Genes, Environment, and Time: The Vietnam Era Twin Study of Aging (VETSA)

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The Vietnam Era Twin Study of Aging (VETSA) is a large-scale investigation of cognitive aging from middle to later age. The intended sample of 1440 twin subjects is recruited from the Vietnam Era Twin Registry (VETR), a registry of middle-aged male-male twin pairs who both served in the military during the Vietnam conflict (1965–1975). VETSA employs a multitrait multimethod approach to cognitive assessment to focus on the genetic and environmental contributions to cognitive processes over time, as well as the relative contributions to cognitive aging from health, social, personality, and other contextual factors. The cognitive domains of episodic memory, working memory, abstract reasoning, and inhibitory executive functioning are assessed through neuropsychological testing. In addition, VETSA obtains the participant's score on the Armed Forces Qualification Test, taken at the time of induction into the military around age 20 years, and readministers the test. Two other projects — VETSA Cortisol and VETSA Magnetic Resonance Imaging — are also in progress using subsamples of the VETSA twins. Prior waves of data collection by VETSA investigators using the VETR have provided historical data on physical and mental health, while future waves of VETSA data collection are planned every 5 years. These methods will provide data on multiple phenotypes in the same individuals with regard to genetic and environmental contributions to cognitive functioning over time, personality and interpersonal risk and protective factors, stress and cortisol regulation, and structural brain correlates of aging processes.

Overview of the Primary VETSA Project

The Vietnam Era Twin Study of Aging (VETSA; principal investigators: Drs Kremen and Lyons) comprises an integrated set of prospective studies of aging funded by the United States National Institute on Aging. The major focus of the primary VETSA project is to elucidate factors affecting cognitive aging. To that end, we seek to understand aging processes by clarifying the relationships between cognition, health, personality, and psychosocial factors, and by quantifying the relative influences of genetic and environmental factors in these major domains of adult development and aging. These domains are intended to cover many of the key factors that are likely to determine successful aging. The primary VETSA project began in 2002. The study acronym is, in part, an acknowledgment of another very valuable twin study of aging: the Swedish Adoption/Twin Study of Aging (SATSA). In addition to the primary VETSA project, the VETSA Magnetic Resonance Imaging (MRI) study incorporates neuroimaging, while the VETSA Cortisol study adds neuroendocrine measures on a large subset of VETSA twins.

Key Features of the Primary VETSA Project

Baseline in midlife. One key feature of the VETSA sample is that all subjects are in their 6th decade of life at the Wave 1 assessment (age range: 52–60 years). This design is different from most twin studies that either begin with elderly subjects, for example, over 65, (Berg et al., 1992; Christensen et al., 1999; Kallman & Sander, 1948, 1949) or include multiple, smaller cohorts covering a wide range of ages (Finkel, Whitfield, et al., 1995; Hayakawa et al., 2002; Kaprio & Koskenvuo, 2002; Pedersen et al., 1991; Whitfield et al., 2003). Beginning in midlife allows initial assessments to be completed while subjects are relatively healthy and before many substantial age-related changes may have taken place. This makes the timing excellent for studying the relative contributions of genes and environment to age-related changes in cognition, health, personality, and psychosocial functioning.

Expectation of change in the near future. Beginning with subjects in their 6th decade of life provides a good balance between obtaining baseline information

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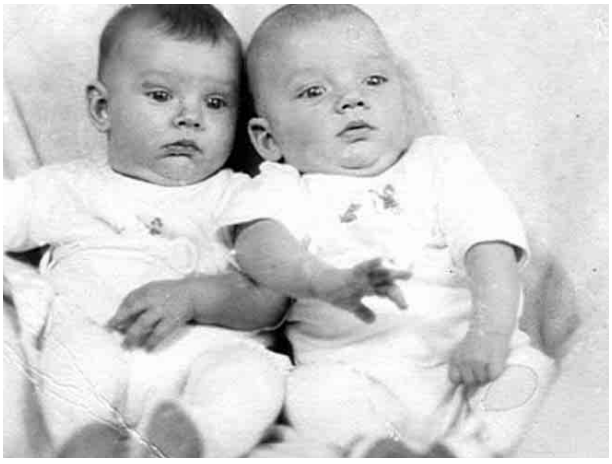

Figure 1
Keith and Ken, age 6 months.

Figure 3
Keith and Ken, age 20 years.

prior to substantial age-related changes and minimizing the time delay needed before being able to observe meaningful differences. Indeed, it may be possible to observe age-related change in the project's first planned follow-up.

