

Cognitive performance in high altitude Andean residents compared to low altitude populations: from childhood to older age

Catherine, M. Hill¹, Dagmara Dimitriou², Ana Baya³, Rebecca Webster⁴, Johanna Gavlak-Dingle⁵, Veline Lesperance¹, Kate Heathcote⁶ and Romola S. Bucks⁷.

² Department of Psychology and Human Development, Institute of Education, University of London, UK

³ Department of Psychology. Universidad Privada de Santa Cruz de la Sierra. Santa Cruz – Bolivia

⁴ Laboratory for Cancer Medicine, Western Australian Institute for Medical Research and University of Western Australia Centre for Medical Research, Perth, Australia

⁵ Institute of Child Health, University College, London, UK

⁶ Department of Otolaryngology, Poole General Hospital, UK

⁷ School of Psychology, University of Western Australia, Perth, Australia.

Corresponding author: Dr Catherine M. Hill

¹ Clinical Experimental Sciences, Faculty of Medicine, University of Southampton, Mail point 803 CB, G level, University Hospital Southampton, Tremona Road, SO16 6YD, UK. Tel +4423 8120 0796091.

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Abstract

Objectives: To assess cognition in populations born and living at high (3700m) and low altitude (500m) in Bolivia, who were similar for both socio-economic status and genetic ancestry. To determine whether high altitude hypoxia influences cognitive decline across the life-span.

Method: In total, 191 healthy participants aged 4 to 85 years were assessed at high (N = 94; 33; 35% male) and low altitude (N = 97; 46, 47% male) on a battery of cognitive tasks: fluid intelligence, attention, short- and long-term memory and psychomotor speed. Saliva samples were obtained for evaluation of genetic ancestry.

Results: High altitude participants were significantly slower on measures of processing speed and speed of attention than individuals born and living at low altitude. High altitude participants had slightly higher percentage of native Andean ancestry than low altitude participants, but this was not associated with cognitive performance.

Conclusions: This is the first study of high altitude residence and neurocognition across the life-span. Given the physiological challenges of high altitude living, the impact on cognition appears to be subtle and related only to the speed of more complex cognitive operations, rather than to their accuracy. Moreover, the impact on cognition does not appear to differ with increasing age or for different degrees of genetic admixture. Further studies recruiting HA participants with a broader range of native Andean ancestry will help to address the issue of to what extent Amerindian ancestry provides neuroprotection to chronic hypoxia in those living at HA.

Introduction

It is well understood that optimal neurocognitive function depends on efficient, uninterrupted oxygen delivery to the brain. A wide literature attests to the injurious effects of both acute and chronic intermittent hypoxia to neurocognitive function across the life-span highlighting deficits in executive function, attention, mental speed and memory (Areza-Fegyveres, Kairalla, Carvalho, Nitrini, 2010; Hogan, de Haan, Datta, Kirkham, 2006; Bucks, Olaithe, Eastwood, 2013).

High altitude (HA) environments, 2500m or more above sea level, present a natural, hypoxic, experimental setting. Barometric pressure drops exponentially with increasing altitude, resulting in parallel reductions in partial pressure of oxygen in the air and, hence, supply of adequate oxygen to the tissues.

High altitude mountaineering has provided the opportunity to study cognitive problems experienced by non-acclimatised sojourners. Both rate of ascent, altitude and location of study (field versus hypobaric oxygen chamber) are key determinants of cognitive findings. Previous studies have reported deficits in reaction time (Dykiert et al., 2010) and psychomotor skill learning, more evident in complex psychomotor tasks (Bouquet & Gardette, 1999). Importantly, studies have demonstrated persistent cognitive impairment after return to sea-level, specifically in long-term visual and verbal memory and reductions in speed on a finger tapping task (Hornbein, 2001). These persistent cognitive impairments are mirrored by quantitative MRI findings in high altitude climbers, which have demonstrated lasting, subtle changes in regional white and grey matter motor pathways (Di Paola et al., 2008).

While such studies provide interesting insights into short-term hypoxia exposure, they are conducted almost exclusively in healthy, young, adult males (often elite athletes) and tell us nothing about the impact of hypoxia on those who are born and live at high altitude. Specifically, little research has considered the challenge of living at HA on cognitive function. This is important as over 140 million people permanently live at HA through economic and social necessity. To thrive at HA, indigenous populations have evolved adaptations in the oxygen delivery chain (Moore, Armaza, Villena & Vargas, 2000). Indigenous Amerindians settled in the HA Andean

mountain range around 10,000 years ago (Moore et al., 1992) and have adapted principally through increased red cell production (erythropoiesis), thus increasing oxygen transport in the blood. However, this adaptation comes at a price - Andeans have an estimated 15% risk of chronic mountain sickness (CMS), (León-Velarde, Arregui, Monge, Ruiz & Ruiz, 1993) characterized by excessive erythropoiesis and severe hypoxemia (León-Velarde et al. 2005). The partial adaptation to HA in Amerindians is, perhaps, not surprising as the Andean topography has permitted travel between the high plains and low altitudes, resulting in genetic admixture between adapted highlanders and non-adapted lowlanders. This genetic dilution was further amplified by European genetic admixture following the Spanish conquest 400 years ago (Moore, et al., 2000).

