

# Demographic, structural and genetic predictors of late cognitive decline after penetrating head injury

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**We examined the relationship of pre-injury intelligence, demographic variables, lesion location, brain tissue volume loss and a number of genetic markers to long-term cognitive decline in a group of Vietnam veterans with predominantly penetrating head injury (PHI) suffered more than 30 years ago. Using linear and stepwise regression procedures, we found that those with PHI demonstrated a greater degree of cognitive decline overall during the years following recovery from injury compared with a control group of uninjured Vietnam veterans. This became increasingly significant later in life. We also found that pre-injury intelligence was the most consistent predictor of cognitive outcome across all phases of potential recovery and decline after such injuries. While laterality of lesion was not a factor, we did find some associations between atrophy and specific regions of tissue loss and long-term cognitive functioning. Finally, we found evidence for an association between level of cognitive decline following PHI and the possession of certain genetic markers that have been linked with brain injury and neurodegeneration. Thus exacerbated decline does occur in Vietnam veterans with PHI and it is apparently unrelated to dementia and is determined by multiple factors (most notably pre-injury intelligence).**

**Keywords:** cognitive decline; brain injury; penetrating brain injury; genetics; predictors

**Abbreviations:** ATP = adenosine triphosphate; AD = Alzheimer's disease; ANOVA = analysis of variance; AFQT = Armed Forces Qualification Test; AIR = Automated Image Registration; BDNF = brain-derived neurotrophic factor; COMT = catechol-*O*-methyl transferase; CHI = closed head injury; DBH = dopamine beta-hydroxylase; GABA = gamma-amino butyric acid; GAD = glutamic acid decarboxylase; MMSE = Mini-Mental State Examination; NMDA = *N*-methyl-*D*-aspartate; PHI = penetrating head injury; P1 = phase 1; P2 = phase 2; P3 = phase 3; TVL = total volume loss; TBI = traumatic brain injury; VA = Veterans Affairs; VHIS = Vietnam Head Injury Study

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This study aimed to investigate the associations between long-term indicators of general intelligence and penetrating head injury (PHI). This has been an area of limited study to date, with the great majority of research involving closed head injuries (CHIs). We examined the relationship between pre-injury intelligence and late cognitive decline 36–39 years post-injury, in a group of Vietnam veterans with PHI. We also investigated whether site or size of lesion within the brain may affect levels of general intelligence decades after a PHI, and if certain genetic polymorphisms may influence long-term cognitive outcome after PHI.

## Importance of traumatic brain injury

Traumatic brain injury (TBI) is the primary cause of death and disability in those under 35 in the USA, with civilian PHI being one of the fastest-growing types of HI. Each year approximately 55 000 deaths result from TBI and an additional 50 000 people suffering from persistent physical, cognitive, behavioral, and social deficits resulting from TBI (Kraus and McArthur, 1996). TBI remains prevalent in combat situations, with nearly two-thirds of injured US soldiers sent from Iraq to Walter Reed Army Medical Center having been diagnosed with traumatic brain injuries.

Of the 58 000 US combat fatalities in the Vietnam war, about 40% were due to head and neck wounds. Overall, about 19% of casualties and 14% of survivors suffered a HI. Early field care and rapid helicopter evacuation, combined with the deployment of neurosurgical teams close to the battlefield resulted in survival of many more severely wounded men than in previous conflicts (Rish *et al.*, 1983; Hammond, 1986; Carey, 1987).

The military population offers a number of advantages for the study of the long-term effects of HI: its size, relative uniformity, and the potential for long-term follow-up. Also, young recruits were, by definition, healthy and employed. Pre-injury, and pre-injury intelligence and aptitude testing is available on most of them for comparison with post-injury performance. Additionally, the Veterans Affairs (VA) medical system has allowed them to be tracked over a long follow-up period. Finally, the low-velocity penetrating fragment wounds typically sustained at the time of Vietnam resulted in relatively focal defects that allow for unique brain structure–function studies. Thus these patients, in particular, can provide unique information regarding the effects of PHI on long-term cognitive and social functioning.

### Connections between TBI and cognitive decline

The possibility of cognitive decline many years following HI remains poorly understood (Brooks, 2003; Himanen *et al.*, 2006). Progress has been hindered by the lack of studies able to examine relatively discrete brain lesions, as little research has been conducted with discrete brain injuries (but see Grafman *et al.*, 1988; Corkin *et al.*, 1989). Additionally, most analyses have focused on the link between HI and dementia, not on the concept of a unique process of accelerated cognitive decline specific to TBI.

In one of the few studies that have examined the effects of focal and penetrating head injuries on long-term cognitive deterioration, Corkin *et al.* (1989) examined PHI survivors from the second world war and found that HI did indeed exacerbate the cognitive decline of normal ageing, with left hemisphere injuries having a greater impact than right hemisphere lesions. There appeared to be some site-specific effects, with subjects with left posterior lesions showing greatest decline on verbal-based cognitive testing (including vocabulary and arithmetic), and those with right parietal lesions showing exacerbated decline on tests of spatial functioning. Additionally, subjects with left parietal lobe damage showed decline in the greatest number of neuropsychological subtests, while those with frontal lobe lesions displayed no increased level of cognitive decline. While the numbers were too small to make any definitive conclusions, this study laid the groundwork for future studies of penetrating head injuries. More recently, Himanen also demonstrated a decline in most cognitive domains many years after severe HI. Subjects showed

greater deterioration on the performance subtests of the WAIS compared to the verbal subtests (Himanen *et al.*, 2006). Those injured in the second or third decade of life showed greater improvement than other HI individuals; however, they still performed at a lower level than controls on all cognitive tasks. Some studies have also shown a link between mild TBI and accentuated ‘normal ageing’, with evidence that even minor CHI leads to earlier onset and accelerated cognitive ageing (Klein *et al.*, 1996).

These data have led to the development of the ‘margin of safety model’ of the long-term effects of HI (Corkin *et al.*, 1989). This relates to the repeated observation that there is not a direct relationship between the degree of brain pathology or damage and the clinical manifestation of that damage (Stern, 2006). There are two proposed explanations for this; the concept of ‘brain reserve’ or ‘threshold model’ (Satz, 1993), which suggests that reserve derives from more richly intra- and inter-connected neuronal networks, so that deficits only occur when brain reserve is depleted beyond a threshold. The second is the ‘cognitive reserve model’ that suggests that the brain attempts to cope with any damage by utilizing either pre-existing networks in a more efficient manner (the ‘neural reserve’ theory) or by recruiting alternative networks (‘neural compensation’), although it is also suggested that the models may not operate in mutual exclusivity (Stern, 2006). Educational attainment has been postulated as a marker for cognitive reserve, although it is likely to be supplemented by genetics, physical conditioning and later life experiences. The idea that cognitive or neuronal reserve may delay the onset of clinically relevant cognitive and functional impairment has been proposed as a way to explain the consistent observation of a lower risk of dementia among intelligent and well educated people (Cervilla *et al.*, 2004). Some studies, however, have suggested that those with a greater cognitive reserve have a more rapid decline once a dementia is detected (Stern *et al.*, 1995).

The link between TBI and increased risk of developing dementia later in life, however, remains ambiguous (Mayeux, 1996; Newcombe, 1996; Mehta *et al.*, 1999; Fleminger *et al.*, 2003; Millar *et al.*, 2003). Some research has suggested that the risk of developing dementia increases as the severity of the injury increases (Mortimer *et al.*, 1991; Mehta *et al.*, 1999; Plassman *et al.*, 2000; Rapoport *et al.*, 2004; Himanen *et al.*, 2006), while other studies have failed to show any increased risk of dementia in following CHI (Mayeux, 1996). In one meta analysis, Fleminger *et al.* (2003) found no significant association between HI and Alzheimer’s disease (AD) in seven studies. A recent hypothesis is that HI may merely lead to earlier onset of dementia, rather than increasing the lifetime risk of developing the disease (Rapoport *et al.*, 2004; Mehta *et al.*, 1999).

### Genetic associations with cognitive decline

It has been established that most neurodegenerative processes results from complex interactions between both

environmental effects and genetic factors (Lindsay *et al.*, 2002). In recent years, there has been increasing evidence of links of between-specific genotypes and risk for accelerated cognitive decline or dementia following TBI. Subsequently, we briefly touch on the data from a few selected genotypes that we examined in this study.

### APO e4

The genetic association between Apolipoprotein E [var-epsilon]4 (APO e4) and late-onset AD has been confirmed by many studies (Corder *et al.*, 1993; Strittmatter *et al.*, 1993; Mayeux *et al.*, 1993a). Several groups have also found that APO e4 is a risk factor for poor outcome after moderate to severe CHI (Mayeux *et al.*, 1993b, 1995; Teasdale *et al.*, 1997; Friedman *et al.*, 1999; Plassman *et al.*, 2000). Although the mechanisms underlying these effects are unclear, some evidence suggests that both APO e4 and CHI may influence the risk of AD via interactions with the amyloid- $\beta$  (A $\beta$ ) peptide. A $\beta$  deposition can be found in ~30% of people who die shortly after CHI (Roberts *et al.*, 1991), and a significant percentage of these patients are APO e4 positive (Nicoll *et al.*, 1995, 1996; Teasdale *et al.*, 1997; Lichtman *et al.*, 2000).

