artificial intelligence approaches such as machine learning may be better suited to extract the most stable/salient features from the multiscale entropy curves of a large number of individuals (Bosl, Tierney, Tager-Flusberg, & Nelson, 2011). Unfortunately, that approach was not feasible in the current study owing to sample-size and technical constraints. EEG researchers should consider coordinated analysis of the extensive repositories of resting-state EEG recordings that are already available. For instance, existing EEG datasets could be subjected to a common, automated multiscale entropy analysis protocol such as that presented in the first empirical study in this dissertation. The marshaling of such “big data” would accelerate the refinement and clinical application of resting-state multiscale EEG entropy-based metrics of neural adaptability.

Crucially, the relationship between EEG entropy and retest improvement reported above emerged only after adjustment for individual differences in conscientiousness. This confirms the beneficial effect of conscientiousness on retest-related performance improvement (Yeo & Neal, 2004). It also illustrates that both conscientiousness and neural adaptability exert a unique positive influence on cognitive practice effects.

There is a conceptual overlap between conscientiousness and dimensions of executive function (Tse et al., 2010). Similar to the lifespan trajectory of executive functioning (Hedden & Gabrieli, 2004), recent studies of longitudinal change in personality suggest that conscientiousness follows an inverted-U pattern, peaking sometime in the 4th to 6th decade (Marsh, Nagengast, & Morin, 2013; Srivastava et al., 2003). Older adults who are higher in conscientiousness show slower rates of decline on tests of executive function (Caselli et al., 2016). In addition, levels of conscientiousness predict orbitofrontal and ventral/dorsal-lateral prefrontal cortical volumes and a reduced rate of cerebral white matter volume loss (Jackson, Balota, & Head, 2011). What is more, those higher in conscientiousness would have been more likely to apply explicit meta-cognitive strategies to encourage across-session performance gains (Ratcliff, 2006; Yeo & Neal, 2004). Considering the significant executive demands of the switch task used in the present study, it is therefore not surprising that those higher in conscientiousness had an advantage.

Conscientiousness was included in the current study in order to investigate and illustrate its importance as a corrective factor. That is, its inclusion in the statistical models served to increase the sensitivity of the practice effect to individual differences in EEG entropy. However previous research highlights the importance of conscientiousness as a cognitive-protection factor in the context of dementia. Higher conscientiousness reflects a reduced risk of Alzheimer disease (Wilson et al., 2007). It also buffers against the cognitive decline-accelerating effects of Lewy bodies (Wilson et al., 2015) and genetic (APOE ε4) risk for Alzheimer disease (Caselli et al., 2016). In fact, worsening

dementia may be preceded by longitudinal declines in conscientiousness (Donati et al., 2013).

The involvement of conscientiousness also implies that there are multiple sources of individual difference in across-occasion learning. Neural adaptability at certain timescales, directly assessed via EEG, might thus be conceived as a metric of "brain reserve" (Stern, 2009a). In contrast, conscientiousness is thought to reflect "motivational reserve" as well as to contribute to the development of "cognitive reserve" (Forstmeier & Maercker, 2008), for example through the pursuit of higher education (Vermetten, Lodewijks, & Vermunt, 2001). The studies cited in the two preceding paragraphs suggest that conscientiousness may also index brain reserve. Moreover, conscientiousness is easily and reliably quantified among older adults with a brief self-report inventory. Along with age and education, conscientiousness may prove a crucial factor for transforming raw practice effect scores into clinically meaningful indices of neurocognitive adaptability.

Limitations and Future Directions

This study highlights the utility of multi-method assessment in conceptualization of neurocognitive aging and preclinical dementia-risk. Self-report, neuroimaging, and standardized neuropsychological performance data are all routinely integrated in the clinical neuropsychological assessment of an individual older adult. However use of computers for the measurement of cognition remains controversial. There are a number of professional risks and opportunities inherent in the adoption of computerized cognitive metrics. Various private corporations as well as research and health sciences centers have recently created computerized assessment screening batteries for older adults. However the field is in its infancy; high-quality data are in short supply (Gates & Kochan, 2015).

The present study demonstrates the potential value of using retest-learning as an index of neurocognitive adaptability using one particular attention-shifting task. However, as with non-computerized cognitive testing, the ideal task (or battery) for a given clinical scenario should be dictated by the individual or population in question (Lezak et al., 2012). Likewise, the ultimate utility

of computerized assessment will depend on the availability of normative data to correct raw scores for expected differences due to age, education, reserve, and personality/motivation.

Widespread adoption of a circumscribed set of computerized neuropsychological test batteries would moreover allow for the development of region-specific normative data. In fact, computerized test data can be easily collected and aggregated across sites (*e.g.* clinics, hospitals, private practices) on secure, publicly-funded servers in order to allow the development of perpetually up-to-date normative data that can be stratified by region or demographic dimension of interest. The availability of "dynamic norms" for computerized neuropsychological test batteries would ensure that individuals seen in clinic are compared to the most appropriate and complete normative data available. Dynamic normative datasets would also help to detect aggregate changes in subpopulations represented within the dataset, or in the dataset as a whole (*e.g.* "real-time Flynn effect").