Previously collected data. Previously collected data are available for Vietnam Era Twin (VET) Registry twins, thus making it possible to perform some longitudinal analyses even at baseline. An exceptionally rare feature of this already existing information is its inclusion of cognitive data going back as far as late adolescence (age range at first Armed Forces Qualification Test [AFQT] administration: 17–25 years).

Narrow age range. It is important for research to focus on variability within age groups as opposed to examining mean differences among different age groups (Bergeman, 1997; Dannefer & Sell, 1988). The large cohort, but very narrow age range of VETSA, means that power will be maximized for longitudinal analyses, that is, for direct examination of change within individuals over time. This feature enhances the ability to study the heterogeneity within an age group, and thus go beyond accounting for differences via age alone (Bergeman, 1997).

Five-year follow-ups. VETSA focuses on the second half of the lifespan. The study design calls for follow-up every 5 years.

Multiple phenotypes characterizing the same individuals. Age-related phenotypes may include complex combinations from multiple domains. It is an advantage of VETSA that all of the assessments for the primary VETSA project are obtained for all subjects. Moreover, all subjects with neuroendocrine data from the VETSA Cortisol study also have all of the data

Figure 2
Keith and Ken, age 4 years.

Figure 4
Keith and Ken, age 58 years.

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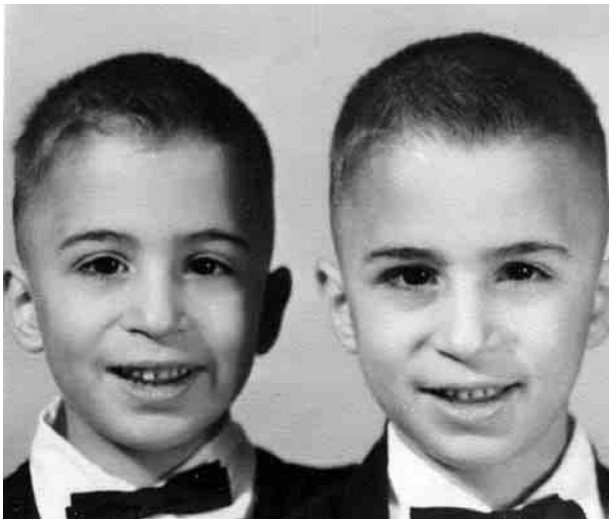

Figure 5
Jim and Joe, age 6 years.

Figure 7
Jim and Joe, age 22 years.

from the primary VETSA project, and all subjects with MRI data have all of the primary study and cortisol data as well.

Subjects

Ascertainment. VETSA subjects are members of male–male twin pairs (both monozygotic and dizygotic) ranging in age from 52 to 60 years at the Wave 1 assessment. These twins are all members of the VET Registry, which was constructed in the 1980s and is described in detail elsewhere (Goldberg et al., 1993; Goldberg et al., 2002). Male twins who served in the United States military during the Vietnam Era were identified from among the approximately 5.5 million men who served during this period through their birth year (between 1939–1957), period of active duty (between 1965–1975), and having the same last name, different first name, same date of birth, and same first five digits of the Social Security number. From this pool, initial confirmation of twin status was ultimately made through match on home address at entry into military service and parental names by review of military service records, and twins were invited to participate in the VET Registry. Zygosity was established with questions on twin similarity and blood group typing data obtained from military records, a method that achieved 95% accuracy (Eisen et al., 1989). The 7375 twin pairs confirmed through this method comprise the VET Registry.

Figure 6
Jim and Joe, age 18 years.

Figure 8
Jim and Joe, age 56 years.

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VETSA twins are recruited from the participant pool of the 1991–1993 Harvard Twin Study of Drug Abuse and Dependence. Investigators in the Harvard Drug Study attempted to contact all available VET Registry members. It is important to note that there were no selection criteria for the Harvard Drug Study; that is, twins were not selected on the basis of any demographic, diagnostic, or other characteristics. A total of 8169 twins (3322 complete pairs) participated in the Harvard Drug Study. Subjects within the appropriate age range are randomly selected for VETSA from these 3322 twin pairs. All of the data already collected in the Harvard Drug Study are available to the VETSA investigators (see Previously Collected Data). These individuals currently live throughout the United States, and virtually all of them have pursued careers outside the military.