It is not clear from the available data at what point in the course of CHI APO e4 has its primary effect. Several reports find that APO e4-positive individuals are more likely to have a poor presentation (Teasdale *et al.*, 1997; Friedman *et al.*, 1999; Millar *et al.*, 2003; Jiang *et al.*, 2006) and lower early cognitive function (Lieberman *et al.*, 2002; Millar *et al.*, 2003; Ariza *et al.*, 2006). Intraneuronal APO e is markedly increased after acute TBI, possibly because it is involved in neural repair and regeneration (Laskowitz *et al.*, 1998; Lichtman *et al.*, 2000; Crawford *et al.*, 2002).

Inheritance of APO e4 may also influence cognitive dysfunction many years following TBI (Starkstein and Jorge, 2005). Several case-control studies indicate that possession of APO e4 together with HI increases the risk of developing AD in later life (Mortimer *et al.*, 1985, 1992; Graves *et al.*, 1990; Mayeux *et al.*, 1993a; Plassman *et al.*, 2000; Lendon *et al.*, 2003), although several investigators were unable to verify these findings (Chandra *et al.*, 1989; Salib and Hillier 1997; O'Meara *et al.*, 1997; Mehta *et al.*, 1999; Millar *et al.*, 2003). Since the increased risk of AD after CHI appears to be influenced by family history of AD (Mayeux *et al.*, 1993b), Mayeux *et al.* (1995) studied a synergistic effect of HI and inheritance of the APO e4 allele. They found that while APO e4 increased the risk of AD 2-fold, the occurrence of CHI in APO e4-positive individuals increased the risk of AD 10-fold. There was no increased risk of AD in subjects who suffered brain injury but were APO e4 negative. Thus, these risk factors appear to act synergistically, in that individuals who are APO e4-positive are even more likely to develop dementia if they sustain CHI at some time in their life (Tang *et al.*, 1996). We were interested in whether APO e4 was associated with change in intelligence,

either in the initial recovery period or in the subsequent years of possible decline following PHI.

### COMT

The catechol-*O*-methyltransferase (COMT) gene is essential for the metabolic degradation of dopamine in the prefrontal cortex. A single nucleotide polymorphism leading to a Val to Met substitution (Val<sup>158</sup>Met) in the coding region of the COMT gene appears to influence activity levels of the enzyme, with the Met allele having one-quarter of the activity of the Val allele (Lachman *et al.*, 1996). Hence, individuals with the Met/Met genotype have been found to display better prefrontal functioning, working, episodic and semantic memory than those with the Met/Val or Val/Val genotypes (Egan *et al.*, 2001; Malhotra *et al.*, 2002; Gothelf *et al.*, 2005; Meyer-Lindenberg *et al.*, 2005). Also COMT has been suggested as a candidate for genetic predictability of memory and cognitive decline in ageing (de Frias *et al.*, 2005).

Regarding TBI, Lipsky *et al.* (2005) found subjects with a history of TBI that were homozygotes for the low enzyme activity polymorphism (COMT Met) performed better on tests of executive functioning than individuals with the high enzyme activity polymorphism. In our study, we hypothesized that the presence of a COMT polymorphism may dictate performance on general cognitive abilities, and in particular, that those with the Met/Met genotype may have a greater level of protection against cognitive decline after PHI.

### GRIN

Experimental animal studies have revealed impaired plasticity following TBI, even in the absence of significant anatomical damage (Giza *et al.*, 2006), evidenced by examining *N*-Methyl-D-aspartate (NMDA). NMDA consists of a number of subunits, including the GRIN glutamate receptor, which seems to be specifically involved in the pathophysiology of CHI, including acting as a marker of neuronal death (Parton *et al.*, 2005). Thus, it is feasible that GRIN genotype may influence initial responses to PHI.

### BDNF

Brain-derived neurotrophic factor (BDNF) is an endogenous protein involved in the maintenance of neuronal function and synaptic plasticity of the adult brain. Levels of BDNF in the brain have been found to correlate with severity of cognitive decline in AD (Chuu *et al.*, 2006; Laske *et al.*, 2006). In fact, up-regulation of trophic factors, such as BDNF, via motor exercise, may prime the brain to respond more favourably to injury, inoculating against further damage and enabling recovery and local compensation (Kleim *et al.*, 2003). Thus, they reflect endogenous attempts at neuroprotection, and so may have both an early and late role following brain injury (Chiaretti *et al.*, 2003).

## DBH

Studies have suggested for some time that dopamine plays a role in CNS plasticity after brain injury (Clifton *et al.*, 1981), reflected in a reduction in dopamine beta-hydroxylase (DBH) immunoreactivity (Zhu *et al.*, 2000). Conversely, DBH has been found to be significantly raised in those with AD (Giubilei *et al.*, 2004). It certainly appears that DBH has some role in facilitating cognitive recovery after brain injury (Zhu *et al.*, 2000).

## GAD

Glutamic acid decarboxylase (GAD) is the rate-limiting enzyme for the production of gamma-amino butyric acid (GABA) in the brain. The adenosine triphosphate (ATP)-mediated control of GABA synthesis gradually declines with age and AD-related neurodegeneration (Marczynski, 1998). Additionally, GAD has been associated with short-term plasticity (Ramsey *et al.*, 2004), and the neurological deficits resulting from brain injury-induced white matter lesions (Robinson *et al.*, 2006). Therefore, it is feasible that both the initial and latter periods after a PHI may be influenced by the presence of GAD genotypes.

Thus, it seems likely that besides the important effects of pre-injury cognitive development, the initial neural response to PHI and any subsequent plasticity or neurodegeneration processes are all heavily influenced by genetic factors (Lindsay *et al.*, 2002), which may impact at variable times post-injury.

## Background and previous relevant findings of the vietnam HI study

The Vietnam Head Injury Study (VHIS) is a prospective, long-term follow-up study of Vietnam veterans with mostly penetrating brain injuries. The subject registry was collated during the Vietnam conflict by Dr William Caveness at the National Institutes of Health. Simple registry forms outlining demographic, injury and initial outcome data were completed by military physicians in Vietnam on head injured soldiers who had survived the first week after a severe HI. About 2000 patients were entered in the registry between 1967 and 1970. Phase 1 (P1) of the VHIS was a medical records review some 5 years post-injury using the military, VA medical and personnel records of 1221 of these men, for whom adequate field, hospital, rehabilitation and follow-up records were available.

Phase 2 (P2) was a collaborative project of the three Military Services; the Department of Veterans Affairs, the National Institutes of Health and the American Red Cross. It consisted of a comprehensive, multidisciplinary inpatient evaluation at Walter Reed Army Medical Center. Approximately 520 head injured subjects from the original registry and 85 matched normal volunteers were evaluated between 1981 and 1984, some 12–15 years post-injury. Of the 520 patients, 77% had missile fragment wounds,

15% had gunshot wounds and only 8% had a CHI. Seventy-eight percent had multiple lobe injuries and 30% had bilateral lesions. When the impact of education, pre-injury intelligence, brain volume loss and lesion location on post-injury intelligence level was examined, it was found that in general, the most important determinant of post-injury intelligence was pre-injury performance as assessed by the Armed Forces Qualification Test (AFQT; Grafman *et al.*, 1988). In addition, the more global the cognitive test, the greater the effect of brain loss volume, with specific cognitive processes being affected relatively more by lesion location (Grafman *et al.*, 1986).

## Difficulties with existing research data

There have been a number of difficulties inherent in the methodology of previous studies of the long-term cognitive outcome following TBI. First, there have been a wide variety of definitions of HI and its severity employed. Additionally, the concept of what represents exacerbated or accelerated cognitive decline has yet to be fully defined, which may also lead to an increased possibility of the misdiagnosis of dementia in some subjects (Fleminger *et al.*, 2003). What represents an abnormal pattern of decline also raises questions regarding what time period post-TBI may be associated with the greatest risk for decline. There is some evidence that motor, sensory and cognitive functions seemed to improve in the first few years after a TBI and then reach a plateau (Walker and Blumer, 1989), but whether the level of initial recovery has any association with subsequent decline remains undetermined.

Regarding the study designs, many have involved small numbers of participants, with most studies focusing on subjects with CHI (Fleminger *et al.*, 2003). There remain important limitations in the large case-control genetic studies, primarily related to recall bias and the lack of access to complete medical records regarding the TBI (Diaz-Arrastia and Baxter, 2006). Finally, a number of studies have recognized the difficulty in accounting for other factors that may contribute to long-term cognitive impairment, such as alcohol use (Walker and Blumer, 1989; Klein *et al.*, 1996).