For broader impact, future studies should incorporate remote assessment through internet- or mobile-based technologies. This could serve to reduce economic and geographic bias in the recruitment of participants. This would facilitate the assessment of cognition in ecological context and alongside other important indicators. For instance, mobile technology is increasingly able to sample data relevant to neurocognitive function through a diversity of modalities. These include the monitoring of movement/activity (accelerometers), performance (human-computer interfaces), self-report (*e.g.* for measurement of conscientiousness), audio, video, and even biometrics such as cardiovascular and brain dynamics. All of these have the potential to show time-varying, within-person associations with neurocognitive function and will help to refine diagnostic algorithms (Brose, Schmiedek, Lövdén, & Lindenberger, 2012; Gamaldo, Weatherbee, & Allaire, 2008; Gamaldo, Allaire, & Whitfield, 2010; Sliwinski, Smyth, Hofer, & Stawski, 2006; Weatherbee, Gamaldo, & Allaire, 2009; Mulligan, Smart, Segalowitz, & MacDonald, *in press*).

Conclusion

This final empirical chapter suggests that intensive computerized cognitive testing represents a feasible, economically-viable means for population-level screening of older adult neurocognitive health. With further study, reliable and valid computerized testing indices can be developed to flag for further assessment those who may be at a heightened risk of neurodegenerative disease. In particular, this study showed that between-person differences in neural adaptability discernible by direct measurement of resting-state EEG activity were also reflected in retest-related improvements in cognitive performance. The current chapter highlighted the practical significance of this finding. The meta-discussion comes next and concludes the dissertation. In the final section it will be argued that the findings in this dissertation compel a reconsideration of existing theories and clinical practices related to neurocognitive adaptability in aging and preclinical dementia.

General Discussion

Typical aging is accompanied by a gradual erosion of neurocognitive adaptability. This fact is implicit in cultural norms related to retirement and to increasing exogenous support for completing tasks necessary for daily living. However, older adults on pathological neurocognitive aging trajectories show signs of deviation from normal aging trajectories decades prior to diagnosis (Steinerman et al., 2010). Even years prior to obvious cognitive impairment, biological and functional declines are evident among those who will eventually develop dementia (Di Carlo et al., 2016; Luck et al., 2011).

For the next few decades there is an expectation of greater and greater numbers of older adults in Canada, and an expected increase in the incidence of dementia (Alzheimer Society of Canada, 2010). It is imperative that better screening tools are developed to detect the earliest, most subtle signs of neurocognitive dysfunction. In order to develop novel, targeted interventions, individual older adults must be identified as early as possible following their divergence from a healthy aging trajectory. The current body of work is a step in that direction. It focused on detecting signs of very subtle losses of neurocognitive adaptability which may be among the earliest signs of prodromal dementia. The three empirical studies presented above afford multiple, complementary perspectives on the neurocognitive adaptability of a sample of healthy older adults. The impetus for this series of studies was therefore twofold: (1) to further the development of economically-feasible neurocognitive health screening protocols, and (2) to better characterize the early losses of neurocognitive adaptability that may portend further pathological neurocognitive aging. In so doing, this body of work also contributes to a unified theory of neurocognitive adaptability in aging by integrating perspectives from clinical neuropsychology, neuroscience, and lifespan development.

Study 1 revealed that older adults with neuropsychological performance indicators of subtle

cognitive decline also showed subtle, timescale-specific differences in their brain's resting EEG adaptability. For the actuarial ascertainment of preclinical dementia-risk, TOPF-estimated premorbid IQ was used to adjust standardized neuropsychological test cutoff scores in order to approximate each participant's cognitive decline with respect to self. Study 2 illustrated the differentiable effects of individual differences in estimated premorbid function and conscientiousness on within- and across-occasion improvement on a computerized attention-shifting (switch) task. Finally, Study 3 demonstrated the unique promotional effects exerted by conscientiousness and resting EEG adaptability on the rate of across-occasion improvement in cognitive performance. It also showed that dementia-risk status as defined by actuarial neuropsychological performance criteria was related to cognitive flexibility at the baseline assessment, but not to across-occasion improvement in performance.

The multi-method studies described herein highlighted distinct measures of neurocognitive adaptability at two within-person timescales: subsecond (EEG entropy) and day/week (retest learning). Also featured was a cross-sectional measure of neurocognitive adaptability (self-rated conscientiousness) that is relatively stable within-persons at the scale of decades (Marsh et al., 2013; Srivastava et al., 2003). The assessment modalities (scalp electrophysiological, computerized cognitive testing, self-report scale) were chosen specifically because they can be deployed remotely, at population-scale, and at low-cost as compared to in-person clinical neuropsychological testing. For this reason the framework presented herein demonstrates a viable direction for the future growth of neuropsychology that would help meet the needs of older Canadians, irrespective of geographical constraints (Muttitt et al., 2004).

Understanding neurocognitive adaptability is crucial for supporting older adult health

In sum, existing evidence suggests that the loss of neurocognitive adaptability that comes with advanced age reflects a combination of normal age-related changes and pathological changes (*i.e.* secondary to some disease process) (Charles & Carstensen, 2010; Raz, 2009).

