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Intra-individual reaction time variability and all-cause mortality over 17 years: a community-based cohort study

Philip J. Batterham[1], David Bunce[2], Andrew J. Mackinnon[3], Helen Christensen[4]

[1]Centre for Mental Health Research, The Australian National University, Building 63 Eggleston Road, Canberra, Australian Capital Territory 0200, Australia
[2]Institute of Psychological Sciences, University of Leeds, Leeds, UK
[3]ORYGEN Youth Research, University of Melbourne, Melbourne, Victoria, Australia
[4]Black Dog Institute, Sydney, New South Wales, Australia

Address correspondence to: P. J. Batterham. Tel: +61 2 6125 1031; Fax: +61 2 6125 0733. Email: philip.batterham@anu.edu.au

Abstract

Background: very few studies have examined the association between intra-individual reaction time variability and subsequent mortality. Furthermore, the ability of simple measures of variability to predict mortality has not been compared with more complex measures.
Method: a prospective cohort study of 896 community-based Australian adults aged 70+ were interviewed up to four times from 1990 to 2002, with vital status assessed until June 2007. From this cohort, 770–790 participants were included in Cox proportional hazards regression models of survival. Vital status and time in study were used to conduct survival analyses. The mean reaction time and three measures of intra-individual reaction time variability were calculated separately across 20 trials of simple and choice reaction time tasks. Models were adjusted for a range of demographic, physical health and mental health measures.

Results: greater intra-individual simple reaction time variability, as assessed by the raw standard deviation (raw SD), coefficient of variation (CV) or the intra-individual standard deviation (ISD), was strongly associated with an increased hazard of all-cause mortality in adjusted Cox regression models. The mean reaction time had no significant association with mortality.
Conclusion: intra-individual variability in simple reaction time appears to have a robust association with mortality over 17 years. Health professionals such as neuropsychologists may benefit in their detection of neuropathology by supplementing neuropsychiatric testing with the straightforward process of testing simple reaction time and calculating raw SD or CV.

Keywords: *all-cause mortality, reaction time, intra-individual variability, coefficient of variation, intra-individual standard deviation, older people*

Introduction

The possibility that within-person reaction time (RT) variability for a given cognitive task is sensitive to neurobiological disturbance has created considerable empirical and clinical research interest, with behavioural investigations confirming that increased intra-individual RT variability (IIV) is associated with traumatic brain injury [1], epilepsy [2] and mild cognitive impairment or mild dementia [3, 4]. Greater IIV is also associated with older age [5, 6], mild psychopathology [7, 8], and, importantly from the present perspective, impending mortality [9]. Additionally, neuroimaging shows associations of IIV with brain structures [10–13] and function [14, 15]. Moreover, work also implicates involvement of striatal dopamine D2 receptor binding [16], a finding that is consistent with the possibility that IIV reflects neural noise in the brain [17]. Previous research on the relationship between cognition and mortality has indicated that poorer cognitive performance, particularly in the memory and processing speed domains, is associated with increased mortality [18–20]. However, other than work by Macdonald *et al.* [9], there has been little examination of the impact of within-person performance variability on mortality. The present study aimed to address this shortfall and assess whether all-cause mortality over 17 years was predicted by mean RT and two measures of IIV in a community-based cohort of older adults. A standard measure of IIV, the intra-individual SD (ISD), was compared with two simpler measures, the raw standard deviation (raw SD) and the coefficient of variation (CV), which may be easily derived in the clinical setting. It was hypothesised that greater IIV would be associated with increased hazard for mortality, due to its sensitivity to neurobiological disturbance, while mean RT would exhibit a weaker relationship with mortality.

Method

Participants

The Canberra Longitudinal Study is an epidemiological survey of mental health and cognitive functioning in older people. Participants were sampled from the compulsory electoral roll for the cities of Canberra and Queanbeyan, Australia. Individuals sampled from the electoral roll were sent a letter inviting participation in the survey and then approached at home by a trained interviewer. The purposes and procedures of the study were explained before informed consent was obtained. Thirty-one percent of those approached refused to participate. This refusal rate is similar to those obtained in other community samples (e.g. 21–23). Participants were 896 community-dwelling adults (456 men and 440 women) aged 70–97 at the baseline assessment, with the sample stratified by age and gender. Participants were followed up every 4 years, with up to four assessments administered between 1990 and 2002. Approval for the research was obtained from the Ethics in Human Experimentation Committee of The Australian National University. Further details of the study design are provided by Christensen *et al.* [24].