Hogan and colleagues (2010) were the first to report cognitive functioning in healthy Andean children. Two hundred and seventy-eight resident children aged 6 months to 16 years were studied across three altitude settings at 500m (Santa Cruz), 2500m (Cochabamba) and 3700m (La Paz) in Bolivia. Differences were found with increasing altitude in specific cognitive measures requiring performance under time-pressure in children and adolescents, although not infants. Specifically, both finger tapping and processing speed measures were sensitive to altitude location. These measures have previously been noted to be highly sensitive to hypoxia-related cognitive impairment at altitude (West, 1984). The authors proposed a 'slower is surer' hypothesis, whereby hypoxic constraint results in slowed cerebral function and a speed-accuracy trade off at HA. Similar evidence is lacking for the Andean adult population. The impact of aging in a HA resident population is, however, an important area of study. Aging may present specific challenges to the brain in this setting due to the high prevalence of chronic mountain sickness (33.7% in 60-69 year-olds) in older adults (León-Velarde, Arregui, Monge, Ruiz y Ruiz, 1993), further threatening cerebral perfusion and oxygenation. The only study of cognitive function in elderly HA residents was in a Ladakhi Himalayan population with unique phenotypic adaptation to HA hypoxia and, unlike Andean HA populations, a history of relative isolation resulting in little, low altitude, genetic admixture (Beall, 2007). The authors reported significantly lower performance on tests of visuo-spatial problem solving and time estimation in 40 HA Ladakhi adults, aged 74.7 ± 3.3 years compared to 324 LA Japanese residents aged 80.7 ± 4.7 years (Otsuka et al., 2005). However, this study failed to control for age, socio-economic status, educational level or genetic admixture, limiting interpretation of the data. This is

important as low socio-economic status, particularly in childhood, is associated with deficits in multiple cognitive domains (Hackman, Farah, Meaney, 2010). While ethnicity and socio-economic factors are frequently inter-related, nonetheless, research indicates ethnic differences in cognitive performance (Ng, Niti, Chiam, & Kua, 2007; Schwartz et al., 2004) as well as cognitive-decline with aging (Moody-Ayers, Mehta, Lindquist, Sands, & Covinsky, 2005) independent of socio-economic status. The unique phenotypic adaptation of Amerindians to high altitude living as well as the significant European genetic admixture found at high altitude in Bolivia make ethnicity an important co-variate in any assessment of cognition.

Thus, although there is evidence that life-time residency at HA in native Andeans is associated with increased morbidity and earlier mortality (Virués-Ortega et al., 2009), to the authors' knowledge, there are no published studies of cognition in these populations who, with their particular phenotypic adaptation to hypoxia, may risk unique cognitive decline.

This study aimed to assess cognitive abilities from childhood to older age in socio-economically and ancestry-similar populations at both high (3700m) and low altitude (500m) settings in Bolivia.

Participants

A total of 229 participants was recruited from a low altitude (LA) city - Santa Cruz, 500m above sea-level, and a high altitude (HA) city – La Paz, 3700m above sea-level where partial pressure of atmospheric oxygen is approximately 2/3 of that at sea-level. At each location, four age groups were studied: children (4-10 years; LA = 44, HA = 52¹); adolescents (13-16 years; LA = 23, HA = 25); young adults (25-40 years; LA = 20, HA = 20) and older adults (≥50 years; LA = 22, HA = 23). All participants were recruited through advertisement in the Universities of each town. Inclusion criteria specified that participants were born at their resident altitude; children and adolescents had continuously resided at this altitude, other than visits of less than 6 months' duration to other altitudes, but not within the last year, and that adults were born at the study altitude and

¹ For the purposes of some analyses, 4-10 year olds were further divided into 4 to 6 years and 7 to 10 years of age, since there are marked changes in cognitive capacity over this age span and separate cognitive assessments were used, as appropriate, for each age-group. Accordingly, the numbers were: 4 to 6 year old children; LA = 20 (13 male), HA = 25 (10 male), 7 to 10 year old children; LA = 24 (14 male), HA = 27 (17 male).

had lived there for the past 5 years. All participants were from families where Spanish was spoken as the first language. Exclusion criteria included participants who were adopted, born pre-term (before 37 weeks' gestation), those with significant developmental delay or learning difficulties, diagnosed with an established neurological or neurodegenerative condition (other than dementia, which could represent a phenotypic expression of cognitive decline at altitude), history of significant brain injury, epilepsy, psychotic disorder, taking psychoactive medication, or smokers. In total, 38 participants did not meet the inclusion criteria², leaving 191. There were no significant differences in the distribution of males and females by age-group for either altitude: LA: $\chi^2(4) = 4.6, p = .118$; HA: $\chi^2(4) = 9.0, p = .061$.

Ethics committee approval for the study was obtained from the Institutional Ethics committees of the Universidad Privada Abierta Latinoamericana, Cochabamba, Bolivia and the University of Western Australia.

Descriptive measures

Socio-demographic data: data were collected for adults and parents of participant children on age of completion of full time education.

Pubertal development: Adolescents (13 to 16 years) completed the 6-item Pubertal Development Scale (Carskadon & Acebo, 1993). Points are averaged to produce a Pubertal Development Scale score.

Chronic Mountain Sickness Score (CMS) (Leon-Valarde, McCullough, McCullough, & Reeves, 2003). High altitude participants were rated using standard CMS scoring based on neurological, cardiovascular, and hematological variables, where a score of 12 is considered normal. Three older adults had abnormal scores, however, all had haemoglobin levels within normal limits (range 12.5 to 15.5g/dl) confirming that none of the HA participants had CMS.

² 2 were born at an altitude other than that being assessed, 1 smoked, 3 had a prior history of brain injury, and 32 provided insufficient information to allow us to determine whether or not they met our inclusion/exclusion criteria.