From a clinical or functional perspective, neurocognitive adaptability allows an individual to adjust their behaviour and physiology to suit the environmental demands and goals of the moment (Tuokko & Smart, 2014). Several researchers have produced useful theories that capture parts of the spectrum of mechanisms implicated in older adult neurocognitive adaptability. For instance, in his theory of reserve, Stern (2009, 2012) posits that early enriching experiences (most often quantified by years of education) predispose individuals to neurocognitive health. Although “reserve” shares conceptual similarities with “adaptability”, the theory is largely agnostic with regards to what reserve is or how exactly it is bolstered through experiences such as education (Morcom & Johnson, 2015). Baltes' (1997) theory of selective optimization and compensation (SOC) provides a framework to classify and study relationships between various classes of explicitly-described psychological (meta-cognitive) mechanisms thought to underlie adaptability. SOC specifically addressed those related to (1) selecting a manageable set of salient goals, (2) focusing available energy and resources on the achievement of those goals, and (3) using strategies to counteract cognitive limitations (*e.g.* using an appointment book to compensate for declining memory).

Horn (1972) was perhaps the first to provide a unifying formulation of neurocognitive adaptability unfolding over time as “a pattern of covariance among distinct processes of memory, reasoning, abstracting, etc” (Horn, 1972, p. 162). He recognized that treating change and fluctuation within persons, over time as “measurement error” was an over-simplification. On the contrary, the stability or rate of change/fluctuation in a given measure actually hints at the processes underlying it.

A recent theoretical formulation of neurocognitive adaptability by Lövdén, Bäckman, Lindenberger, Schaefer, & Schmiedek (2010) linked Horn's pioneering work to emerging neuroscientific evidence. Their framework highlights the distinct neural mechanisms that operate to support behavioural adaptations of two different classes. Flexible adaptations are more rapid/reversible compared to plastic adaptations, which are slower and more persistent. Thus changes in behaviour –

whether immediate or prolonged – are mirrored by some change in nervous system structure or function. Considering flexibility and plasticity as distinct categories may be misleading. Rather, *flexibility* and *plasticity* are perhaps better understood as anchor points at the ends of a continuum of adaptability mechanisms ordered according to the timescale at which they are expressed.

Environmental parameters vary at multiple timescales. Likewise, evidence of older adult neurocognitive adaptability has been found at many different timescales. Indicators of these adaptations encompass a broad array of physiological mechanisms and behavioural homologues (see Table 1 on p. 4 of this document). A benefit of the timescale continuum approach is that it allows an intuitive appreciation for the variety of neural and behavioural manifestations of adaptability. It also provides a framework within which to organize new discoveries related to neurocognitive adaptability, regardless of mechanism or timescale.

Neurocognitive aging trajectories emerge from the interaction of adaptive mechanisms at various timescales with age- and disease-related decline processes. The current series of studies employed various methods to capture estimates of neurocognitive adaptability at distinct timescales. For instance, Study 1 capitalized on recent developments related to (1) the diagnosis of subtle cognitive decline (an indicator of very early-stage prodromal dementia) according to actuarial neuropsychological performance-based criteria and (2) an electroencephalographic (EEG) marker of neural adaptability (multiscale sample entropy). The latter measure is thought to reflect the subsecond-timescale adaptability of the brain (Garrett et al., 2013). In contrast, the former approach involved a comparison of each individual's current neuropsychological performance to an “estimated peak level” (*i.e.* premorbid level) as a proxy measure for within-person declines in neurocognitive adaptability at the timescale of decades/years (Rentz et al., 2004). In line with general expectations, individuals with the clinical classification of subtle cognitive decline (relative to their own estimated premorbid level) showed timescale-specific changes in their multiscale EEG entropy profiles relative to more- or less-

impaired participants. This finding suggests that EEG sample entropy – especially at shorter timescales – is sensitive to the earliest detectable stages of pathological cognitive aging. It also shows the inter-relation of neurocognitive adaptability markers derived via multiple methods targeting the two ends of the adaptability timescale continuum.

Practice-effect or brain-physiological measures may thus be sensitive to early, subtle declines in neurocognitive adaptability that are not captured by many current standard neuropsychological tests. It is already known that evidence of accumulating neuropathology consistently anticipates within-person declines in cognitive performance (Dodge et al., 2014; Hayden et al., 2011). In the same way, neuroimaging and/or practice effect data can be used as follow-up testing for older adults who present with subjective cognitive decline (SCD; Jessen, 2014). These individuals report self-perceived declines in their own cognitive function but score in the expected range on standardized neuropsychological testing. Prichep and colleagues (2006) showed that prospective declines in cognitive performance among a sample of older adults with SCD (subjective but no objective cognitive impairment) could be predicted from spectral-power features of their resting-state EEG recorded 7 to 9 years prior. Thus, the optimal preclinical dementia screening battery is likely to include multiple testing modalities in order to provide timely clinical care tailored to each older individual's biopsychosocial and environmental context.

Next, Study 2 adopted a wholly different perspective on neurocognitive adaptability. The study considered the covariation of proxy (conscientiousness and premorbid function) with direct-observation methods (manifest performance improvement within and between testing occasions) of adaptability assessment. In line with prior research, performance differences due to reserve/premorbid function were present only at the first testing occasion but did not predict differences in the rate of across-occasion performance improvement. On the other hand, those higher in conscientiousness tended to perform better at baseline and to show more improvement in performance across occasions. This latter

finding replicates previous findings. However it also makes a novel contribution in that it shows the differential sensitivity of conscientiousness and premorbid function to distinguishable features of manifest behavioural adaptability. Again, this study illustrates the utility of considering multiple methods targeting distinct timescales to help illuminate the nature of neurocognitive adaptability. Clinical neuropsychologists can use insight gained through multiple metrics of adaptability to better understand the relationship between clinical and day-to-day functional status.