Of the original sample of 896 participants, 185 (20.6%) were deceased by four years, 363 (40.5%) were deceased by eight years, and 544 (60.7%) were deceased by 12 years. Vital status was collected until June 2007. At this time, 687 (76.7%) participants were deceased. Of the surviving participants at each measurement occasion, response rates of 85.9, 78.9 and 78.9% were obtained for the three follow-up interviews.

Procedure

Interviews were conducted by trained professional interviewers, who administered a comprehensive survey and conducted physical assessments. Baseline assessments lasted approximately two hours, and covered background characteristics, physical health and disease status, mental health status and cognitive performance.

Measures

Vital status and date of death were established using the National Death Index, a register of all deaths in Australia based on data collected by the Registrars of Births, Deaths and Marriages in each State and Territory in Australia. Additional sources of death reporting were used to confirm the validity of the mortality status data, including contacting relatives and searching death notices in the local newspaper. Vital status was followed for up to 17 years, from the start of baseline interviews in September, 1990 until June 30, 2007.

In addition to measures of mean RT and RT variability described below, models were adjusted for a number of

baseline risk factors for mortality. These included age, gender, marital status and number of years of education. Presence of possible preclinical dementia was determined using the Mini-Mental State Examination (MMSE) [25], based on scoring ≤24 out of 30 at any of the four assessments. Given that very few participants met dementia criteria early in the study, this liberal criterion evaluated over an extended period was used to ensure that presence of preclinical cognitive decline could be adequately identified. Physical health measures included smoking status (never, previous or current), Activities of Daily Living (ADL, a scale ranging from 0 to 22), disease count (self-reported history from a list of 14 diseases), self-reported use of antihypertensive medication and grip strength (measured in kilograms using a hand dynamometer). The ADL scale assessed the presence or extent of physical disability [26]. Grip strength is a reliable and objective indicator of physical functioning in late life [27] that has been shown to have strong associations with mortality [18]. Mental health was adjusted for using the Goldberg Depression and Anxiety Scales [28] to assess the number of depression and anxiety symptoms experienced in the two weeks prior to the interview. These scales consist of nine binary items assessing symptoms of depression and anxiety, with scores on each scale reflecting a symptom count ranging from 0 to 9.

RT assessment and computation of IIV measures

Simple and choice RT were each assessed over 20 trials. The simple RT trials consisted of ten left hand stimuli followed by ten right-hand stimuli. Binary choice RT trials consisted of a random combination of left- and right-hand stimuli. The stimuli were two lights controlled by the interviewer away from the participant's view. Participants pressed one of two buttons in response to the corresponding light (left or right). The interviewer said 'ready' before turning on the first light, with interstimulus intervals ranging from 0.5 to 2.0 s. Participants were given 5 practice trials before the left hand simple RT stimuli, 4 practice trials before the 10 right-hand simple RT stimuli trials and 4 practice trials before the 20 choice RT stimuli trials. Further detail of the RT protocol is provided by Christensen *et al.* [29]. Data preparation for the computation of IIV measures followed procedures commonly used elsewhere (e.g. [30]). Initially, RTs for incorrect trials were removed together with unusually fast responses (<150 ms) and those greater than the age group mean + 3 age groups SDs. Age group means and SDs were computed for age ranges 70–75, 76–80, 81–85 years and 86 years and older. These exclusions resulted in the loss <2.1% of trials across the sample. MRT and three commonly used measures of IIV were then computed. Specifically, the raw SD was simply the ISD across the 20 trials. The CV was computed as the raw ISD divided by the raw intra-individual *M* RT. A regression procedure was used to compute the ISD, where residuals were saved having partialled out categorical effects for trial (i.e. time-on-task effects), age group and their interaction. The residuals obtained for this ISD were then standardised. The process of calculating CV and ISD was conducted separately for simple and choice RT data.