Cognitive measures

All cognitive measures selected were chosen to be suitable to measure the same cognitive construct from age 4 to older adulthood, and were available in Spanish.

Raven's Matrices

Raven's Matrices were used as a measure of the ability to form perceptual relations and to reason by analogy. The matrices are independent of language and formal schooling. The Standard Progressive Matrices (Raven, Raven, & Court, 2000) were used for participants aged 7+ and the Coloured Progressive Matrices (Raven, Raven & Court, 1998) for children aged 4 to 6 years.

Cognitive Drug Research (CDR) battery

The CDR offers the advantage, over most cognitive tools, of both continuity across the life-span from 4 years of age and computerised measures of speed and accuracy, in a Spanish version (Wesnes, Ward, McGinty & Petrini, 2000). It has been used extensively in assessing subtle cognitive changes with illness (Keith, Stansilav & Wesnes, 1998; Forton et al., 2002; Kennedy, Scholey, & Wesnes, 2001; Wesnes et al., 2000), including the impact of oxygen on performance (Scholey, Moss, & Wesnes, 1988). Task outcomes from the CDR collapse into two broad categories of memory and attention comprising five factors derived by factor analysis (Wesnes et al., 2000).

Memory factors:

'Quality of Episodic Secondary Memory': derived by combining the percentage accuracy scores (adjusted for proportions of novel and original stimuli, where appropriate) from four secondary memory tests - delayed word recognition, delayed picture recognition, immediate word recall, and delayed word recall (with adjustments to the total % correct for errors and intrusions on the latter two tasks); 100% accuracy across the four tasks generates a maximum score of 400³.

³ 4 to 6 year olds were not given the word recall task, since this contained words they would have been unable to read. Accordingly, quality of episodic memory is based on percentage correct delayed picture recognition performance only, in

'Quality of Working Memory': derived by combining the percentage accuracy scores from two working memory tests - spatial and numeric; 100% accuracy across the two tasks generates a maximum score of 200.

'Speed of Memory': derived by combining the reaction times of the four computerized memory tasks - numeric working memory, spatial working memory, delayed word recognition, and delayed picture recognition (units are summed milliseconds for the four tasks)⁴.

Attention factors:

'Accuracy of Attention': derived by calculating the average percentage accuracy across choice reaction time and digit vigilance tasks (adjusted for false alarms from the latter test); 100% accuracy across the tasks generates a maximum score of 100.

'Speed of Attention': derived by combining the reaction times of three attentional tasks - simple and choice reaction time, and digit vigilance (units are summed milliseconds for the three tasks).

Psychomotor speed:

Simple motor speed:

The CDR battery also offers a Tapping Task (Bosanac, Kurlender, Norman & Hallam, 2007), in which the participant is required to tap a button continuously, as quickly as possible, for a 30 second period. Participants responded using the dominant hand. The total number of taps is taken as the outcome measure.

Cognitive psychomotor speed (from the Weschler scales)

Finally, across all ages, the processing speed measures (Digit Symbol/Coding substitution and Symbol Search subtests) from Spanish versions of the Weschler scales: WPPSI III (age 4 to 6 yrs.; Wechsler, 2002), WISC IV

this age-group. To be comparable to the scores for older participants, this value was then multiplied by 4, giving a maximum of 400.

⁴ Likewise, for 4 to 6 year olds only, speed of memory retrieval was based on numeric working memory, spatial working memory and delayed picture recognition reaction times, multiplied by 4 and divided by 3 to be comparable to older age-groups.

(form A age 7, form B 8 to 16 years; Wechsler, 2004) or WAIS III (age 25 +; Wechsler, 1997) were administered.

Genetics

DNA were extracted from saliva samples (Western Australia DNA Bank, University of Western Australia) and whole gene amplified (K BioSciences, Hoddesdon, UK). Individual European, Native American and African admixture proportions were estimated using a panel of 28 ancestry informative markers (AIMS) previously noted to demonstrate high frequency differences in allele frequency between these different ancestry groups (Tsai et al. 2006; Brutsaert et al. 2004). The admixture modelling program admixmap (Hoggart, Shriver, Kittles, Clayton & McKeigue, 2004) (<http://homepages.ed.ac.uk/pmckeigu/admixmap/index.html>) was used to model the distribution of admixture in the cohort and to generate individual ancestry estimates. AIM ancestry-specific allele frequencies were estimated from their reported counts in modern European, African and Native American populations (Tsai et al., 2006; Brutsaert et al., 2004).

Procedure

All participants were provided with information sheets about the study and adults signed consent forms, whilst children gave verbal consent, with parental signed consent. Data collection took place within University premises at UPSA, Santa Cruz (500m) and Universidad de La Salle, La Paz (3700m). Neuropsychological assessment took place within a quiet room. All child participants received a small gift for their participation such as a toy or game (<US\$3 in value). The study took place in the spring months when the temperature was temperate at high altitude and warm at low altitude.