## Aims of this study

Largely by virtue of the unique focal nature of their injuries, and their comparable personal status at the time of injury, the VHIS population can provide novel insights into a number of questions relating to brain function and recovery from TBI. We aimed to address the link between general demographic factors, such as educational level and race, as well as the site and size of PHI, and long-term cognitive outcome as measured by an intelligence score surrogate. We also wanted to examine the possible impact of genetic polymorphisms on neuroplasticity in the ageing,

**Table 1** Comparison of HI and control subjects at P3

		Mean	SD	P
Age at testing	Control	59.15	3.873	0.061
	Head-injured	58.11	2.940	
	Total	58.31	3.155	
Years of education	Control	14.16	2.398	0.922
	Head-injured	14.20	2.270	
	Total	14.19	2.283	
Pre-injury intelligence	Control	65.40	22.91	0.238
	Head-injured	59.91	25.54	
	Total	60.8	25.18	

damaged brain and whether they play a part in predicting exacerbated cognitive decline or onset of dementia.

## Methodology

### Subjects

The subjects were drawn from the VHIS registry, 92% of whom had a history of a PHI. Phase 3 (P3) has been modeled upon the P2 VHIS. Of the 520 HI subjects who were assessed in P2, 484 are still alive and 182 attended P3 of the study. Additionally, 17 patients identified in P1 who did not attend P2 were assessed. Of the original 80 control subjects without head injuries recruited in P2, 32 attended P3 and a further 23 were recruited for P3, through advertisements in veteran publications. Subjects were assessed over 5–7 days at the National Naval Medical Center in Bethesda, MD, USA.

At P3, there were no significant differences between the HI and control subjects in terms of age, total years of education or induction intelligence level (as measured by the AFQT) (Table 1). One hundred and eighty-six were right-handed (144 HI, 42 controls) and 28 were left-handed (20 HI, 8 controls). In addition, 13 of the HI group were originally right-handed but now are forcibly left-handed (because of hemiparesis), and 6 were originally left handed but now are forcibly right-handed. Six of the HI group and three control subjects described themselves as ambidextrous.

### CT scan analysis

Brain lesions were identified by CT scan, and the data were reconstructed with a 1 mm overlapping slice thickness and a 1 mm interval. Lesions were processed using ABLe software ('Analysis of Brain Lesions'; Makale *et al.*, 2002; Solomon *et al.*, 2007). ABLe is an interactive program run via MedX medical imaging software (Medical Numerics Inc., Sterling, VA, USA), that determines the lesion size and cytoarchitectonic brain regions contained within the lesion space. Within ABLe, the lesions were drawn manually in native space on each 1 mm thick slice by V.R. (a psychiatrist with clinical experience of reading CT scans), and reviewed by J.G., enabling a consensus decision to be reached regarding the limits of each lesion. Lesion volume was calculated and the brain images automatically registered to a template brain in Talairach space (Talairach and Tournoux, 1988). The template image we used was derived from a CT scan of a 27-year-old male, conformed to Talairach dimensions in MedX using an affine 12-parameter transformation derived from the Automated Image Registration

(AIR) software within MedX (Makale *et al.*, 2002). Computerized graphics of Brodmann areas were derived by mapping onto a re-sliced version of the CT image. Thus, the intersection of lesions with Brodmann areas could be determined using the VOTL database within ABLe, as could the coordinates comparable with the templates produced by Damasio and Damasio (1983). This procedure allowed the measurement of normalized lesion volume and percentage of brain regions involved. We used the difference in the lesion volume calculated in P2 and P3 to give one estimated measurement of atrophic change over time. In addition, three other measurements of atrophy were made via a consensus decision between a trained neurologist (A.S.) and V.R. from P3 CT scans: corpus callosum width (millimetres), a rating of global brain atrophy (on a scale of 0–7) and ratings from 0 to 7 of atrophy in each lobe. Third ventricle width had previously been shown to correlate well with other measures of brain atrophy on CT scans (Reider-Groswasser *et al.*, 2002). An analysis was carried out to assess the correlation between these measures. Third ventricle width correlated significantly with the corpus callosum width measurements ( $r=0.416$ ,  $P<0.001$ ;  $r=0.296$ ,  $P=0.001$ ;  $r=0.352$ ,  $P<0.001$ ), as well as the global assessment of atrophy ( $r=0.377$ ,  $P<0.001$ ).

### Tests

Subjects were assessed using a composite group of tests designed to measure cognitive abilities, consisting of a 5–7 day battery of tests that assessed a wide variety of neuropsychological functions, including memory, language, executive functioning and social cognition. In this study, we focus on the AFQT (AFQT-7A, DoD 1960). This is a standardized multiple choice test of cognitive aptitude, devised by the Department of Defense. The test measures verbal ability, visual-spatial organization, arithmetic and functional associations via 100 multiple choice questions. The total score range is from 0 to 100, and the subtest scores range from 0 to 25 (Fig. 1). It was also the only pre-injury cognitive assessment available in this study. The same version of the AFQT was used during pre-injury, P2, and P3 assessment.

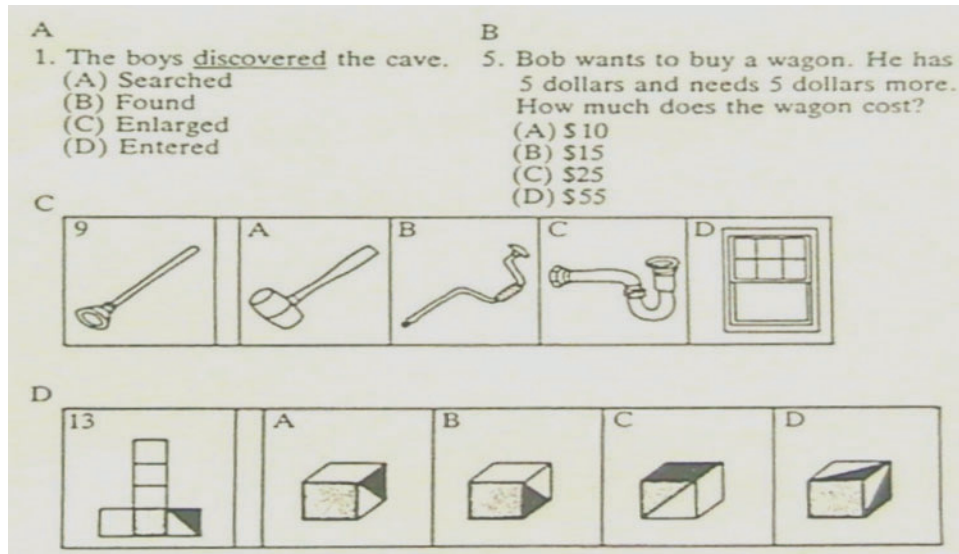
A correlation analysis was run to assess if current AFQT score was a valid proxy measure for intelligence (as measured by the WAIS-III Full-Scale IQ score taken in P3 of the study). In both HI subjects and controls the two were significantly correlated ( $r=0.845$ ,  $P<0.001$  HI;  $r=0.816$ ,  $P<0.001$  controls).

### Genetic analysis

See supplementary material.

### Statistical analysis

A variety of parametric procedures were used in this study. In particular, analysis of variances (ANOVAs), linear logistic and stepwise multiple-regression procedures were performed to assess the impact of demographic factors, pre-injury intelligence, brain volume loss, lesion location and genetic markers on cognitive ability 36–39 years post-injury, and possible intellectual decline 12–15 years and 36–39 years post-injury. A significance level of  $P=0.05$  or less was required to enter and remain in the stepwise regression procedures. This analysis allowed an estimation of the relative contribution of each predictor to each dependent measure's test score or score decline.



**Fig. 1** Sample of questions from the AFQT test (A = vocabulary subtest; B = arithmetic subtest; C = tools subtest; D = boxes subtest).

## Results

### Are subjects P2 and P3 comparable?

A *t*-test was run to compare those who underwent assessment only in P2 (338 HI and 48 controls), compared with those who attended both P2 and P3. Age (at the start of P3 testing), total years of education, pre-injury AFQT, P2 AFQT score and total lesion volume loss and laterality were compared between attenders and non-attenders of P3. Comparing the whole group (HI and controls), there were no significant differences in age between P3 attenders and non-attenders. However, those that attended P3 had more years of education ( $t = -3.062$ ,  $df = 601$ ,  $P = 0.002$ ), and a higher AFQT score both pre-injury ( $t = -4.851$ ,  $df = 581$ ,  $P < 0.001$ ) and at P2 ( $t = -6.151$ ,  $df = 571$ ,  $P < 0.001$ ), than P3 non-attenders. This was also the case when the HI group was assessed alone. However, within the controls, there were no significant differences in educational attainment, pre-injury AFQT or P2 AFQT between those who did and did not attend P3.