Analysis

Sample characteristics were tabulated based on vital status at the end of the study period. Cox proportional hazards regression models were used to assess the relationship of MRT, CV and ISD with all-cause mortality. Each RT measure was entered into a separate model, resulting in six models (three measures each for simple and choice RT). The models were estimated both with and without adjustment for mortality risk factors. Models that included both the effects of MRT and either CV or ISD were also estimated. The sample size was 790 for the simple RT models and 770 for the choice RT models, due to participants with missing RT trials [simple missing: 71 (7.9%); choice missing: 94, (10.5%)] and missingness on other independent variables (61, 6.8%). In all models, the three IIV measures were standardised (to mean = 0, SD = 1) to enable comparison between models. All analyses were conducted in SPSS version 20 (IBM Corporation, 2011).

Results

Sample characteristics based on vital status at June 2007 are displayed in Table 1. All variables in the table were assessed during the first wave, with the exception of possible dementia which was assessed as MMSE ≤24 at any wave. Participants who died in the follow-up period had significantly slower mean RT and greater RT variability than those who survived. This relationship was consistent across all measures of RT and for both simple and choice RT. Decedents were also older, had greater physical impairment, reported more diseases, had weaker grip strength, were more depressed and were more likely to be male, meet criteria for possible dementia or smoke. There were no significant effects of education, anxiety, marital status or medication use on mortality. Simple MRT ranged from 1.8 to 9.7 s, choice MRT ranged from 2.2 to 9.3 s, simple raw SD ranged from 9.9 to 244.0 ms, choice raw SD ranged from 21.2 to 188.2 ms, simple CV ranged from 0.04 to 0.58, choice CV ranged from 0.05 to 0.48. Simple ISD was a standardised score ranging from −1.34 to 5.19, with choice ISD ranging from −1.68 to 4.78.

Table 2 shows the unadjusted and adjusted relationships between MRT, CV and ISD with all-cause mortality, for both simple and choice RT tasks. The third models for CV and ISD also added adjustment for MRT, along with other independent variables. All estimates come from Cox proportional hazard regression models, which take into account time to death and censoring for those participants who survived until the end of follow-up. The unadjusted models included only the effect of a single RT variable (MRT, CV or ISD) alone. Adjusted analyses were separately estimated for each of the RT variables, with adjustment for all of the variables shown in Table 3. The models that added adjustment

Table 1. Sample characteristics based on vital status after 17 years

		Living (n = 209)		Deceased (n = 687)			
	n	M	SD	M	SD	F	P-value
Simple RT— mean (ms)	825	282.38	86.65	303.27	103.21	6.63	**0.010**
Simple RT—raw SD	825	52.14	29.29	63.35	37.87	14.62	**<0.001**
Simple RT—CV	825	0.18	0.07	0.20	0.08	11.08	**0.001**
Simple RT—ISD	825	−0.24	0.80	0.08	1.04	15.49	**<0.001**
Choice RT—mean (ms)	802	331.96	80.82	353.82	99.33	7.69	**0.006**
Choice RT—raw SD	802	58.52	21.27	69.84	27.18	27.93	**<0.001**
Choice RT—CV	802	0.18	0.05	0.20	0.07	18.68	**<0.001**
Choice RT—ISD	802	−0.33	0.80	0.10	1.03	27.60	**<0.001**
Age	896	74.09	3.38	77.30	5.09	73.58	**<0.001**
Education	894	11.17	2.29	11.41	2.66	1.39	0.239
ADL score	877	0.98	1.31	2.14	2.78	34.09	**<0.001**
Disease count	896	2.35	1.66	2.96	1.72	20.15	**<0.001**
Grip strength	868	25.90	9.90	24.26	9.46	4.57	**0.033**
Goldberg depression score	865	1.71	1.79	2.13	2.00	7.06	**0.008**
Goldberg anxiety score	870	2.49	2.35	2.46	2.25	0.02	0.876
		Count	%	Count	%	χ^2	P
Gender	896					13.63	**<0.001**
Male		83	39.7%	373	54.3%		
Female		126	60.3%	314	45.7%		
Marital status	896					5.35	0.148
Married		127	60.8%	366	53.3%		
Single		10	4.8%	24	3.5%		
Widowed		63	30.1%	261	38.0%		
Divorced/separated		9	4.3%	36	5.2%		
Possible MMSE dementia	896					7.17	**0.007**
Yes		181	86.6%	537	78.2%		
No		28	13.4%	150	21.8%		
Smoking status	877					7.65	**0.022**
Never		110	52.9%	281	42.0%		
Past		78	37.5%	305	45.6%		
Current		20	9.6%	83	12.4%		
Using AH medication	879					1.00	0.317
Yes		62	29.8%	225	33.5%		
No		146	70.2%	446	66.5%		