Statistical analysis

Data were checked for multivariate normality. All data from children included in this study were entered in the analyses. Between-altitude and age-group differences were explored using analysis of variance (ANOVA/MANOVA), of altitude (Low altitude, High altitude) by age group (children [or 4 to 6, 7 to 10 year olds, for cognitive measures], adolescents, adults, and older adults). Given marked, uncorrectable skewness, genetic admixture data were analysed using non-parametric statistics. Because Bolivian age-norms were not available for any of the neuropsychological tests, and several of the scales had different maximum scores for the different age groups, to explore altitude effects mean scores from the LA participants for each age group were used to calculate Z scores for each individual, dividing by the pooled standard deviation (plots by age and altitude of raw scores can be found in the online supplement).⁵ While the Ravens Matrices test is reported to be unbiased by culture, for consistency across the measures (and because the versions also have different maximum scores), we also reported z scores for this scale. That is, the mean for each high altitude group represents the effect size of the difference between high and low altitude performance, where effects of ≤ 0.20 are considered small, $= 0.50$ medium, ≥ 0.80 large and ≥ 1.00 very large. Although it is usual to report the Processing Speed Index for the WISC/WAIS, this is based on the sum of scaled scores for Coding and Symbol Search, thus requiring norms. Instead, we explored the impact of age and altitude on these tasks with a multivariate analysis of variance. An alpha level of .05 was used throughout.

Due to the exploratory nature of the current study, Bonferroni adjusted alpha levels were not calculated for multiple comparisons (see Perneger, 1998; Rothman, 1990).

Results

Data were obtained from 191 individuals across the two altitude locations (see Table 1). There were no differences between altitudes for age, gender or socio-economic status (SES), defined by maternal education

⁵ Z scores for each neuropsychological test for each age group were calculated using the equation $Z = (\text{Mean LA} - \text{test score}) / \text{SQRT}((SD_{LA}^2 + SD_{HA}^2) / 2)$

for children and maximal educational level for adults. The majority of participants were of middle-to-high social strata, many being professionals or the children of professionals.

Ethnicity was examined using multiple means. All but one low altitude resident child was born in Bolivia, and all but one child (born in Bolivia) had at least one Bolivian parent (this child was of Argentinian ancestry). All older adults were born in Bolivia, whilst 94% of 25-40 year old adults were born in Bolivia (the other two were born in Argentina and Brazil).

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Table 1 about here

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DNA ancestry

Saliva samples were collected from 180 participants. Of these, 2 were poor quality, and 23 were excluded from altitude by age-group comparisons because they were from siblings from the same family, leaving 155 (86.1%) samples.

Analysis of the AIMs indicated an admixed population comprising: low altitude 46% (95% CI = 44-48%) Native American, 52% (95% CI = 50-54%) European, and 2% (95% CI = 2-3%) African ancestry, and high altitude 50% (95% CI = 48-52%) Native American, 48% (95% CI = 46-50%) European, and 2% (95% CI = 1-2%) African ancestry. As was anticipated, high altitude participants had slightly higher Native American, $H(1,154) = 5.85$, $p = .016$, and lower European admixture $H(1,154) = 4.28$, $p = .039$, but no differences in African admixture ($p = .612$). There were no age-group differences (all $p \geq .40$). Given that admixture was not a significant covariate of neuropsychological performance, these differences were not considered further.

Pubertal development

Pubertal development scores were available for 13 (87%) of low altitude and 13 (76%) of high altitude adolescents and did not differ by altitude for either gender: males – LA 2.9 ± 0.3 , HA 2.3 ± 0.6 ; females – LA 3.0 ± 0.5 , HA 3.1 ± 0.3 , both $X^2 < 1$.

Taken together, these data suggest that the age-groups were well matched across low and high altitude.

Neuropsychological functioning

Raven's Matrices

Despite **a trend towards significance** for an altitude difference on Raven's Matrices, $F(1,173) = 3.20$, $p = .076$, $\eta_p^2 = .02$, none of the within age-group comparisons revealed a significant altitude difference (**see Figure 1i**).

CDR battery tests:

There were no effects on the Quality of Episodic Memory (all $F < 1$), on the Quality of Working Memory (all $F < 1.8$), or on speed of retrieval from memory (all $F < 1.2$) (**see Figures 1e, f and g**).

There were no effects on accuracy of attention (all $F < 2$) (**see Figure 1c**), although there were altitude differences in speed of attention, $F(1,172) = 3.92$, $p = .049$, $\eta_p^2 = .02$, such that HA participants had slower response times on the attention tasks in comparison to the LA participants (see Figure 1d). In addition, there was a trend towards significance for an age-group effect, $F(4,172) = 2.22$, $p = .069$, $\eta_p^2 = .05$, and for an interaction between age and altitude, $F(4,172) = 2.22$, $p = .069$, $\eta_p^2 = .05$. **Given the moderate effects found, we explored altitude differences by age-group. These effects were** driven by HA slowing in the 7 to 10, 13 to 16, and 25 to 40 year olds which **likewise approached significance**, all $p = .081$, **and significant high-altitude slowing** in the adolescents, $p = .017$ (**see Figure 1d**).

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Figure 1 about here

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Finger tapping rate, a measure of simple motor speed, was not impacted by altitude or age (all $F < 2.1$) (**see Figure 1h**). However, there was a significant effect of altitude on processing speed (Coding and Symbol Search), omnibus $F(2,164) = 4.28$, $p = .015$, $\eta_p^2 = .05$, characterised by differences in Coding, $F(1,165) = 8.17$, $p = .005$, $\eta_p^2 = .05$ (**see Figure 1a**), but not in Symbol Search, $F(1,165) = 1.14$, $p = .284$, $\eta_p^2 = .01$ (**see Figure 1b**), such that HA participants had poorer Coding scores than LA participants. Post hoc, within age-group comparisons revealed significant altitude differences favouring low altitude in 25 to 40 year olds, $p = .043$. This suggests that cognitive psychomotor speed is slower in HA populations. However, there were no effects of age and no interaction (both $F < 1.5$; see Figure 1a, b).