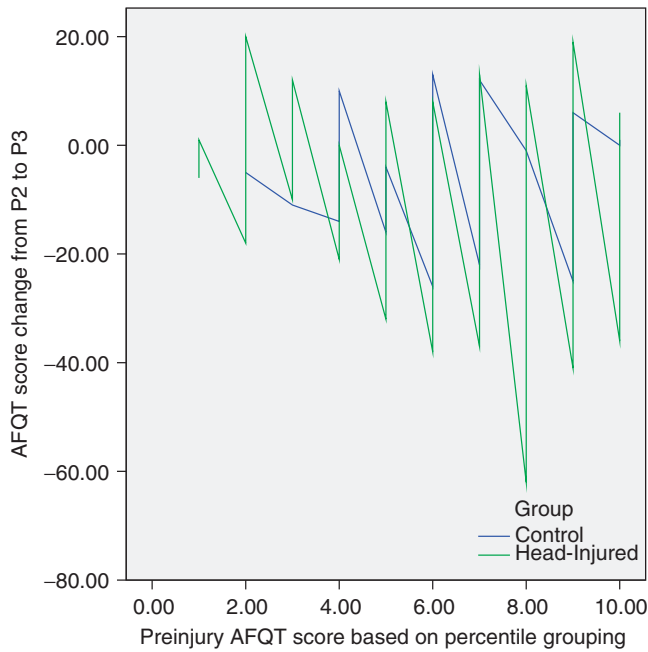
Another *t*-test was run to compare P3 AFQT scores between existing and newly recruited controls, and P2 and P1 identified HI subjects. There were no significant differences found. However, as the newly recruited control subject group consisted of a large number of officers, a similar *t*-test was run to examine for any differences in intelligence between enlisted and officer controls. Officers did have greater P3 AFQT scores, both in the existing and new control group ( $t = -4.000$ ,  $df = 233$ ,  $P < 0.001$ ). Thus, for statistical purposes, it was decided to include both new and existing control subjects in one group, but to include rank as a fixed factor in any regression analysis. Race was also recoded for Caucasians and non-Caucasians, because of low numbers in individual racial groups. It should be noted, however, that the newly recruited control subjects

may well represent a different population in terms of other factors that may impact on intelligence, such as social background and tendency to seek support for any cognitive difficulties. In fact, as we found those attending P3 had a higher level of pre-injury intelligence than those attending P2, as well as more years of education, it is feasible that those studied at P3 differed in many ways from P3 non-attenders, which may have impacted on the longitudinal results.

### How do HI and control subjects' AFQT scores compare?

The median AFQT score at P3 in the entire sample was 65.0. In controls ( $n = 55$ ), this was 74.0 and in the HI ( $n = 199$ ) it was 54.0. The median rise in AFQT score from pre-injury to P2 was +11.5 in controls and +1.0 in those with HIs, while from P2 to P3 controls showed a median decline of -4.0 and the HI of -7.0.

A *t*-test was run to compare the change in AFQT scores across three time-periods (pre-injury to P2, P2 to P3, and pre-injury to P3). This was computed as a one way *t*-test, as we anticipated that those with head injuries were unlikely to perform better than the control subjects. Those with head injuries had a lower AFQT score at P3 (mean = 52.58) than controls (mean = 68.50;  $t = 4.265$ ,  $df = 246$ ,  $P < 0.001$ ). In the group as a whole, the HI subjects had a significantly greater decrease in their AFQT score (mean = -9.64) compared with controls (mean = -5.39) from P2 to P3 ( $t = 1.826$ ,  $df = 202$ ,  $P = 0.035$ ), as well as from pre-injury to P3 ( $t = 4.504$ ,  $df = 57$ ,  $P < 0.001$ ). Additionally, the controls' AFQT score increased significantly more from pre-injury to P2 (mean = 10.42;  $t = 4.043$ ,  $df = 60.07$ ,  $P \leq 0.001$ ), compared with those with head injuries (mean = 0.43), suggesting that those with HIs showed less



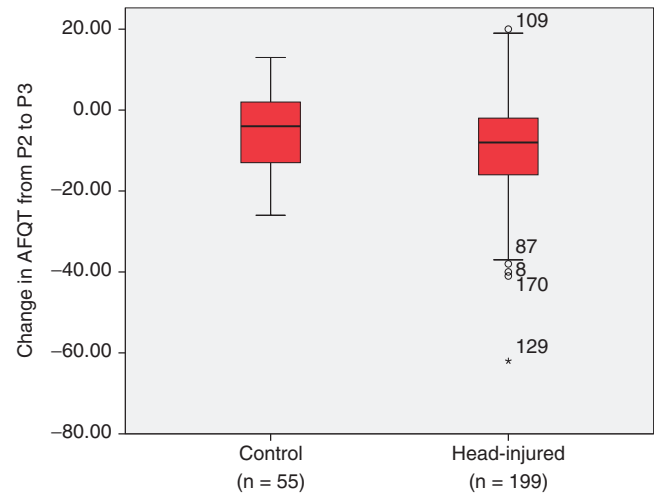
**Fig. 2** Change in AFQT score from P2 to P3 based on pre-injury percentile grouping.

initial improvement and greater later decline in intelligence. Figure 2 shows the change in AFQT score from P2 to P3 in the control and HI group, broken down into 10 groups based on their pre-injury AFQT percentile (with 1 being the lowest percentile, and 10 being highest).

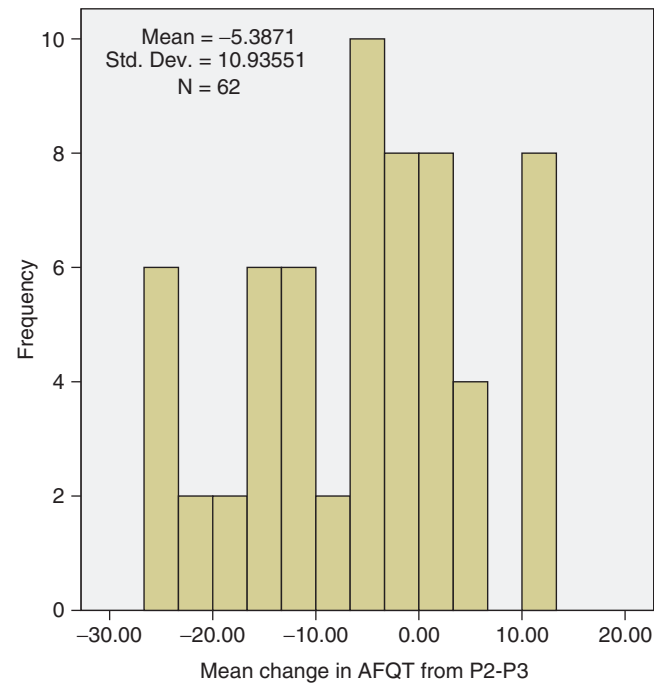
If the officers were excluded from the sample, the HI subjects' ( $n = 177$ ) AFQT score significantly decreased more than that of controls ( $n = 38$ ) from over the entire period pre-injury to P3 ( $t = 3.151$ ,  $df = 178$ ,  $P = 0.001$ ). In addition, there was again a significant difference in decline between those with head injuries and controls from P2 to P3 ( $t = 1.751$ ,  $df = 176$ ,  $P = 0.041$ ) (Fig. 3). Figures 4 and 5 show the range of changes in AFQT scores from P2 to P3.

### What predicts current (and changes in) intelligence level?

A univariate linear regression procedure was performed to assess the predictability of P3 AFQT score, with race, age, military rank, education and VHIS group (i.e. whether a participant was a HI subject or a control) as covariates. Race ( $F = 24.618$ ,  $df = 1$ ,  $P = 0.021$ ), rank ( $F = 3.555$ ,  $df = 1$ ,  $P = 0.031$ ), VHIS group ( $F = 7.142$ ,  $df = 1$ ,  $P = 0.008$ ), age ( $F = 4.245$ ,  $df = 1$ ,  $P = 0.041$ ) and education ( $F = 19.667$ ,  $df = 1$ ,  $P < 0.001$ ) were all significant in predicting AFQT score. However, when pre-injury AFQT score was added as a covariate (or P2 AFQT when looking at P2 to P3 change), only pre-injury AFQT score ( $F = 94.444$ ,  $df = 1$ ,  $P < 0.001$ —with a higher pre-injury AFQT score predicting a higher score at P3) and presence of PHI ( $F = 9.414$ ,  $df = 1$ ,



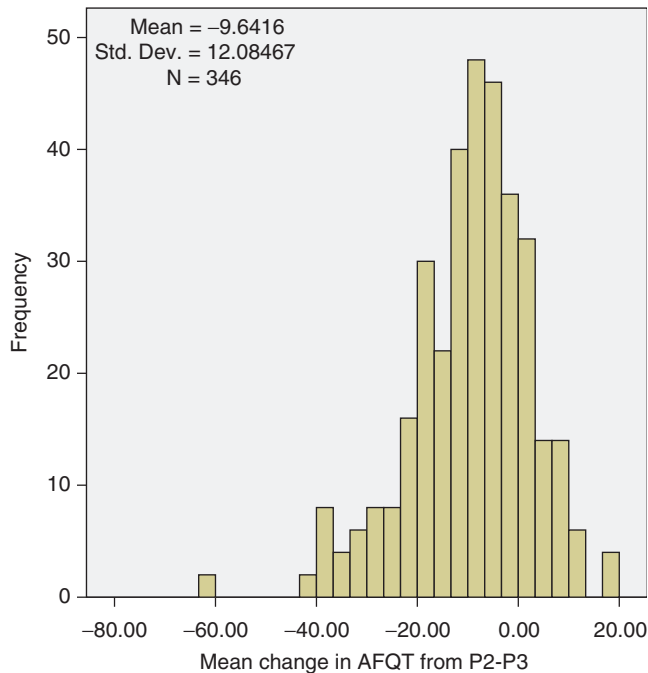
**Fig. 3** Mean change in AFQT score from P2 to P3 according to subject grouping.