The third and final study was both an agglomeration of the previous two and an assessment of the feasibility and utility of using multi-method protocols for population-wide neurocognitive health screening. From this perspective the main finding was encouraging: across-occasion improvements in cognitive performance were uniquely related to individual differences in EEG entropy, above and beyond individual differences due to conscientiousness. In fact, the relationship between resting-state EEG entropy and retest learning on the computerized cognitive task was not evident until statistical adjustments for conscientiousness were made. In other words, both adaptability at the timescale of decades/years (conscientiousness) and of subseconds (multiscale EEG entropy) related uniquely to adaptability at the scale of weeks/days (retest learning). Also, this study also showed that actuarial preclinical dementia-risk, determined by premorbid IQ-adusted cutoffs on standardized neuropsychological tasks, was sensitive to individual differences in flexibility at baseline but not in plasticity (across-occasion improvement in performance). These finding should guide future development of standardized computerized cognitive tests. In addition to demographic variables (age, education), stratifying normative data by level of conscientiousness may improve the sensitivity and utility of new measures. The present body or work suggests that this may be especially relevant when those instruments are intended for intensive (short-term longitudinal) assessment.

Taken together, these studies serve to underline the complicated inter-relationships that exist between measures derived from diverse conceptualizations of neurocognitive adaptability. The findings

reported above therefore have both theoretical and practical (clinical) significance.

Theoretical and practical implications

This series of studies provides novel evidence relevant to the theoretical underpinnings of neurocognitive adaptability. In particular, the findings detailed in preceding chapters provide convergent evidence that resting-state brain electrical entropy, retest-related improvement in cognitive performance, and conscientiousness (measured via self-report) reflect a common underlying capacity for neurocognitive adaptability. This is significant because these techniques measure adaptability via different means – avoiding the pitfalls of shared common method variance (Avolio, 1991; Brannick et al., 2010; Doty & Glick, 1998; Podsakoff et al., 2003, 2011). They also consider different points along the timescale continuum. For example, the third study showed that individual older adults with greater across-timescale increases in EEG entropy (an index of subsecond neurocognitive adaptability) tended to show greater improvement in cognitive performance at retest intervals of days/weeks. Thus, a link was found between neural flexibility and cognitive plasticity. This relationship was above and beyond differences in self-rated conscientiousness (an index of adaptability that changes on the timescale of years/decades) (Marsh et al., 2013; Srivastava et al., 2003).

With this partial convergence of multiple metrics of adaptability, it is easy to lose sight of the complexity and variety of adaptability mechanisms. To take behavioural manifestations of adaptation as an example, it is plain to see that certain adaptability processes are selectively impaired/preserved with particular clinical presentations. For example, while some individuals may have good “immediate adaptability” (*i.e.* attention, immediate recall), their longer-term (minutes, hours, days) adaptability (*e.g.* learning) may be meager. In other cases (*e.g.* moderate dementia), basic adaptations in the moment may be almost totally lacking. However, among these individuals behaviour can often still be shaped over the longer term using consistent environmental structure and implicit learning. This reflects the fact that attention and memory, broadly speaking, are related to multiple dissociable neural

processes – some shared and some unique to one or the other (Horn, 1972; Lezak et al., 2012).

Thus neurocognitive adaptability is not a singular process that can be reduced to a single dimension, but a series of inter-related processes that can be ordered according to the timescale at which they are expressed (Lövdén et al., 2010). In the case of multiscale sample entropy, shorter and longer timescale bands within the subsecond band of EEG entropy are likewise thought to represent distinct neural processes, differentially susceptible to aging and disease (McIntosh et al., 2014). In the same way, various trajectories of aging and dementia might be associated with particular profiles of adaptability mechanism preservation/loss. Consider the differentiable cognitive and functional course of older adults on healthy trajectories compared to those who develop different variants of MCI or dementia (Alexopoulos, Grimmer, Perneczky, Domes, & Kurz, 2006; Fischer et al., 2007; Rasquin, Lodder, Visser, Lousberg, & Verhey, 2005). Rather than clustered according to the classical cognitive domains impacted, might the wide variety of prodromal dementia variants be expressed in terms of adaptability-across-timescale profiles?

Within the macro end of the adaptability spectrum, plasticity-related changes can thus be reflected as individual differences in personality or practice effects. In comparison, existing neuropsychological tests are sufficient to characterize individual differences in macro-flexibility. For example, from a macro-adaptability point of view, classical “memory-impaired” individuals (*e.g.* older individuals with amnestic-MCI or Alzheimer's type dementia) could be described as having suppressed long-timescale adaptability – as a result of the primary involvement of limbic and temporal structures – but with preserved short-timescale adaptability (assuming intact attention). On the other hand individuals with executive dysfunction (*e.g.* older individuals with single non-memory domain MCI or vascular-type dementia) could be described as having impaired short-term cognitive adaptability but preserved long-term adaptability (assuming intact memory). Multi-domain MCI – if it impacted both executive and memory domains – would have a uniformly-suppressed macro-adaptability profile.