DISCUSSION

The challenge of permanent residence at altitude on the most defining human characteristic, namely, cognitive function, is a relatively neglected area of study. Limited research, to date, has focused either on a narrow age range of Andean children or older Himalayan adults. To our knowledge, this is the first study to compare a population born and permanently living at HA across the life-span with a matched low altitude population. Data from 191 participants, aged 4 to 85 years, of mixed Andean-European genetic ancestry revealed no altitude-related differences in a suite of higher order cognitive functions. Specifically, no differences were found in fluid intelligence, episodic memory accuracy, working memory accuracy or speed of memory retrieval. Nor were there altitude-related differences in simple motor speed. By contrast, we observed significantly slower psychomotor speed in attention and digit symbol coding tasks. Where there were altitude differences (psychomotor speed – digit symbol coding), or **a trend towards significant differences** (speed of attention) these appear to arise either in adolescence or in younger adulthood, and seem not to be evident earlier or later in the lifespan. Moreover, these data suggest that, despite the physiological challenges of HA living, its impact on cognition appears to be subtle.

These findings extend those of the earlier Andean childhood study (Hogan, et al., 2010), which also found subtle differences between high and lower altitude groups of 6 to 10 year old children and 13 to 16 year old

adolescents in processing speed, using the same measures. Our data also show interesting parallels to neurocognitive studies in non-acclimatised lowlanders exposed to HA. For example, Hayashi and colleagues (2005) reported prolonged P300 latencies to an auditory stimulus after brief exposure to hypobaric hypoxia in healthy lowland volunteers, while a Thakur and colleagues (2011) reported increased P300 latency, with no difference in amplitude using the novel oddball paradigm in healthy, young, male, Indian army recruits after 6 months living at 4115m ; providing neurocognitive evidence of processing speed delay. Wilson et al. (2009), in their review of the cerebral effects of ascent to high altitudes, noted that impairment of complex reaction time and psychomotor speed emerge in sojourners at altitudes up to around 4000m, while learning and memory impairments are more typical at very high altitudes up to 5500m. Thus, consistent across both sojourner and native highlander studies is the finding of psychomotor slowing after short and long-term exposure to HA hypoxia.

The physiological mechanism by which speed of processing is compromised in HA settings is not well understood. One possibility is that hypoxia impacts directly on neurotransmitter production. Early animal studies have revealed altered synthesis of monoamines under hypoxic conditions in rats (Freeman & Gibson, 1988). Furthermore, recent data have demonstrated memory deficits in rats exposed to extreme hypobaric hypoxia (7600m) associated with abnormal glutamate excitotoxicity (Hota , Barhwal, Singh, Sairam, Ilavazhagan , 2008) and perturbations of choline acetyltransferase/acetyl cholinesterase expression in murine models exposed to simulated altitude of 5000m (Guerra-Narbona , Delgado-García, López-Ramos, 2013). While these animal studies involve non-acclimatised animal models and extreme altitude simulation, it is tenable that more subtle effects may be seen in adapted, human altitude residents. Certainly, there is evidence of cerebral hypo-metabolism in young adult Andean Quechuas born and living between 3,700 and 4,900 m (Hochachka, et al., 1994). Positron emission tomographic measures shortly on arrival at low altitude demonstrated reduced cerebral glucose metabolism, particularly in brain regions associated with higher order function such as the frontal cortex. Whether this is an adaptive strategy that facilitates more efficient cognitive function with lower energy demand or whether reduced metabolism correlates with altered cognitive function is unclear, as the latter was not studied.

The cognitive processing-speed digit symbol test of the adult WAIS III has recently been mapped to white matter in the parietal and temporal lobes bilaterally and in the left middle frontal gyrus using voxel-based morphometry applied to diffusion tensor imaging data (Turken, et al., 2008). It is understood to depend on the functionality of major white matter fibre tracts integrating frontal and parietal lobes. Similarly, diffusion tensor imaging studies of information processing speed in children demonstrate that development of regional white matter organization underpins increased speed of visual searching with age (Mabbott, Noseworthy, Bouffet, Laughlin & Rockel, 2006). This is relevant, as diffusion tensor imaging studies of young HA mountaineers (ascending to over 6000m with no supplemental oxygen) have shown compromised white matter microstructural integrity on return to sea-level (Zhang et al., 2012). It is feasible that long-term HA residence in incompletely acclimatised populations may lead to similar, white matter abnormalities that may underpin psychomotor slowing.

Finally, it is possible that slower processing speed is a deliberate cognitive strategy to maintain performance. However, the failure to find speed differences in retrieval from memory in this study speaks against such an account.

The absence of abnormalities of hippocampal function in our study, as evidenced by no differences in episodic memory accuracy or speed, suggests that there is functional, but imperfect, adaptation to hypobaric hypoxia that appears to take the form of a speed-accuracy trade-off. As, Hogan et al. (2010) suggested, slower may be surer.