**Fig. 4** Mean change in AFQT score from P2 to P3 in control subjects.

$P = 0.003$ ) were found to have a significant impact on the level of current AFQT.

A similar model was used to examine the changes in AFQT score across all time-periods (i.e. pre-injury to P2, P2 to P3, and pre-injury to P3). Looking at change in AFQT score from pre-injury to P2, education ( $F = 4.168$ ,  $df = 1$ ,  $P = 0.043$ —with a higher level of education predicting a lower degree of drop in AFQT) and pre-injury AFQT ( $F = 18.752$ ,  $df = 1$ ,  $P < 0.001$ ) were both significant predictors. VHIS group was marginal in terms of its



**Fig. 5** Mean change in AFQT score from P2 to P3 in HI subjects.

significance as a predictor ( $F=3.338$ ,  $df=1$ ,  $P=0.070$ ). Greater levels of pre-injury intelligence were associated with lesser decline in long-term AFQT scores.

Regarding AFQT change from P2 to P3, P2 AFQT ( $F=11.453$ ,  $df=1$ ,  $P=0.001$ ) and VHIS group ( $F=7.713$ ,  $df=1$ ,  $P=0.006$ ) were significant predictors.

Similarly, when we analysed AFQT change from pre-injury to P3, only pre-injury AFQT ( $F=27.658$ ,  $df=1$ ,  $P<0.001$ ) and VHIS group ( $F=9.414$ ,  $df=1$ ,  $P=0.003$ ) were significant as predictors. Again, higher pre-injury AFQT scores were protective in terms of later decline. When these regression procedures were repeated for HI subjects only, there were no significant changes in the results, except for a slight increased predictability of education when looking at AFQT change from pre-injury to P2.

### Does brain volume loss (or atrophy) predict intelligence level?

Correlation analyses were used to assess if AFQT score changes were associated with total volume loss (TVL) on CT scan at either P2 (P2 TVL) or P3 (P3 TVL) or the various measures of atrophy (global and regional ratings of atrophy, third ventricle width, change in volume loss from P2 to P3). AFQT score changes from pre-injury to both P2 and P3 were significantly correlated with both P2 TVL ( $r=-0.367$ ,  $P<0.001$ ;  $r=-0.446$ ,  $P=0.00$ ) and P3 TVL ( $r=-0.330$ ,  $P<0.001$ ;  $r=-0.414$ ,  $P<0.001$ ). Interestingly, later changes in intelligence (as measured by change in

AFQT score from P2 to P3) were not significantly correlated with volume loss at either P2 or P3.

In terms of ratings of atrophy, third ventricle width was significantly correlated with AFQT score change from pre-injury to P3 and pre-injury to P2 ( $r=-0.236$ ,  $P=0.002$ ;  $r=-0.175$ ,  $P=0.030$ ), and global atrophy rating was significantly correlated with AFQT score change from pre-injury to P3 ( $r=-0.174$ ,  $P=0.023$ ). There were also correlations between the current degree of left parietal ( $r=-0.222$ ,  $P=0.003$ ) atrophy and decline in intelligence from pre-injury to P3. A logistic regression analysis was carried out to assess if particular areas of atrophy could predict current or change in intelligence. Left parietal ( $F=5.178$ ,  $P=0.024$ ,  $df=1$ ) and right frontal ( $F=7.897$ ,  $P=0.006$ ,  $df=1$ ) atrophy predicted current AFQT score. Change in AFQT score from pre-injury to P3 was predicted by degree of left parietal ( $F=5.178$ ,  $P=0.024$ ,  $df=1$ ) and right frontal ( $F=7.897$ ,  $P=0.006$ ,  $df=1$ ) atrophy. From P2 to P3, the only significant predictor of change in intelligence was right parietal atrophy ( $F=4.252$ ,  $P=0.041$ ,  $df=1$ ).

### Is there evidence of dementia in the sample group?

The Mini-Mental State Examination (MMSE; Folstein *et al.*, 1975) is a commonly used screening tool used to detect significant cognitive decline. A score below 24 out of a possible 30 is considered indicative of likely dementia (Tariq *et al.*, 2006), yet only 4.5% ( $n=6$ ) of our subjects had a recorded score of below 24 out of 30 on the MMSE. The median score for controls was 30 and for those with head injuries was 29. Not surprisingly, these subjects with a score of below 24 on the MMSE showed a significantly greater level of decline in intelligence from pre-injury to P3 than those with higher scores ( $t=-2.458$ ,  $df=116$ ,  $P=0.015$ ), but they also tended to have a lower pre-injury AFQT score ( $t=-1.811$ ,  $df=118$ ,  $P=0.073$ ), suggesting that they may have had some early risk factor for decline. Those with abnormal MMSE scores had significantly larger lesions (mean total volume loss=101.38cc versus 29.64cc for those with higher scores;  $t=-4.566$ ,  $df=112$ ,  $P<0.001$ ), with greater degrees of atrophy ( $t=3.292$ ,  $df=109$ ,  $P=0.001$ ) and wider third ventricles ( $t=2.935$ ,  $df=109$ ,  $P=0.004$ ).

An MMSE score below 27 out of 30 is sometimes used to indicate mild cognitive decline (Robert *et al.*, 2006). Of our subjects, 15.7% ( $n=21$ ) had a recorded score of below 27 on the MMSE. Those in our sample with a score below 27 had significantly larger lesions than those with the higher scores (mean total volume loss=52.45cc versus 29.10cc for those with higher scores;  $t=-2.496$ ,  $df=112$ ,  $P=0.014$ ).

There was no correlation between global rating of atrophy or third ventricle width and MMSE score in this group. Although increasing age did correlate with global atrophy ( $r=-0.159$ ,  $P=0.030$ ), there was no significant



correlation between age and MMSE score. There was an increased tendency for subjects with low MMSE scores to have the COMT rs2020917 ( $\chi^2 = 6.279$ ,  $P = 0.043$ ) allele, but none of the other genetic markers were related.

We also recorded if subjects had any family history of dementia. This included 16.57% of HI subjects and 8.16% of controls. There were no significant differences in terms of current MMSE score, degree of atrophy on CT scan or decline in intelligence from pre-injury to P3 in those with a family history of dementia compared with those with no such family history.

Additionally, we noted any current or lifetime prevalence of alcohol abuse or dependence (based on DSM-IV criteria—DSM-IV, 1994), as it was possible that such diagnoses may influence tendency to cognitive decline. In those with head injuries, 30.05% had a lifetime diagnosis of alcohol abuse and 20.20% of dependence. Only 2.59% of those with alcohol diagnoses fulfilled diagnostic criteria at the time of P3. In the controls, 36.54% had a lifetime diagnosis of alcohol abuse and 17.30% of dependence, with 5.77% of those with alcohol diagnoses with fulfilled diagnostic criteria at the time of P3. Those with a lifetime history of alcohol use did not have significantly greater levels of decline, lower MMSE scores or greater levels of brain atrophy. Also, when the psychiatric symptoms reported by the next of kin (via the Neuropsychiatric Inventory—Cummings *et al.*, 1994) were examined they did not correlate with change in intelligence.

The univariate linear regression procedure containing pre-injury intelligence, race, age, rank, education and VHIS group (i.e. whether a participant was a HI subject or a control) as covariates was repeated, adding family history of dementia and lifetime and current alcohol diagnoses into the model. Both history of alcohol diagnoses and family history of dementia had no significant impact on P3 AFQT score or decline from pre-injury to P3.