Bold values indicate $P < 0.05$; RT, reaction time; CV, coefficient of variation; ISD, intra-individual standard deviation; ADL, activities of daily living; MMSE, Mini-Mental State Examination; AH, antihypertensive.

for MRT were included to account for the correlations between MRT and raw SD ($r_{simple} = 0.69$, $r_{choice} = 0.50$), MRT and CV ($r_{simple} = 0.24$, $r_{choice} = -0.11$) and MRT and ISD ($r_{simple} = 0.71$, $r_{choice} = 0.52$).

The significant univariate hazard ratios in Table 2 indicate that 1 SD increase in MRT was associated with 15% increased hazard of death for simple RT and 18% for choice RT. Increased RT variability, measured both by CV and ISD, was also associated with significantly increased hazard of death. Table 2 also indicates that mean RT was not significantly associated with mortality after accounting for the effects of gender, age, education, marital status, possible dementia, physical health and mental health. Table 3 provides details of the fully adjusted Cox proportional hazard regression models. There was very little attenuation of the simple RT variability measures, with all three IIV measures remaining significantly associated with all-cause mortality after adjustment. There was greater attenuation of the choice RT effects, with all three IIV effects becoming non-significant after adjustment for MRT and the assessed risk factors. The greater attenuation of choice RT measures was tested in three models (not displayed) that included (i) both simple raw SD (OR = 1.13, $P = 0.055$) and choice raw SD (OR = 1.05, $P = 0.316$), (ii) both simple CV (OR = 1.12, $P = 0.011$) and choice CV ($OR = 1.05$, $P = 0.328$), and, (iii) both simple ISD (OR = 1.14, $P = 0.037$) and choice ISD (OR = 1.05, $P = 0.307$), along with adjustment for the variables listed in Table 3. Other consistent significant effects in the final Cox proportional hazards regression models replicated previous findings [18, 19]: male gender, older age, greater physical impairment, more diseases and weaker grip strength were associated with greater hazard of all-cause mortality.

Discussion

The present study broadly supports and extends the findings of Macdonald *et al.* [9], with RT variability having a strong association with all-cause mortality in a community-based cohort of older adults. The findings also support those of

Table 2. Summary of Cox proportional hazards regression models of all-cause mortality

		Unadjusted				Adjusted				Adjusted + adjusted for MRT			
		Estimate	SE	HR	*P*-value	Estimate	SE	HR	*P*-value	Estimate	SE	HR	*P*-value
Simple RT (n = 825)	Mean	0.136	0.038	1.146	**<0.001**	0.054	0.045	1.055	0.231	—			
	Raw SD	0.170	0.039	1.185	**<0.001**	0.106	0.041	1.111	**0.010**	0.133	0.056	1.143	**0.018**
	CV	0.143	0.040	1.154	**<0.001**	0.132	0.040	1.142	**0.001**	0.128	0.041	1.137	**0.002**
	ISD	0.175	0.038	1.192	**<0.001**	0.108	0.041	1.114	**0.008**	0.140	0.057	1.150	**0.014**
Choice RT (n = 802)	Mean	0.168	0.039	1.183	**<0.001**	0.064	0.045	1.066	0.161	—			
	Raw SD	0.268	0.040	1.307	**<0.001**	0.087	0.043	1.091	**0.042**	0.076	0.049	1.079	0.123
	CV	0.196	0.040	1.217	**<0.001**	0.069	0.043	1.071	0.107	0.075	0.043	1.078	0.079
	ISD	0.269	0.040	1.309	**<0.001**	0.090	0.043	1.094	**0.037**	0.079	0.050	1.082	0.110

Bold values indicate $P < 0.05$; RT, reaction time; CV, coefficient of variation; ISD, intra-individual standard deviation; RT measures are standardised to mean = 0, SD = 1 for comparability; adjustment was for age, gender, marital status, years of education, presence of possible preclinical dementia, smoking status, Activities of Daily Living, disease count, self-reported use of antihypertensive medication, grip strength and the Goldberg Depression and Anxiety Scales.