A novel aspect of our study was the investigation of cognition across the age-span. Recent studies in Alzheimer's disease have shown that the expression of dementia-related genes is sensitive to altitude (Sun et al. 2006). Studies at sea-level have emphasized the role of oxidative damage in the aetiology of neurodegenerative diseases including Alzheimer's disease, fronto-temporal dementia and Parkinson's disease (Gerst, et al., 1999; Zheng, Marcusson & Terman, 2006). In the light of this evidence, we predicted deterioration in cognitive performance in older adults (over 55 years). Intriguingly this was not the case. While younger adults (25 to 40 years) demonstrated the same pattern of cognitive impairment for psychomotor

(coding and attention) speed measures at high altitude that we observed in children and adolescents in our earlier study (Hogan et al., 2010), surprisingly, altitude differences were absent in the older adults. Further consideration of our HA older adult group suggests selection bias. Leon-Valarde et al., (1993) reported a prevalence of chronic mountain sickness of up to one third in older adults. None of our adult participants had chronic mountain sickness. Furthermore, data from similar Andean samples (Virues-Ortega et al., 2009) indicated that life-time residency at HA is associated with earlier mortality and that this difference is significant at the age of 60 years, the mean age of the older adults in our study. It is possible, therefore, that the older adults in our study represented extreme selection bias, namely, they were survivors. A longitudinal study design would avoid such selection bias in our older sample but would present considerable challenges in HA settings. An alternative would be to recruit adults aged 40 to 50 years.

Higher cognitive reserve in the study population, that is, the capacity of the brain to compensate for oxygen delivery constraint, either through inter-individual differences in neural reserve or enhanced ability to adapt neural processing (Stern, 2009), may have masked altitude related cognitive differences. The study sample was skewed towards highly educated participants, with 73% of all high altitude adults having a University degree. Future studies would usefully include a broader socio-economic sampling frame to include participants with lower IQ, where altitude related differences may be amplified.

Another explanation for the relatively subtle differences seen in our study relate to the level of altitude studied. Sojourner research demonstrates that increasing ascent beyond 3500m in non-acclimatised mountaineers is associated with a changing profile of cognitive impairment (Wilson et al., 2009). Virués-Ortega et al. (2011) compared children living at altitudes above 4000m in El Alto, Bolivia to socio-demographically similar children living at 3700m. Significant differences were noted in executive function tasks above 4000m although there was no further deterioration in psychomotor tasks; supporting the concept of an altitude threshold for neuropsychological impairment. It is therefore possible that age-dependent differences in the profile of cognitive impairment would be more apparent at altitudes above 4000m. Such a threshold for increased risk of neurocognitive impairment could be explained by altered cerebral perfusion at

extremes of altitude. Jansen et al., (2007), reported loss of cerebral autoregulation between 3,500 and 4,243 m in Nepali Sherpas. Similar studies in an Andean population would be instructive.

Genetic ancestry data indicated approximately 50% European DNA ancestry within our HA study population. The principle reason for studying DNA ancestry was to ensure that our altitude samples were similar. That the HA sample had cognitive impairment similar to findings reported in non-adapted sojourners may reflect this significant European genetic ancestry admixture and, thus, incomplete adaptation. Future studies purposively recruiting individuals with a higher proportion of Amerindian genetic ancestry would clarify whether there is a 'dose-response' relationship between Amerindian ancestry and protection from cognitive impairment at altitude.

Finally, given the proposed, frontally-mediated nature of the cognitive impact of hypoxia, another possibility is that the cognitive measures were insensitive. The prefrontal cortex (PFC) is the largest and last part of the brain to develop and changes throughout the lifespan (Fuster, 2002). However, traditional neuropsychological measures are often insensitive to frontal changes (Sbordone, 2010). One reason is that the structured nature of many tasks obviates the need for participants to exert much cognitive control over their behaviour, or to make decisions about a task, both of which require an understanding of the consequences of future outcomes (Coutlee & Huettel, 2011). Cognitive control is the ability selectively to attend and to respond to task-relevant events while inhibiting distracting information or interference from prepotent (often automatic) responses (Miller & Cohen 2001). Both cognitive control and decision-making have been shown to be highly sensitive to medial PFC changes and may, therefore, be sensitive to the impact of hypoxia. Functional imaging (e.g. fMRI or EEG/ERP) would complement such assessments and provide evidence of the neurological changes underlying any altitude effects if found.

To summarise, this is the first study of HA residence and neurocognition across the life-span. Given the physiological challenges of HA living, the impact on cognition appears to be subtle and related only to the speed of more complex cognitive operations, rather than to their accuracy. Moreover, the impact on

cognition does not appear to differ with increasing age or for different degrees of genetic admixture. Further studies, recruiting a larger sample of HA participants with a broader range of native Andean ancestry, from higher altitudes, and across a wider socio-economic sampling frame, will help to address the issue of to what extent Amerindian ancestry provides neuroprotection to chronic hypoxia in those living at HA.