### How do those with right, left and bilateral lesions compare?

The number of subjects with left, right and bilateral lesions were similar, as were their demographic data and level of lesion size. There was no significant correlation between lesion laterality and pre-injury AFQT and TVL, or current AFQT in all three HI subject groups.

### Does specific brain structure involvement predict AFQT score or change in AFQT?

A stepwise regression analysis was performed to look for predictors of current AFQT and change in AFQT over all phases. The dependent variables included current AFQT scores, right hemisphere volume loss (judged by V.R. and J.G. to be specific to the initial lesion, rather than additional atrophy) left hemisphere volume loss, change in total volume loss from P2 to P3, three measurements of

corpus callosum width, involvement of the following brain structures: caudate, substantia nigra, globus pallidus, white matter, thalamus, hippocampus and the specific lateral and overall involvement of the following regions of the cortex: the frontal, parietal, temporal and occipital lobes, as well as the insula and amygdala. Hence, these measurements focused on differences in location of the primary lesion, rather than any subsequent atrophic change.

Lesions in the caudate nucleus ( $t = -5.623$ ,  $P < 0.001$ ), left parietal lobe ( $t = -3.225$ ,  $P = 0.002$ ), right amygdala ( $t = 2.241$ ,  $P = 0.026$ ), hippocampus ( $t = -3.292$ ,  $P = 0.001$ ) and right frontal lobe ( $t = -2.055$ ,  $P = 0.042$ ) along with the width of the corpus callosum ( $t = -2.992$ ,  $P = 0.004$ ) were predictive of P3 AFQT score, while change in AFQT score from pre-injury to P3 were predicted by lesions in the caudate nucleus ( $t = -5.623$ ,  $P = 0.006$ ), left parietal lobe ( $t = -3.225$ ,  $P = 0.002$ ), right amygdala ( $t = 2.241$ ,  $P = 0.026$ ), hippocampus ( $t = -3.292$ ,  $P = 0.001$ ) and right frontal lobe ( $t = -2.055$ ,  $P = 0.042$ ) along with the width of the corpus callosum ( $t = -2.992$ ,  $P = 0.004$ ). All other areas of brain involvement were excluded from further analyses. In terms of change in intelligence from P2 to P3, the only significant predictor was left hemisphere volume loss ( $t = -2.188$ ,  $P = 0.030$ ).

### Does performance on specific subtests of the AFQT predict AFQT score or change in AFQT?

A univariate linear logistic regression analyses was completed to assess whether performance in the individual subtests of the AFQT at P3 could predict change in AFQT over time. The AFQT test has four main measures that assess verbal comprehension (vocabulary subtest), visual-spatial imagery (boxes subtest), arithmetic word problems (math subtest) and object-function matching (tools subtest). Performance on three subtests significantly predicted decline in intelligence from P2 to P3: boxes ( $F = 20.371$ ,  $df = 1$ ,  $P < 0.001$ ), math ( $F = 18.816$ ,  $df = 1$ ,  $P < 0.001$ ) and tools ( $F = 10.675$ ,  $df = 1$ ,  $P = 0.001$ ). From pre-injury to P3, performance on all four subtests predicted decline in intelligence (vocabulary:  $F = 10.073$ ,  $df = 1$ ,  $P = 0.002$ ; boxes:  $F = 29.085$ ,  $df = 1$ ,  $P < 0.001$ ; math:  $F = 28.870$ ,  $df = 1$ ,  $P < 0.001$ ; tools:  $F = 19.376$ ,  $df = 1$ ,  $P < 0.001$ ).

A stepwise regression analysis was performed to examine whether performance on individual subtests of the AFQT interacted with lesion location to predict decline in AFQT scores from P2 to P3. The boxes subtest, math subtest and tools subtest only interacted with left parietal lobe lesions ( $R^2 = 0.421$ ,  $t = -2.056$ ,  $P = 0.041$ ) to predict P2 to P3 decline in the overall AFQT score. Similarly, from pre-injury to P3, all the AFQT subtests interacted significantly with lesions in the left parietal lobe to predict AFQT score decline ( $R^2 = 0.645$ ,  $t = -2.550$ ,  $P = 0.012$ ).

## Do genetic markers predict AFQT score change?

We found broadly similar incidences of the genetic polymorphisms in our sample compared with other human studies (See Supplementary Material). Crawford *et al.* (2002) found that 72.7% lacked APO e4 in a HI sample; a result not significantly different from our group. For COMT, other studies have found an incidence of Val/Val at 27–40%, 42–55% for Val/Met and 18–21% for Met/Met in the target population, and our numbers were also not deviant from that expected for genotypes in the Hardy–Weinberg equilibrium (Egan *et al.*, 2001; Malhotra *et al.*, 2002; Stefanis *et al.*, 2005). Additionally, regarding BDNF, Chuu *et al.* (2006) and Laske *et al.* (2006) reported similar rates of genotypes to this sample. The remaining genetic polymorphisms have had limited testing in human HI populations. A linear logistic regression analyses was completed to assess the predictability of pre-injury AFQT, P3 AFQT and change in AFQT from pre-injury to both P2 and P3 based on a number of genetic markers that have been associated with response to brain injury (APO e4, COMT, GRIN, BDNF, GAD and DBH), together with race, age, rank, education and VHIS group (i.e. whether a participant was a HI subject or a control) as covariates. These analyses were repeated in the HI subjects alone, as well in the entire sample.

### Pre-injury AFQT Score

A large number of the genetic markers we examined predicted pre-injury AFQT score. These included GRIN2C rs689730 ( $F=3.615$ ;  $P=0.029$ ,  $df=2$ ), GAD2 rs2839670 ( $F=6.815$ ;  $P=0.010$ ,  $df=1$ ) and DBH444 ( $F=3.239$   $P=0.042$ ,  $df=2$ ). GRIN2B rs1805482 ( $F=2.972$ ;  $P=0.054$ ,  $df=2$ ), COMT: rs9332330 ( $F=2.597$ ,  $P=0.078$ ,  $df=2$ ) and the presence of an APOE 4 allele ( $F=3.238$ ,  $P=0.074$ ,  $df=1$ ) came close to significance in their ability to predict pre-injury intelligence score. The total amount of variance in pre-injury AFQT score accounted for by these genetic markers was assessed by repeating the logistic regression analyses, including just those genetic markers highlighted above with and without the variable of racial grouping only (as it was anticipated that the other covariates, such as years of education, would have a comparatively later impact on performance). When racial group was assessed alone it produced a  $R^2$  value of 0.180, and when the genetic markers were added this value increased to 0.335, implying that the presence of all of these markers could account for a further 15.5% (33.5–18.0%) of the variability in pre-injury intelligence. It should be noted, however, that this analysis involved the relevant genetic markers being entered into the model in a stepwise arrangement, with the  $R^2$  -value reflecting the order of presentation of each marker as described earlier in the article.

### P3 AFQT Score

Only GRIN2A rs968301 was found to be able to predict current AFQT score at a significant level ( $F=3.802$ ;  $p=0.025$ ,  $df=2$ ).

### Change in AFQT score from pre-injury to P2

Two of the GAD markers significantly predicted AFQT score change; GAD1 rs11682957 ( $F=4.673$ ;  $P=0.011$ ,  $df=2$ ) and GAD1 rs2241165 ( $F=3.182$ ;  $P=0.045$ ,  $df=2$ ). COMT rs9332330 also significantly predicted recovery of AFQT score ( $F=4.259$ ;  $P=0.016$ ,  $df=2$ ), with the analysis suggesting that the homozygotes had a better recovery of function based on AFQT score compared with heterozygotes (homozygotes,  $B=-7.234$ ).

### Change in AFQT score from P2 to P3

The only genetic marker that was found to significantly predict overall change in AFQT score from P2 to P3 was GRIN2A rs968301 ( $F=4.033$ ;  $P=0.020$ ,  $df=2$ ). All subjects with GRIN2A rs968301 were either homozygous dominant (A1), homozygous recessive (A2) or were heterozygotes. An ANOVA was carried out to see if there was a significant difference in decline based on genotype. Whilst there was a trend for dominant homozygotes to have a greater level of decline in intelligence from P2 to P3 (mean =  $-11.714$ ,  $SD=15.663$ ) compared with recessive homozygotes (mean =  $-9.071$ ,  $SD=12.608$ ) and heterozygotes (mean =  $-8.519$ ,  $SD=10.988$ ), this did not reach significance.

### Change in AFQT score from pre-injury to P3

Similarly, the only genetic marker that was found to significantly predict overall change in AFQT score from pre-injury to P3 was GRIN2A rs968301 ( $F=3.802$ ;  $P=0.025$ ,  $df=2$ ). An ANOVA procedure was carried out to see if those with a GRIN2A rs968301 allele showed an increased level of decline in intelligence from pre-injury to P3. Again, although there was a trend for dominant homozygotes to have a greater level of decline in intelligence from P2 to P3 (mean =  $-9.429$ ,  $SD=22.849$ ) compared with recessive homozygotes (mean =  $-8.021$ ,  $SD=18.432$ ) and heterozygotes (mean =  $-5.548$ ,  $SD=18.205$ ), this did not reach significance.