Table 3. Fully adjusted Cox proportional hazards regression models of all-cause mortality, based on RT variability measures

	Simple RT						Choice RT					
	Raw SD model		CV model		ISD model		Raw SD model		CV model		ISD model	
	HR	*P*-value	HR	*P*-value	HR	*P*-value			HR	*P*-value	HR	*P*-value
Mean RT	0.956	0.477	1.022	0.653	0.950	0.427	1.026	0.639	1.078	0.117	1.024	0.667
Raw SD	1.143	**0.018**					1.079	0.123				
Coefficient of variation			1.137	**0.002**					1.078	0.079		
Intra-individual SD					1.150	**0.014**					1.082	0.110
Gender (female versus male)	1.643	**<0.001**	1.656	**<0.001**	1.643	**<0.001**	1.616	**<0.001**	1.614	**<0.001**	1.616	**<0.001**
Age	1.078	**<0.001**	1.079	**<0.001**	1.078	**<0.001**	1.076	**<0.001**	1.075	**<0.001**	1.076	**<0.001**
Years of education	1.015	0.372	1.016	0.344	1.015	0.382	1.015	0.397	1.015	0.386	1.015	0.400
Marital status		0.318		0.351		0.321		0.234		0.233		0.244
Single versus married	0.894	0.518	0.899	0.540	0.893	0.514	0.885	0.483	0.885	0.481	0.885	0.482
Widowed versus married	1.017	0.861	1.018	0.849	1.015	0.875	1.006	0.948	1.011	0.909	1.006	0.951
Div/sep versus married	1.234	0.183	1.220	0.207	1.236	0.178	1.275	0.121	1.270	0.128	1.273	0.123
Possible dementia (MMSE <24)	0.904	0.065	0.906	0.069	0.904	0.066	0.913	0.099	0.912	0.091	0.913	0.097
ADL score	1.101	**<0.001**	1.102	**<0.001**	1.101	**<0.001**	1.098	**<0.001**	1.099	**<0.001**	1.098	**<0.001**
Disease count	1.087	**0.001**	1.085	**0.002**	1.088	**0.001**	1.083	**0.003**	1.081	**0.004**	1.083	**0.003**
Smoking status		0.911		0.880		0.904		0.918		0.923		0.919
Previous versus never	0.986	0.830	0.983	0.797	0.986	0.833	0.995	0.940	0.996	0.945	0.996	0.946
Current versus never	1.037	0.672	1.044	0.619	1.039	0.660	1.032	0.718	1.031	0.729	1.032	0.724
Taking AH medication	0.942	0.210	0.944	0.223	0.942	0.211	0.929	0.124	0.929	0.125	0.929	0.124
Grip strength	0.978	**0.002**	0.978	**0.002**	0.978	**0.002**	0.980	**0.005**	0.980	**0.005**	0.980	**0.005**
Goldberg depression	1.049	0.082	1.048	0.089	1.048	0.087	1.040	0.165	1.041	0.158	1.039	0.176
Goldberg anxiety	0.958	0.060	0.959	0.067	0.958	0.058	0.967	0.146	0.967	0.148	0.967	0.150

Bold values indicate $P < 0.05$; RT measures are standardised to mean = 0, SD = 1; RT, reaction time; MMSE, Mini-Mental State Examination; ADL, activities of daily living; AH, antihypertensive.

Shipley *et al.* [31] and Deary and Der [32], who reported comparable results in two population-based cohorts using the raw ISD. Although mean RT measures exhibited univariate relationships with mortality, these effects were explained by age, gender and poor physical health. Variability on the simple RT task had the most robust association with all-cause mortality, with the three types of RT variability measures showing comparable relationships with outcome up to 17 years in the future.