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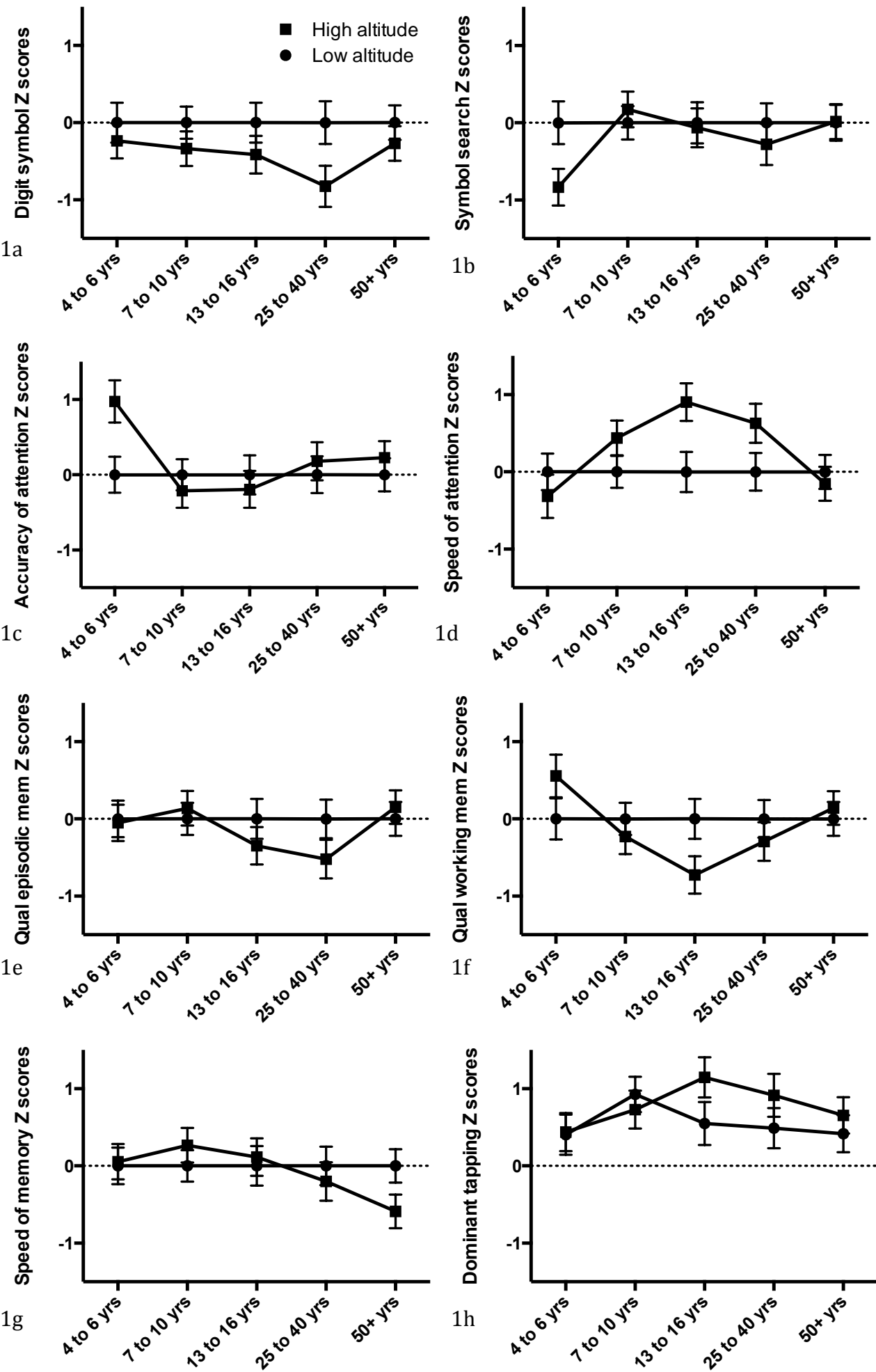
Table 1. Age, gender and socio-economic status of sample, by altitude group (*N* = 191)

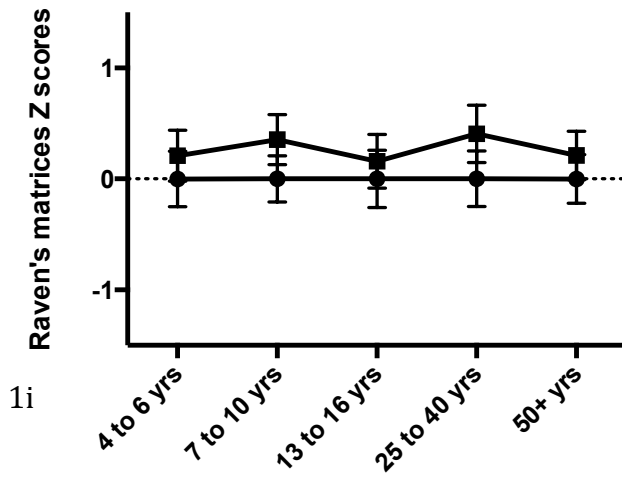
	Low altitude	High altitude	Sig.
Mean age (<i>SD</i>)			
Children (4 to 10) (yr)	7.0 (1.9)	7.0 (2.0)	.979
4 to 6 years	5.1 (0.8)	5.2 (0.8)	.711
7 to 10 years	8.4 (0.9)	8.7 (1.1)	.331
Adolescents (yr)	14.7 (1.1)	14.0 (1.1)	.715
Adults (yr)	33.3 (4.9)	31.9 (5.9)	.476
Older adults (yr)	60.1 (8.6)	61.3 (7.1)	.609
Number of participants [Gender (M: F)]			.979
Children (4 to 10)	42 [25 : 17]	40 [19 : 21]	
4 to 6 years	18 [11 : 7]	19 [6 : 13]	
7 to 10 years	24 [14 : 10]	21 [13 : 8]	
Adolescents	15 [6 : 9]	17 [4 : 13]	
Adults	18 [6 : 12]	16 [5 : 11]	
Older adults	22 [9 : 13]	21 [5 : 16]	
Age maternal education completed			
Children	21.6±5.3	25.4±4.3	.255
Adolescents	24.9±6.0	25.3±8.1	.484
University educational level attained			.104
Adults	17 (94%)	14 (88%)	
Older adults	12 (57%) ²	13 (62%)	

Note. Educational level is missing for 1 older adult at LA.