We also repeated the above analyses on subjects in the Caucasian racial group, to ascertain whether any of the genetic variability found was robust enough to be present even when racial background was removed from the model. The results were similar to the above with the identical genetic markers as described above found to have a significant impact on both current and change in intelligence across the various stages. The only exception was that GAD1 rs11682957 was no longer found to significantly predict change in AFQT score from pre-injury to P2 ( $F=2.611$ ;  $P=0.078$ ,  $df=2$ ).

## What are the overall factors that best predict exacerbated decline in AFQT scores?

We computed a linear logistic regression analysis including all the factors found to be predictive of alterations in AFQT

**Table 2** Relative contribution to AFQT at P3 made by significant predictive factors

Model		B	SE	t	P	R <sup>2</sup>	R <sup>2</sup> change
1	(Constant)	7.808	3.746	2.084	0.039	0.510	0.510
	Pre-injury AFQT	0.728	0.056	12.936	0.000		
2	(Constant)	11.386	3.485	3.267	0.001	0.592	0.082
	Pre-injury AFQT	0.730	0.051	14.170	0.000		
3	Phase 3 CT: caudate involvement	-18.193	3.201	-5.684	0.000	0.615	0.023
	(Constant)	12.387	3.409	3.634	0.000		
4	Pre-injury AFQT	0.747	0.050	14.805	0.000	0.636	0.020
	Phase 3 CT: caudate involvement	-16.462	3.167	-5.199	0.000		
5	Left parietal involvement	-8.979	2.884	-3.114	0.002	0.647	0.011
	(Constant)	21.745	4.593	4.734	0.000		
6	Pre-injury AFQT	0.744	0.049	15.109	0.000	0.670	0.023
	Phase 3 CT: caudate involvement	-15.522	3.108	-4.993	0.000		
7	Left parietal involvement	-8.728	2.817	-3.098	0.002	0.680	0.010
	Phase 3 CT: distance 2 of CC	-1.497	0.506	-2.957	0.004		
8	(Constant)	21.962	4.536	4.842	0.000	0.670	0.023
	Pre-injury AFQT	0.742	0.049	15.248	0.000		
9	Phase 3 CT: caudate involvement	-17.819	3.234	-5.510	0.000	0.670	0.023
	Left parietal involvement	-8.039	2.798	-2.873	0.005		
10	Phase 3 CT: distance 2 of CC	-1.552	0.500	-3.101	0.002	0.680	0.010
	Phase 3 CT: right amygdala involvement	15.305	6.787	2.255	0.026		
11	(Constant)	22.251	4.403	5.053	0.000	0.670	0.023
	Pre-injury AFQT	0.746	0.047	15.789	0.000		
12	Phase 3 CT: caudate involvement	-12.402	3.551	-3.493	0.001	0.670	0.023
	Left parietal involvement	-6.921	2.738	-2.528	0.012		
13	Phase 3 CT: distance 2 of CC	-1.615	0.486	-3.323	0.001	0.670	0.023
	Phase 3 CT: right amygdala involvement	26.335	7.404	3.557	0.000		
14	Phase 3 CT: hippocampus involvement	-15.812	4.846	-3.263	0.001	0.670	0.023
	(Constant)	24.466	4.466	5.479	0.000		
15	Pre-injury AFQT	0.740	0.047	15.814	0.000	0.680	0.010
	Phase 3 CT: caudate involvement	-11.899	3.515	-3.385	0.001		
16	Left parietal involvement	-7.983	2.747	-2.906	0.004	0.680	0.010
	Phase 3 CT: distance 2 of CC	-1.419	0.488	-2.904	0.004		
17	Phase 3 CT: right amygdala involvement	28.642	7.390	3.876	0.000	0.680	0.010
	Phase 3 CT: hippocampus involvement	-17.123	4.824	-3.549	0.001		
18	Right frontal involvement	-5.375	2.446	-2.198	0.029		

**Table 3** Relative contribution to change in AFQT from P2 to P3 made by significant predictive factors

Model		B	SE	t	P	R <sup>2</sup>	R <sup>2</sup> change
1	(Constant)	-1.682	2.527	-666	0.507	0.064	0.064
	P2 AFQT	-0.120	0.037	-3.248	0.001		

score in the previous analyses reported in this article. These included; pre-injury AFQT, total years of education, right amygdala involvement, caudate involvement, left parietal involvement, right frontal involvement, hippocampal involvement, left temporal involvement, globus pallidus involvement, third ventricle width, global rating of atrophy, width of the corpus callosum (all based on measurements taken at P3) and the presence of GRIN2A rs968301.

When looking at the overall changes in intelligence from pre-injury to P3, the following were significant in their prediction of decline (in order according to

regression coefficient value); right amygdala involvement ( $B = -28.261$ ,  $F = 10.546$ ,  $df = 1$ ,  $P = 0.001$ ), hippocampal involvement ( $B = 16.851$ ,  $F = 9.840$ ,  $df = 1$ ,  $P = 0.002$ ), caudate involvement ( $B = 9.558$ ,  $F = 5.798$ ,  $df = 1$ ,  $P = 0.017$ ), left parietal involvement ( $B = 8.984$ ,  $F = 7.066$ ,  $df = 1$ ,  $P = 0.009$ ) and pre-injury AFQT ( $B = -0.293$ ,  $F = 27.523$ ,  $df = 1$ ,  $P < 0.001$ ). For change in AFQT score from P2 to P3, the only factor that was significant in its predictability when the same factors were entered was AFQT score at P2 ( $B = -0.150$ ,  $F = 8.932$ ,  $df = 1$ ,  $P = 0.003$ ). Given that GRIN2A genotype variation has been found to potentially influence the age of onset in the Huntington's Disease (Arning *et al.* 2005), we hypothesized that the caudate nucleus linked with GRIN2A genotype. Thus, we repeated the analysis without the inclusion of caudate involvement as a covariate, but the results did not differ.

Finally, we carried out a stepwise linear regression analysis to identify the relative contributions each significant factor may have had in predicting change in intelligence (Tables 2–4). In terms of AFQT at P3, the

**Table 4** Relative contribution to change in AFQT from preinjury to P3 made by significant predictive factors

Model		B	SE	t	P	R <sup>2</sup>	R <sup>2</sup> change
1	(Constant)	7808	3.746	2.084	0.039	0.127	0.127
	Pre-injury AFQT	−0.272	0.056	−4.837	0.000		
2	(Constant)	11.386	3.485	3.267	0.001	0.274	0.147
	Pre-injury AFQT	−0.270	0.051	−5.253	0.000		
3	Phase 3 CT: caudate involvement	−18.193	3.201	−5.684	0.000	0.315	0.042
	(Constant)	12.387	3.409	3.634	0.000		
4	Pre-injury AFQT	−0.253	0.050	−5.017	0.000	0.351	0.036
	Phase 3 CT: caudate involvement	−16.462	3.167	−5.199	0.000		
5	Left parietal involvement	−8.979	2.884	−3.114	0.002	0.372	0.020
	(Constant)	21.745	4.593	4.734	0.000		
6	Pre-injury AFQT	−0.256	0.049	−5.187	0.000	0.412	0.040
	Phase 3 CT: caudate involvement	−15.522	3.108	−4.993	0.000		
7	Left parietal involvement	−8.728	2.817	−3.098	0.002	0.429	0.018
	Phase 3 CT: distance 2 of CC	−1.497	0.506	−2.957	0.004		
8	(Constant)	21.962	4.536	4.842	0.000	0.372	0.020
	Pre-injury AFQT	−0.258	0.049	−5.304	0.000		
9	Phase 3 CT: caudate involvement	−17.819	3.234	−5.510	0.000	0.412	0.040
	Left parietal involvement	−8.039	2.798	−2.873	0.005		
10	Phase 3 CT: distance 2 of CC	−1.552	0.500	−3.101	0.002	0.372	0.020
	Phase 3 CT: right amygdala involvement	15.305	6.787	2.255	0.026		
11	(Constant)	22.251	4.403	5.053	0.000	0.412	0.040
	Pre-injury AFQT	−0.254	0.047	−5.377	0.000		
12	Phase 3 CT: caudate involvement	−12.402	3.551	−3.493	0.001	0.412	0.040
	Left parietal involvement	−6.921	2.738	−2.528	0.012		
13	Phase 3 CT: distance 2 of CC	−1.615	.486	−3.323	0.001	0.412	0.040
	Phase 3 CT: right amygdala involvement	26.335	7.404	3.557	0.000		
14	Phase 3 CT: hippocampus involvement	−15.812	4.846	−3.263	0.001	0.412	0.040
	(Constant)	24.466	4.466	5.479	0.000		
15	Pre-injury AFQT	−0.260	0.047	−5.569	0.000	0.412	0.040
	Phase 3 CT: caudate involvement	−11.899	3.515	−3.385	0.001		
16	Left parietal involvement	−7.983	2.747	−2.906	0.004	0.412	0.040
	Phase 3 CT: distance 2 of CC	−1.419	0.488	−2.904	0.004		
17	Phase 3 CT: right amygdala involvement	28.642	7.390	3.876	0.000	0.412	0.040
	Phase 3 CT: hippocampus involvement	−17.123	4.824	−3.549	0.001		
18	Right frontal involvement	−5.375	2.446	−2.198	0.029	0.412	0.040