In comparison, the multiscale EEG entropy paradigm represents a metric of neurocognitive micro-adaptability (at the extreme flexibility end of the spectrum). It shows differences according to age (McIntosh et al., 2014; Sleimen-Malkoun et al., 2015) and diagnostic status (Mizuno et al., 2010; J.-H. Park et al., 2007; A. C. Yang et al., 2013) at specific timescale bands within the subsecond range. Though the present dissertation and other studies have found significant timescale-specific age and diagnostic group differences in EEG entropy, the relation and importance of these differences to underlying neural function remain obscure. Current conceptualizations suggest that, in part, entropy at distinct timescales reflects meaningful differences in functional and anatomical interactions between different brain regions. Local interactions are thought to be captured in fine-grained and longer-range interactions in coarse-grained entropy (McIntosh et al., 2014). Clinical neurophysiologists (*e.g.* in hospitals) could adopt standardized approaches to the quantification of multiscale entropy and provide these profiles along side their typical qualitative and spectral description of EEG recordings. This would help to attune clinicians working with older adults to the significance of differences in entropy profiles, especially in relation to anatomical (structural imaging) and performance (neuropsychological testing) data.

Cognitive performance measurements and personality self-ratings such as those in the present study could both be feasibly administered via remote computer assessment in the patient's home or community clinic. Soon, thanks to advances in lightweight, mobile EEG technology, the same will be true of electrophysiological indicators (De Vos, Kroesen, Emkes, & Debener, 2014; Anderson S Oliveira et al., 2016; Ries et al., 2014). Moreover, self-report, baseline cognitive performance, and resting-state EEG data can be collected in a matter of minutes. However it will take much longer to develop meaningful normative datasets, especially for novel metrics such as multiscale EEG entropy and across-occasion learning profiles on computerized tasks. In the near future, clinical assessment of older adult neurocognitive adaptability could be accomplished in three stages.

First, individual older adults would be screened at baseline with remotely administered self-report, baseline performance, and (if feasible) physiological measures. With semi-automated assessment protocols, this first stage would facilitate a near-immediate assessment of dementia-risk relative to population-normed levels. An initial complication of the first-pass stage would be identifying those who may be better served by immediate psychological consultation rather than further testing. For this and other reasons, it would be useful to have verified reports from health care professionals, friends, and/or family members. Next, if appropriate based on findings from stage one, a burst of computerized testing sessions would be administered to assess across-session changes and fluctuations in cognitive performance. At this point, key indicators of the need for further follow-up would likely include a lack of expected retest gains.

Finally, when indicated, individuals would be offered formal in-person evaluation in stage three. At present, testing with standardized neuropsychological instruments at annual or bi-annual intervals remains the only way to reliably detect serial declines in neurocognitive function. However, earlier triage of individual older adults in terms of their multi-faceted dementia-risk profile will facilitate earlier initiation of treatments that are appropriate and tailored to each individual, even if a conclusive diagnosis is still pending.

Limitations and Future Directions

The present study, though a proof of concept, relied on rigorous laboratory measures and involved considerable time and energy investment from experimenter and participants. What is more, though intriguing, this series of studies provides only preliminary evidence in support of the clinical utility of novel markers of neurocognitive adaptability.

To be sure, there is much work left to be done; most obvious is the need to establish the adaptability metrics outlined herein as valid longitudinal predictors of incident change in diagnostic status. Future analysis of follow-up data from the present sample of older adults will help to answer this

need. Along similar lines, it would be useful to replicate the present studies using a sample of older adults that includes individuals with diagnoses of different dementias and dementia prodromes. The present sample excluded individuals with dementia, chronic neurological conditions (*e.g.* Parkinsonism, multiple sclerosis), other common causes of neurocognitive disorder (*e.g.* stroke, head injury), or functional impairment. Based on actuarial diagnostic criteria (Edmonds et al., 2015), the over-whelming majority of the study participants were classified as normal. There was significant distribution of individuals across diagnostic groups after the premorbid IQ-adjustment was applied, but the findings may nonetheless represent normal variation in neurocogntive adaptability in the healthy population. In other words, the present diagnostic protocol may have been too sensitive and led to an excessive number of false positives. This fact limits the significance and potential impact of the findings. However, for this reason it remains to be seen if the individual differences in adaptability described above will predict prospective pathological neurocognitive aging. Individuals with varying types or severities of dementia may differ quantitatively (level) and/or qualitatively (pattern of inter-correlation between measures) compared to healthy individuals (Molenaar, 2004).

On a related note, replications and extensions should employ more diverse samples of older adults. The present sample size was adequate to address the study questions because of the intensive, within-person measurement protocol and the relative demographic homogeneity of the participants. Yet the generalizablility, even to other samples of healthy older adults, of the findings reported herein is particularly limited by this same reality. Older adults comprising the present sample were predominantly of European-Canadian ethnicity, and unusually high in education attainment and premorbid function. This was in part expected given the community of origin. However, the time-intensive requirements and voluntary nature of participation in this research project also likely biased participant self-selection.

It is well known that individuals who are younger, healthier, and have more education are less

likely to drop out of participation in research (Radler & Ryff, 2010). Very few individuals dropped out or were screened out of the present study (see Study 1). The time commitment was clearly outlined in recruitment materials and may have dissuaded some individuals from volunteering in the first place. Further, there is evidence that older adult volunteerism tends to be driven by motives of generativity (Yamashita, López, & Keene, 2017). This is salient since many of the participants in the present study were former university employees or faculty. In fact, during initial screening, the majority of participants indicated that valuing research or an interest in learning about and supporting research was their primary motive for volunteering. Tangible incentives were limited to reimbursement for parking or transportation costs. Future studies should target recruitment and retention of those older individuals who are less likely to self-select into research projects. For instance, researchers could focus on recruiting all individuals within a pre-defined geographic region, and reduce barriers to participation by facilitating transportation or providing at-home appointments.