Figure

Figure 1. Neuropsychological test performance by age and altitude (Z scores from low altitude means)

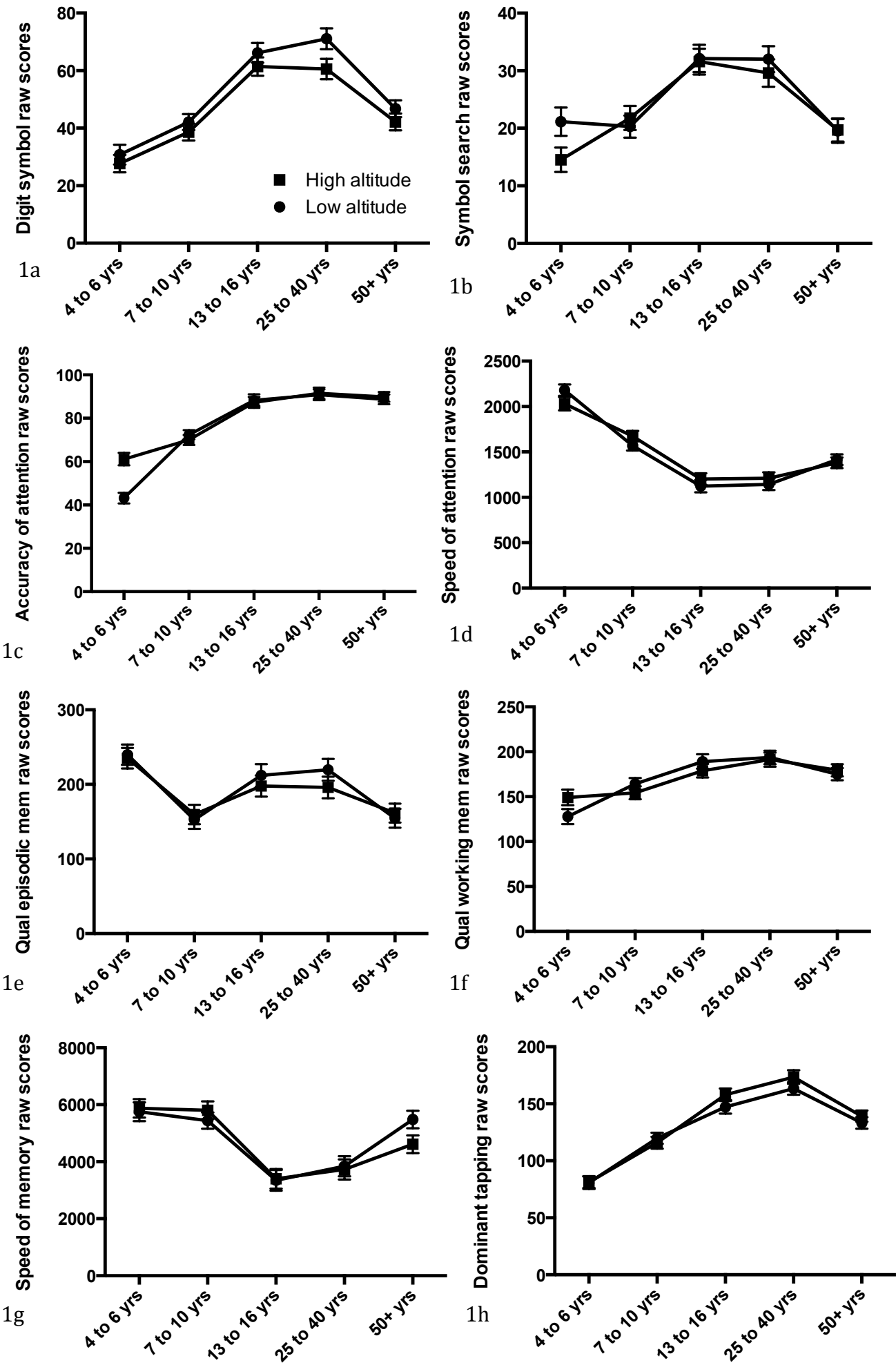


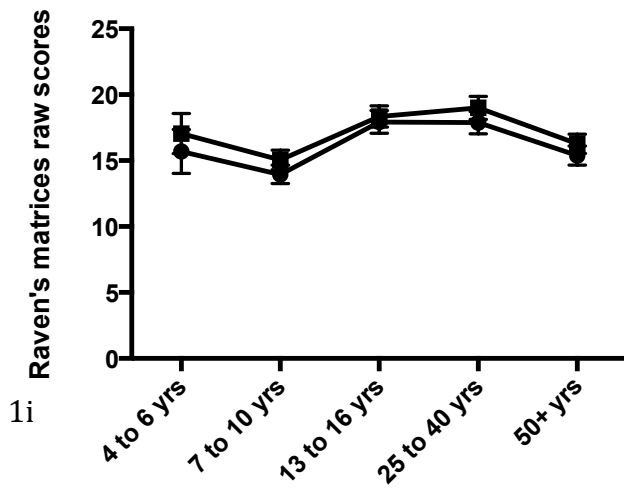


Note. The mean Z scores for each high altitude group represents the effect size of the difference between high and low altitude, where effect sizes of ≤ 0.20 are considered small, $= 0.50$ medium, ≥ 0.80 large and ≥ 1.00 very large. Higher scores indicate better performance, with the exception of speed of attention and speed of memory, where higher scores indicate slower performance.

Figure

Online Appendix 1. Neuropsychological test performance by age and altitude groups (raw scores)





Note Higher scores indicate better performance, with the exception of speed of attention and speed of memory, where higher scores indicate slower performance. Maximum scores vary by age and test, such that mean values are not comparable across age, only across altitude.

Checklist

[Click here to download Supplemental Materials: Neuropsychology Author\(s\) Agreement Checklist.pdf](#)