Representativeness. Twins in the general VET Registry may differ in health and socioeconomic status from men who did not serve in the military. However, several studies of both the draft-era veterans and the all-volunteer force have shown that differences in socioeconomic status between the military and nonmilitary, when observed, are modest in size, contrary to popular assumption that military men come from lower socioeconomic strata than does the population as a whole (Boulanger, 1981; Cooper, 1977; Fernandez, 1989; Fredland & Little, 1982). Researchers evaluated the VET Registry for bias related to incomplete ascertainment of twin pairs who served in the military during the Vietnam War (Goldberg et al., 1987). Male–male twin pairs born in the state of Connecticut who served in the military service during the Vietnam War and who were identified or not identified by the method described above (see Ascertainment) were compared on a variety of self-reported health characteristics obtained in 1987. No consistent differences in health habits, physical health, or psychosocial health factors were detected. Thus, the VET Registry cohort is likely to represent the cohort of all twin pairs who served in the military.

VETSA subjects appear to be representative of the Harvard Drug Study subject pool from which they were selected. Table 1 compares the first 746 VETSA subjects for whom we have complete, cleaned data and nonparticipating (non-VETSA) subjects' demographic and military service-related characteristics. VETSA and non-VETSA subjects do not differ significantly in age at induction, race, marital status at time of Harvard Drug Study, education at induction, branch of military, Vietnam service, or combat experience. The only difference found to be significant between the two groups was on the AFQT score at time of induction. The AFQT is a general cognitive ability measure described in greater detail below (see Neuropsychological Measures). VETSA participants appear to possess somewhat higher AFQT scores than non-VETSA subjects. This difference may be due to a number of factors. People of higher cognitive ability may be more inclined to participate in scientific research, or they may be easier for us to locate. Recent research also shows that IQ in late adolescence predicts mortality by mid-adulthood (Hemmingsson et al., 2006). Therefore, more subjects of high rather than low cognitive ability may be surviving to the age range targeted by VETSA. Other longitudinal studies of cognition have observed similar effects of attrition which suggests that this phenomenon may be inevitable. For example, the MRC National Survey of Health and Development (Richards & Sacker, 2003) which collected cognitive data from a birth cohort when they reached age 53 found that having a father in a manual occupation, lower cognitive test scores at age 8 years, lower educational attainment, and a manual adult occupation, were each associated with a lower probability of participating in the age 53 follow-up. In the study of Deary et al. (2000) in which the same test of general cognitive ability was administered to individuals at age 11 and again at age 77, the mean score at age 11 of participants in the follow-up at age 77 was 0.57 standard deviation units higher than the mean of the total population at age 11. It is important, however, that we do not overstate the magnitude of the AFQT difference that we observed. Though significant, it equals only about one third of a standard deviation; this would be equivalent to about five points on a Wechsler IQ score.

VETSA subjects also do not differ from the overall subject pool in psychopathology. Lifetime prevalence of common psychological disorders were similar for the two groups, VETSA participants-to-date versus nonparticipants-to-date: 47.5% vs. 47.6% for nicotine dependence; 8.7% vs. 9.6% for drug dependence; 34.4% vs. 35.8% for alcohol dependence; 7.1% vs. 10.3% for PTSD; and 8.0% vs. 9.8% for depression.

As of July 2006 we have collected data from 1006 individuals for VETSA Wave 1. VETSA subjects have a mean age at assessment of 55.3 ± 2.3 (range 52–60) and mean years of education of 13.9 ± 2.1 (range 4–20). Mean current life satisfaction on the Life Complexity Inventory (Gribbin et al., 1980) was rated as 7.6 ± 1.6, with 0 being *worst* and 10 being *best,* and mean self-rated health on the Short Form-36 (Ware et al., 1993) was 2.5 ± .90, with 1 being *excellent* and 5 being *poor*. Self-reported prevalences of common health conditions were 37% for hypertension, 6.6% for heart attack, and 11.9% for diabetes. These prevalences for health conditions are consistent with population data for American men in this age range (Lethbridge-Cejku & Vickerie, 2005).

Recruitment. Contact information for eligible twins is provided to the survey research firm of Schulman, Ronca, Bucuvalus, Inc. (SRBI; Silver Spring, MD, United States) by the VET Registry located at the Department of Veterans Affairs Medical Center in Seattle, United States. SRBI sends letters of introduction to potential subjects. If there is no response within two weeks, SRBI follow up the letters with a