predictors in order of significance were pre-injury AFQT (which was found to account for 51% of the proportion of variance in P3 AFQT test scores), caudate involvement (8.2%), left parietal involvement (2.3%), hippocampal involvement (2.3%), corpus callosum distance (2%), right amygdala involvement (1.1%) and right frontal involvement (1%). In combination, these factors accounted for nearly 70% of the variation in P3 AFQT test scores. For change from P2 to P3, the only significant predictor was AFQT score at P2. For change in intelligence from pre-injury to P3, the predictors accounted for less of the variance. They were, in order of significance, were pre-injury AFQT (12.7%), caudate involvement (14.7%), left parietal involvement (4.2%), corpus callosum distance (3.6%), hippocampal involvement (4%), right amygdala involvement (2%) and right frontal involvement (1.8%).

## Discussion

We found evidence that patients with PHI, compared with matched controls, demonstrate significantly exacerbated

decline in general intelligence. This is consistent with a number of previous studies that supported the concept of a process of exacerbated decline after TBI (Corkin *et al.*, 1989; Klein *et al.*, 1996; Himanen *et al.*, 2006). However, it should be noted that the HI participants in our study with the lowest pre-injury and P2 AFQT scores, as well as lower levels of education tended not to attend P3 of the study. Additionally, only 182 of the 520 HI subjects who attended P2 were assessed at P3, meaning we were unable to include 65% of the sample from P2 in our evaluation of long-term outcome. This may have caused a significant selection bias, implies we were only able to review the long-term demographic, clinical and genetic predictors in those Vietnam Veterans who were probably least at risk from the outset (Grafman *et al.*, 1988) and suggests that the results may have been even more dramatic if those non-attendees had been included. If the theory of cognitive reserve is valid, we may well have seen differing results if we had been able to examine the entire HI sample in P3 of the study, with possibly even greater levels of decline in cognition apparent. We did not, however, find evidence

of increasing levels of frank dementia, maybe as a result of the still relatively young age of the majority of the participants, or perhaps as a result of our sample consisting of those with higher levels of pre-morbid intelligence. Again, these results may have been altered if we had been able to assess a more representative group at all phases of the study.

Our data did show, however, that AFQT scores at the time of military induction was the greatest predictor of P3 AFQT scores for both PHI and control groups. A higher AFQT score before injury acted in a protective manner and even predicted a higher AFQT score over 30 years post-PHI. Change in AFQT score in the first two decades after injury was most associated with pre-injury intelligence, and to a lesser extent educational duration. Thus, it appears that educational level has an impact earlier in the process of recovery from HI. However, AFQT score prior to injury remained the greatest forecaster of overall cognitive outcome at P3, almost four decades after a PHI. In fact, during the latter decades following TBI only pre-injury AFQT and that attained after initial recovery (at P2) was able to predict final AFQT score. Thus, across all time-periods (pre-injury to P2, P2 to P3 and pre-injury to P3), pre-injury AFQT score was the most consistent predictor of later AFQT score, with higher pre-injury scores associated with a lesser degree of decline in the long-term. These veterans were tested on the AFQT three times but the duration between tests was 15 years. Since it is unlikely that our Veterans practiced on similar problems between testings, we believe that while being exposed to the test again might allow for some minimal practice effects, it would not be sufficient to change the pattern of results. Additionally, it should be noted that effects of epilepsy are being examined in a separate study, but the preliminary results indicate that the presence of epilepsy would not mitigate the current findings.

Our data mirror the findings in P2 of the VHIS (Grafman *et al.*, 1988), and studies that have linked early TBI with accelerated cognitive decline later in life (Klein *et al.*, 1996). Given that we have replicated other research that is not specific to PHI, we would cautiously suggest that the results in our sample of veterans with PHI may be generalized to those with both closed and penetrating TBI.

We found no evidence that laterality of lesion affected the level of overall current intelligence or decline. Similar to Corkin *et al.* (1989), we found the only predictor of change from P2 to P3 was left hemisphere volume loss. However, we did not find any specific brain structure lesions that predicted change in AFQT score from P2 to P3. With respect to change in AFQT score from pre-injury to P3, we did find an association between corpus callosum thickness, third ventricle width and rating of global atrophy and change in AFQT score. Thus, degree of atrophy as well as involvement of the caudate nucleus, left parietal lobe, right amygdala, hippocampus and right frontal lobe in a PHI appeared to influence level of performance over the 30

years post-injury. We also found that lesions in the left parietal region interacted with performance on the math, boxes and tools subtests of the AFQT. The brain regions we found to have a significant role in terms of decline in intelligence can be related to the subtests of the AFQT test, performance on all of which was correlated with change in intelligence over time. The caudate nucleus has been found to have a role in language comprehension (Grossman *et al.*, 2002). The parietal lobes are associated with visual-spatial judgements (Ekstrom *et al.*, 2003; Sack *et al.*, 2007), sometimes in conjunction with networks involving the frontal lobes (Chun and Turk-Browne, 2007). The hippocampus is of course vital for memory and attentional tasks (Aalto *et al.*, 2005), and has been linked to networks involving the amygdala in processing of emotional information (Richardson *et al.*, 2003).

Interestingly, we also found an association between atrophy in the left parietal and right frontal regions and degree of decline in intelligence over the 30 years following TBI. It should be noted that the atrophy most often occurred adjacent to the location of the original lesion and in the corresponding lobe. Given the marginal group differences in decline between P2 and P3, what was apparent in the head injured group was a slow decline that started post-injury against a foreground of recovery of function. So it is feasible that what we are calling an exacerbated decline likely had its origins in the injury and not a dementia, and could have been modified by severity (i.e. volume loss) and location of injury, education, intellectual development and genetic endowment.

In terms of genetic predictors, we found no apparent associations between APO e4 (or for that matter family history of dementia) and cognitive degeneration, as in some other studies, suggesting that exacerbated decline is a phenomenon independent of at least some forms of Alzheimer's disease. Our analysis of the data involving the COMT genotypes was similar to other studies, in that we found that having the Val/Val polymorphism led to the most pronounced intellectual decline. However, prior studies have reported associations with the known functional variant COMT Val158Met (rs4680). It should be noted that in the current study, an association was seen between low MMSE score and the intronic marker rs2020917 that is in a different LD block than rs4680. Of all the polymorphisms examined, we found that GRIN2A rs968301 was the most important predictor of exacerbated decline. Interestingly, GRIN2A genotype variation has been found to potentially influence the age of onset in the Huntington's Disease (Arning *et al.* 2005). GRIN 2A is one of the genes that codes for the different subunits of NMDA receptors, including NR2A. NMDA receptor subunit composition has also been found to predict brain plasticity, with NR2A being linked to reduced plasticity (Barria and Malinow, 2005). Additionally, we showed a link between GRIN, GAD, DBH and COMT and pre-injury intelligence, suggesting that these genotypes may have their greatest influence via

their effects on protective mechanisms in PHI. By performing our analyses in the entire population, it is possible that the findings could have been affected by potential population stratification. However, we found similar results regarding the impact of genetic markers when the analysis was rerun on the Caucasian subpopulation, so that would have reduced the false positive due to allele frequency differences between populations. These findings show that genetic markers may play a small but significant role in different stages of cognitive recovery or decline after HI. This is an interesting but tentative result that obviously requires further investigation to establish its significance both in terms of degree and timing of its impact following TBI.

We have presented a number of important findings from this large, long-term follow-up study of subjects with penetrating brain injuries. Our findings suggest that exacerbated decline in intelligence is a significant risk for those with PHI, but that intelligence prior to PHI is the most vital predictor of outcome 30 years after the injury. However, we have also been able to demonstrate that specific regions of brain damage affect this change, as does the degree of local and global atrophy, even in the absence of frank dementia. Additionally, this is the first study to examine genetic factors in the long-term outcome following PHI. Our findings indicate that genotype variations do play a role in exacerbated decline after HI, and warrant further investigation. Clinicians treating veterans with PHI should evaluate any changes in their neurobehavioural status carefully so as to not confuse an exacerbated decline in function with frank dementia. This additional burden to brain-injured veterans should be considered when estimating their future health care needs.

### Supplementary material

Supplementary material is available at *Brain* online.

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