Future research should consider the conceptual and methodological overlap between some forms of neurocognitive adaptability and executive function. For instance, the computerized switch task was originally designed to capture particular sub-dimensions of prefrontal/executive functioning (Rogers & Monsell, 1995). Its alternating “stay” and “switch” trials provided a convenient way to track participant responses to a persistent, dynamic cognitive challenge. While other neurocognitive processes known to be important to functional independence (*e.g.* episodic memory) were presumed to have little bearing on switch task performance, they may provide important insight into the capacity for across-occasion changes in performance. Moreover, as already discussed, conscientiousness is similar in its ties to executive functioning and the structure and function of prefrontal regions. And, while educational attainment is in part biased in favour of those with the opportunity and means to pursue it, there is evidence that education causes discernible increases in performance on tests of fluid cognition (Clouston et al., 2012). In the same way, because they were collected under resting conditions, the

multiscale EEG entropy data presented in Chapter 1 might be expected to reflect immediate adaptability processes (attention and executive) more than longer-timescale processes (episodic memory).

Future theoretical challenges lie in understanding the unity and diversity of neurocognitive adaptability. This is reminiscent of the state of executive function theory and research prior to Miyake's seminal paper (Miyake et al., 2000). What followed were efforts to refine the construct of executive function through a focus on integrating theories that each outlined parts of its multidimensional structure (Jurado & Rosselli, 2007). It might be argued that the chief purpose of executive functions is also adaptation. An important benefit of the adaptability framework proposed herein, which builds on that proposed by (Lövdén et al., 2010), is its accommodation of the inherent ordering of the inter-related processes of neurocognitive adaptability according to the timescale at which they are expressed. Timescale provides a useful and intuitive dimension against which to observe and integrate all of the distinct manifestations of adaptability. It also allows for the correlation of observed changes in behaviour with concrete changes in the structure or function of the nervous system. In contrast, theories of executive function ascribe observable changes in behaviour to inferred, unobservable cognitive processes; the idea of a “central executive” that coordinates lower-order processes is twice abstracted from the manifest cognitive performance level. Employing timescale as an organizational principle will help to establish a more unified and empirically-grounded theory of neurocognitive adaptability in older adulthood.

In terms of future practical developments, it should be noted that the computerized task used in the present study involved responding to simple letter-number stimuli. As a result, anecdotal participant reports suggested that boredom and reduced motivation may have occurred following many occasions of testing. Useful computerized assessment protocols will therefore need to be reliable and in widespread use while also being dynamic and adaptable enough to capture a wide range of

performances and maintain participant engagement. Also, while adjusting for certain traits – such as age, education, personality – will be obvious, other unwanted sources of variance will take years to detect and accommodate. For instance, the most useful computerized assessment tools must be validated for use under a variety of testing circumstances and via diverse hardware and software platforms. Moreover, testing individuals via mobile, internet-based measures implicates a naturalistic context that does not allow direct comparison with laboratory-based studies such as the present one. However a lack of available data should not deter exploration. On the contrary; the 21st century revival of clinical neuropsychology demands that scientists and practitioners embrace the realities and opportunities of *in situ* (ecologically-situated) neurocognitive assessments (Spooner & Pachana, 2006).

One outstanding issue with the proposed approach relates to using the group differences reported above to make inferences about (*i.e.* prospective diagnoses of) particular individuals seen in the clinic. Robinson (1950) pointed out that patterns of change and fluctuation within individual persons can differ quantitatively and qualitatively from predictions based on aggregate (group-level) profiles. It is now known and increasingly appreciated that within-person patterns of change, fluctuation, and covariance in physiological and psychometric indices of neurocognitive function show extensive, meaningful differences across persons (Molenaar, 2004; Mulligan, Smart, Segalowitz, & MacDonald, *in press*). In recognition of this fact, the models of cognitive performance over time detailed above allowed for random across-person variation in level (intercept) and across-occasion change (slope). This was made possible because of the intensive within-person design – by considering the cognitive performance of each individual at multiple longitudinal time points. Rather than a group-differences approach (flagging individuals who perform within certain ranges of the across-person distribution), a longitudinal monitoring approach allows quantification of uncertainty at the within-person level. Individual older adults could be prospectively monitored and flagged for follow-up when they show a significant deviation from their own longitudinal trajectory, above and beyond what is

considered within their own individual “expected limits”. This would align professional neuropsychology with the personalized medicine movement (Hamburg & Collins, 2010). The basic utility of examining longitudinal changes in intensively assessed cognitive performance has already been demonstrated (Rast et al., 2012). As data accrue for particular batteries and populations, computerized testing is likely to become increasingly implicated in assessments of older adult neurocognitive health. The predictive validity of practice effects in particular will be examined in future analyses of annual longitudinal follow-up data from individuals in the present sample. The same will be done for longitudinal changes in multi-timescale resting-state EEG entropy.