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Table 1

Comparison of VETSA and Non-VETSA Subjects

	VETSA subjects (Total *n* = 746)	Non-VETSA subjects (Total *n* = 7423)
Age at induction (years)	19.9 ± 1.4 (17–25)	19.9 ± 1.7 (16–31)
	(*n* = 746)	(*n* = 7420)
Race		
White	95.4% (*n* = 712)	93.1% (*n* = 6911)
Black	4.0% (*n* = 30)	6.5% (*n* = 483)
Hispanic	0.3% (*n* = 2)	0.0% (*n* = 1)
Missing	0.3% (*n* = 2)	0.4% (*n* = 28)
Marital status in 1991–1993		
Married	78.3% (*n* = 584)	75.7% (*n* = 5616)
Single	8.3% (*n* = 62)	7.7% (*n* = 568)
Widowed	0.7% (*n* = 5)	0.4 (*n* = 26)
Separated	1.9% (*n* = 14)	2.4% (*n* = 177)
Divorced	10.9% (*n* = 81)	14.0% (*n* = 1036)
Education at induction (years)	12.4 ± 1.3 (7–20)	12.2 ± 1.5 (5–20)
	(*n* = 740)	(*n* = 7386)
AFQT at induction[a]	61.6 ± 22.1 (10–99)	53.7 ± 23.5 (10–99)
	(*n* = 744)	(*n* = 6879)
Branch of Military		
Army	48.0% (*n* = 358)	50.5% (*n* = 3746)
Air Force	21.2% (*n* = 158)	17.8% (*n* = 1325)
Marines	7.1% (*n* = 53)	6.9% (*n* = 511)
Navy	23.7% (*n* = 177)	24.8% (*n* = 1839)
Vietnam service	38.2% (*n* = 285)	37.5% (*n* = 2782)
Combat index score[b]	3.2 ± 3.3 (0–13)	3.5 ± 3.2 (0–15)
	(*n* = 273)	(*n* = 2807)

Note: [a] The difference in AFQT (Armed Forces Qualification Test) scores is estimated to be equivalent to about five points on a Wechsler IQ score.

[b] An individual's combat index score was derived by summing all positive responses to a combat instrument, the Combat Exposure Index (Janes et al., 1991), which assesses various combat situations. Specifically, each veteran was asked whether he had engaged in 18 diverse combat experiences, such as acting as a 'tunnel rat' checking enemy base camps, receiving incoming fire, flying in an attack helicopter, and/or being wounded.

phone call. Interested subjects submit an authorization form to SRBI in which the subject gives his permission for the investigators to contact him and states a study site preference. The authorization forms are forwarded to the VET Registry headquarters, and the VET Registry sends the forms to the San Diego site at the University of California, San Diego or the Boston site at Boston University. Upon receiving the authorization forms, project staff contact the twins, set up an appointment date, and ensure that all travel arrangements are made. If subjects are interested in participating in the VETSA MRI study, they are screened for safety issues that might preclude their participation (e.g., metal in the body, severe claustrophobia). Twins are told in advance that both members of a pair must agree to participate in order for them to be included in the VETSA projects. To date, the majority of twins (95.6%) have traveled to the research sites for testing; the remaining minority are visited in their home towns by research assistants who conduct the assessments in a small conference room at a local hotel (an option offered to all twins in order to obtain representativeness in health and mobility status). All twins who participate give informed consent as approved by the Institutional Review Boards of the participating institutions.

Procedure. At home, prior to arriving at a study site, subjects complete a series of paper-and-pencil measures that include many of the personality and psychosocial measures as well as some self-report health measures. As part of the VETSA Cortisol study, subjects also provide saliva samples for neuroendocrine assays on two different weekdays while they are at home. Five samples on each of these days are provided and then shipped to our laboratory. When subjects visit one of the two sites, assessments are carried out for a full day (approximately 8.00 am to 4.30 pm with breaks). More detail is provided on all of these measures in sections below.

An identical set of assessments is administered by each study site. Reliability across raters, sites, and over time is maintained through detailed scoring manuals, weekly scoring and administration conference calls, regular cross-checking of scoring decisions, and periodic in-person meetings. Many questions are