These findings have important clinical implications. Although computation of ISDs may be subject to practical difficulties in clinical contexts, it is relatively straightforward for the clinician to administer a series of simple RT trials and calculate the intra-individual mean and standard deviation to obtain either the raw SD or the CV. There is no requirement to use normative regression processes to obtain standardised ISD scores. The raw SD and CV for simple RT are clearly metrics that have robust relationships with subsequent mortality. Importantly, our findings suggest similar predictive utility for all three IIV measures. This relationship is likely to be reflected in a range of other outcomes, including the presence of mild psychopathology [7, 8] and mild cognitive impairment or mild dementia [3, 4]. Further research comparing the predictive power of raw RT, CV and ISD on a range of psycho- and neuro-pathological outcomes may advance and inform the clinical utility of the simpler metrics. The raw SD and CV measures may supplement other neuropsychiatric tests in assessing risk of pathological outcomes. By illustration, an individual

with simple RT CV of 0.35 would have 29% increased hazard of mortality compared with an individual with simple RT CV at the sample mean of 0.19 in the present cohort.

There are a number of possible explanations for the relationship between within-person RT variability and mortality. Increased IIV in late life is likely to be indicative of neurological dysfunction [33], which may arise from life-long accumulation of neurological insult and vascular events. This dysfunction may manifest in the form of increased neural 'noise' arising from the reduced efficiency of the central nervous system generally, and neurotransmitter signalling in particular [17]. From a clinical perspective, therefore, our findings suggest that increased variability may mark neurobiological disturbance that accompanies impending mortality, and thereby may aid practitioner intervention.

As seen in the present analyses, markers for physiological integrity, including functional ability, disease count and grip strength, have strong associations with mortality and somewhat attenuate the effects of RT variability on mortality. However, our findings suggest that an independent relationship between RT variability and mortality remains. Additional research linking RT variability to direct markers of neurological dysfunction, and then linking specific neurological dysfunction to disease and terminal decline is needed. Furthermore, focused research is required to more explicitly test how the cascade of risk factors, from behavioural and biological influences, to subclinical and clinical disease, leads to mortality [34]. The finding that simple RT variability was more strongly predictive of mortality than choice RT variability is also worth noting. Previous research has found that choice RT slows throughout adulthood, whereas simple RT begins to slow in the 50 s [35]. Likewise, the effect of age on IIV has previously been shown to be stronger for simple RT than choice RT [6]. It is possible then that simple RT is more strongly influenced by age-related pathological states.

There were some limitations of the study. RT data from a single time point were used to predict mortality. It is not clear how changes in mean RT or RT variability over time might influence the findings. For example, participants may have had an aberrant result on the day of their interview due to illness or distraction. While this issue was partially addressed by careful cleaning of RT data, large sample size and adjustment for confounders, further study of changes in RT variability may shed light on the bases of the observed relationships. In addition, the examination of variability on a broader range of tasks, including verbal, numerical and memory tasks may better identify the pathways by which performance variability is associated with mortality. Likewise, additional assessment of health behaviours, cognitive performance, physical health and mental health may help to disentangle the pathways by which performance variability may lead to mortality.

In conclusion, the relationship between RT variability and all-cause mortality appears to be robust, even over extended time periods. The findings suggest that further understanding may be gained into the processes that lead to mortality through investigation of the neurobiological disturbances associated with increases in intra-individual variability. The relationship was most apparent for the simple RT task, and measures of RT variability that may be easily assessed. Simple RT variability, like other measures of health status, can be readily assessed using mobile and other portable devices by health professionals such as neuropsychologists. These tests seem to be as effective as more complex measures in predicting subsequent mortality. In contrast, the link between mean RT and mortality may be explained by age, gender and physical health.

Key points

- Intra-individual simple RT variability was strongly associated with an increased hazard of all-cause mortality.
- The raw SD and the coefficient of variability are simple measures of intra-individual variability that may be used by clinicians.
- Mean RT was not significantly associated with mortality risk after adjusting for physical and mental health.

Conflicts of interest

The funding body had no input into the study or the paper.

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