To date, no longitudinal aging studies of multiscale EEG entropy have been published. The role or importance of changes in resting-state EEG in the pathophysiology of aging and dementia are likewise a matter of dispute. Some clues as to their significance could be gleaned by including measures of multiscale EEG entropy in dementia intervention studies. For example, among individuals with AD, treatment with acetylcholinesterase inhibitors is known to improve cognitive function and produce “normalizing” changes in resting-state EEG; namely, a suppression of delta- and theta-range and an enhancement of alpha-range EEG spectral power (Babiloni et al., 2013). Non-pharmacological interventions such as mindfulness training are also known to impact the brain and cognitive functioning of older adults who may be at increased risk for dementia (Smart, Segalowitz, Mulligan, Koudys, & Gawryluk, 2016). Effects of potential treatments for dementia on EEG entropy curves are not known. If, for instance, all of the original data from the studies reviewed by (Babiloni et al., 2013) were available, it would be relatively straightforward to apply the protocols presented in this dissertation in order to derive multiscale entropy estimates. In that way new discoveries might be gleaned from existing datasets, and developments in assessment and intervention could be drastically accelerated.

Conclusion

There is an urgent need for the early identification of individual older adults who may be at an

elevated risk for dementia. Existing research has established that among the very earliest signs of dementia is a subtle loss of neurocognitive adaptability. The results reported above suggest that the conceptualization of preclinical dementia would be improved by considering multiple metrics of neurocognitive adaptability, including those based on self-report, cognitive performance, and direct measures of brain function. Governments and community health agencies have a duty to develop and implement efficient and reliable neurocognitive health screening protocols that are accessible to all older adults, regardless of economic, geographic, or other social barrier. The present work offers such a multi-method neurocognitive health screening protocol that is feasible for population-wide deployment. In so doing, this body of work also helped to broaden and unify the concept of older adult neurocognitive adaptability.

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Appendix 1: MATLAB script for pre-processing raw EEG data

```
%Start EEGLAB.
[ALLEEG EEG CURRENTSET ALLCOM] = eeglab;

%Load dataset.
EEG = pop_loadbv('/media/bpm/Caviar/Projects/ALB_EEG', 'RestingALB001.vhdr', [], [1 2 3 4 5 6 7
    8 9 10 11 12 13 14 15]);
[ALLEEG EEG CURRENTSET] = pop_newset(ALLEEG, EEG, 0,'setname','001','gui','off');
EEG = eeg_checkset( EEG );

%Scroll plot.
pop_eegplot( EEG, 1, 1, 1);

%This renames the channels and then locates them using the 10-5 standard
%positions.
EEG=pop_chanedit(EEG,
    'lookup','/usr/local/MATLAB/R2012a/toolbox/eeglab13_3_2b/plugins/dipfit2.3/standard_BESA/st
    andard-10-5-cap385.elp','changefield',{15 'labels' 'IO1'},'changefield',{14 'labels'
    'LO2'},'changefield',{13 'labels' 'LO1'},'changefield',{12 'labels' 'M1'},'append',15,'changefield',
    {16 'labels' 'M2'},'setref',{'1:15'
    'M2'},'lookup','/usr/local/MATLAB/R2012a/toolbox/eeglab13_3_2b/plugins/dipfit2.3/standard_B
    ESA/standard-10-5-cap385.elp');
[ALLEEG EEG] = eeg_store(ALLEEG, EEG, CURRENTSET);
EEG = eeg_checkset( EEG );

%Re-reference from the right mastoid (M2) to Cz.
EEG = pop_reref( EEG, 6,'refloc',struct('labels',{'M2'},'type',{''},'theta',{100.419},'radius',
    {0.74733},'X',{-10.9602},'Y',{-59.6062},'Z',{-59.5984},'sph_theta',{-100.419},'sph_phi',{-
    44.52},'sph_radius',{85},'urchan',{16},'ref',{''},'datachan',{0}),'keepref','on');
[ALLEEG EEG CURRENTSET] = pop_newset(ALLEEG, EEG, 2,'setname','001_Prn_Cz','gui','off');
EEG = eeg_checkset( EEG );

%Re-reference from Cz to linked mastoids (M1 M2).
```

```
EEG = pop_reref( EEG, [12 16] ,'keepref','on');
[ALLEEG EEG CURRENTSET] = pop_newset(ALLEEG, EEG,
      3,'setname','001_Prn_M1M2','gui','off');
EEG = eeg_checkset( EEG );


%High-pass filtering at 1 Hz.
EEG = pop_eegfilt( EEG, 1, 0, [], [0], 0, 0, 'fir1', 0);
[ALLEEG EEG CURRENTSET] = pop_newset(ALLEEG, EEG,
      4,'setname','001_Prn_M1M2_1Hz','gui','off');
EEG = eeg_checkset( EEG );


%Low-pass filtering at 40 Hz.
EEG = pop_eegfilt( EEG, 0, 40, [], [0], 0, 0, 'fir1', 0);
[ALLEEG EEG CURRENTSET] = pop_newset(ALLEEG, EEG,
      5,'setname','001_Prn_M1M2_1_40Hz','gui','off');


%Scroll plot.
pop_eegplot( EEG, 1, 1, 1);


%Artifact Subspace Reconstruction.
EEG = clean_rawdata(EEG, 5, [0.25 0.75], 0.8, 4, 5, 0.5);
[ALLEEG EEG CURRENTSET] = pop_newset(ALLEEG, EEG,
      6,'setname','001_Prn_M1M2_1_40Hz_ASR','gui','off');


%Scroll plot.
pop_eegplot( EEG, 1, 1, 1);


%Split the dataset into epochs (eyes closed and eyes open)
EEG = pop_epoch( EEG, {  }, [0  120], 'newname', '001_Prn_M1M2_1_40Hz_Epochs', 'epochinfo',
      'yes');
[ALLEEG EEG CURRENTSET] = pop_newset(ALLEEG, EEG, 7,'gui','off');


%Selects only "Eyes Closed" epochs (for only "Eyes Open", change S2 to S1
```

```
EEG = pop_selectevent( EEG, 'type',{'S  2'},'deleteevents','off','deleteepochs','on','invertepochs','off');
[ALLEEG EEG CURRENTSET] = pop_newset(ALLEEG, EEG,
    8,'setname','001_Prn_M1M2_1_40Hz_ASR_Epochs_EC','gui','off');


eeglab redraw


%Scroll plot.
pop_eegplot( EEG, 1, 1, 1);


%Export the dataset as a text file for MMSE processing in R.
pop_export(EEG,'/media/bpm/Caviar/Projects/ALB_EEG/PreProcOut/001_W1','transpose','on','precisi
    on',4);
```

Appendix 2: MATLAB script for computing multivariate multiscale sample entropy from pre-processed EEG data

```
%EEG_MMSE_FCP.m

% This script is run after EEG preprocessing.
% Reads EEG text files, and transposes the files to "wide" format.
% Then, multivariate multiscale entropy (MMSE) is computed.
% This code was developped with Corson, to create frontal, central, and
% parietal multivariate subsets for use in the MMSE.
% (Note: use of all the data from all of the channels in one multivariate
% analysis would draw an inaccessible amount of RAM, unless SHARCNET).

% Unfortunately, since MATLAB cannot handle text files with non-numerical
% values, the EEGLAB-exported text files must be opened in another
% application (e.g. R or LO Calc) in order to remove channel labels.

% Below uses the MMSE function mvsampen_full.m
% MATLAB code available from:
% http://www.commsp.ee.ic.ac.uk/~mandic/research/Complexity_Stuff.htm

% For discussion see: Ahmed, M. U., & Mandic, D. P. (2011). Multivariate
% multiscale entropy: A tool for complexity analysis of multichannel data.
% Physical Review E - Statistical, Nonlinear, and Soft Matter Physics,
% 84(6), 1–10. http://doi.org/10.1103/PhysRevE.84.061918

%The rest of the code creates an empty matrix for each of the frontal,
%central and parietal subsets and then populates them with the multivariate
%entropy estimates.
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% data = Input data must have row as sensor, column as time (Note that this
%may require a transpose (heance the ' at the end of the csv command).
% M = embedding dimension ("pattern length"), a vector, specified for each
%of the channels comprising the multivariate series.
% r = threshhold parameter, a scalar (how similar is similar enough?)
% segments = matrix denoting EEG segments, e.g. @500Hz, 1000 = 2 seconds
% n_scales = number of scales at which entropy will be calculated
% Chan(1-9) = values of rows, which correspond to EEG channels


% Input arguments.
data =
    csvread('/media/bpm/Caviar/Dropbox/Credit/Dissertation/DissEntropy/RestructOutput/001_W1.csv')';
M = [2 2 2];
r = 0.5;
n_scales = 30;
segments = [1 20000;
        20001 40000;
        40001 60000;
        60001 80000;
        80001 100000;
        100001 120000;];


Chan1 = 2; % 2 = F3
Chan2 = 3; % 3 = Fz
Chan3 = 4; % 4 = F4
Chan4 = 6; % 6 = C3
Chan5 = 7; % 7 = Cz
Chan6 = 8; % 8 = C4
Chan7 = 10; % 10 = P3
Chan8 = 11; % 11 = Pz
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Chan9 = 12; % 12 = P4


%Stage I: Frontal channels

% Create an empty matrix (timescale by segment) to populate with entropies.
e_matrix_F = nan(n_scales, size(segments,1));


% The business.
for i = 1:size(e_matrix_F,1)
   for j = 1:size(e_matrix_F,2)
      e = mvsampen_full(M, r, i*ones(1,3), data([Chan1 Chan2 Chan3], ...
                  segments(j,1):segments(j,2)));
      e_matrix_F(i,j) = e;
   end
end



%Stage II: Central channels

% Create an empty matrix (timescale by segment) to populate with entropies.
e_matrix_C = nan(n_scales, size(segments,1));


% The business.
for i = 1:size(e_matrix_C,1)
   for j = 1:size(e_matrix_C,2)
      e = mvsampen_full(M, r, i*ones(1,3), data([Chan4 Chan5 Chan6], ...
```

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                segments(j,1):segments(j,2)));
        e_matrix_C(i,j) = e;
    end
end



%Stage III: Parietal channels

% Create an empty matrix (timescale by segment) to populate with entropies.
e_matrix_P = nan(n_scales, size(segments,1));



% The business.
for i = 1:size(e_matrix_P,1)
    for j = 1:size(e_matrix_P,2)
        e = mvsampen_full(M, r, i*ones(1,3), data([Chan7 Chan8 Chan9], ...
                segments(j,1):segments(j,2)));
        e_matrix_P(i,j) = e;
    end
end



% Now combine the matrices and write them as a text file.
csvwrite('/media/bpm/Caviar/Dropbox/Credit/Dissertation/DissEntropy/EntData/001_W1_F.txt',
        e_matrix_F)
csvwrite('/media/bpm/Caviar/Dropbox/Credit/Dissertation/DissEntropy/EntData/001_W1_C.txt',
        e_matrix_C)
csvwrite('/media/bpm/Caviar/Dropbox/Credit/Dissertation/DissEntropy/EntData/001_W1_P.txt',
        e_matrix_P)
```