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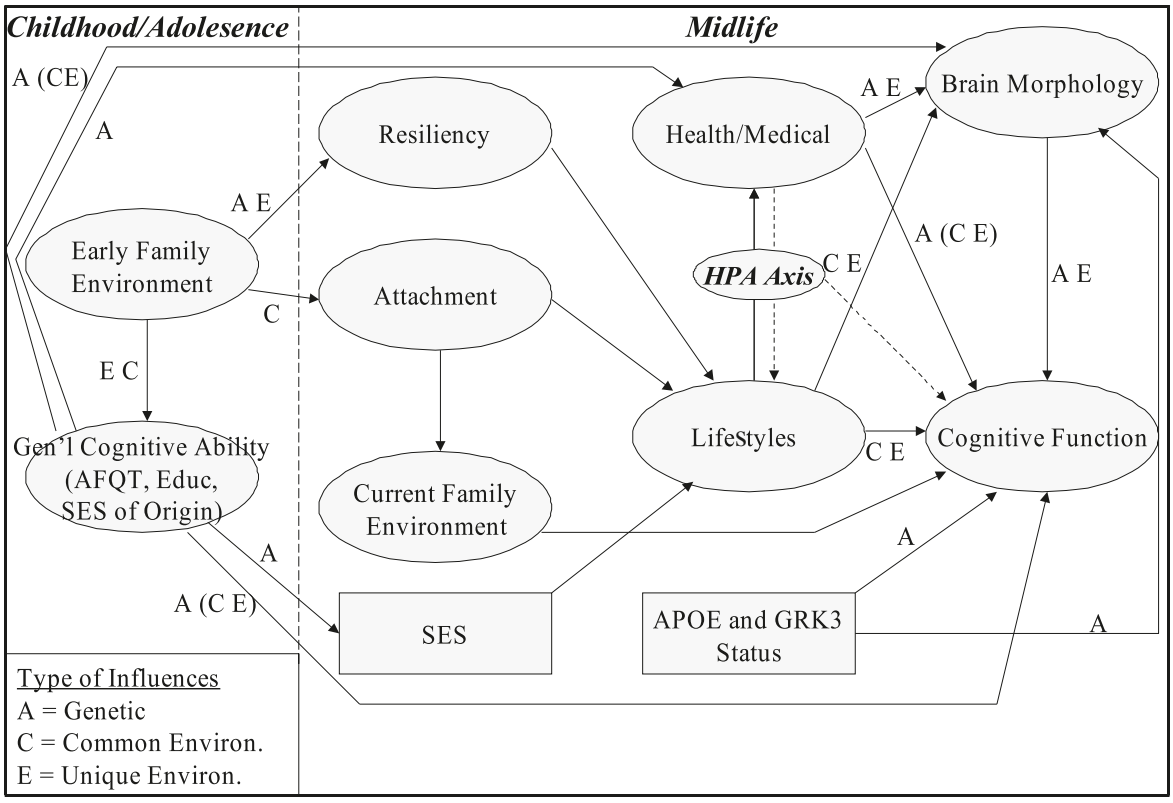

Figure 9

Conceptual model for VETSA's approach to cognitive aging.

also resolved on a day-to-day basis by e-mail. An advantage of using e-mail is that individual questions and their resolution are easily distributed to all project staff. The scoring manuals are regularly updated with examples from these scoring questions. Following manual data entry and cross-checking at the San Diego and Boston sites, data entry forms are sent to another study site at Washington University/St. Louis VA Medical Center where the central database for the VETSA projects is maintained.

Measures

As noted previously, the domains of assessment for VETSA include an extensive neuropsychological test battery, as well as health, personality, and psychosocial indicators. The domains of assessment, and examples of measures for each domain, are listed in Tables 2 to 4. Figure 9 depicts an overall model for the VETSA projects based on both theory and empirical findings. This model is a conceptual, rather than a technical model; however, portions of the model can be easily adapted for statistical analysis using structural equation modeling and other techniques.

Neuropsychological measures. Table 2 delineates the neuropsychological measures. The neuropsychological battery was designed to assess a broad range of functions with emphasis on systems disproportionately affected by age-related change. The latter cognitive domains include: (1) working memory (Rajah & D'Esposito, 2005; Salthouse, 1991; Wingfield et al., 1988), (2) inhibition of off-target thoughts and stimuli (Zacks et al., 2000), (3) effectiveness in learning and retrieval from episodic memory (Kausler, 1994; Rajah & D'Esposito, 2005), and (4) processing speed (Salthouse, 1996, 2000).

The selection of tests was guided by the need to cover a broad range of cognitive domains and to avoid floor and ceiling effects. Given the time constraints, the neuropsychological battery includes a mix of traditional neuropsychological tests and some tests based in experimental cognitive psychology. The latter tests tend to be longer but are more geared toward parsing the components of cognition. We are interested in examining components within experimental cognitive tests as well as comparing and contrasting performance across different neuropsychological domains. To the extent possible, a key aim of VETSA is to utilize this information to understand what cognitive subprocesses account for better or worse performance on various tests. In addition, the VETSA battery includes assessment of sensory and motor functions known to influence cognitive performance in older adults, as deficits in these areas could mistakenly be attributed to deficits in higher order functions.

A particularly important measure in the VETSA battery is the AFQT, a 50-minute paper-and-pencil test

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Table 2

Neuropsychological Measures

Function	Tests
Handedness	Oldfield Handedness Inventory
General cognitive	WASI (vocabulary and matrix reasoning); AFQT
Working memory	Digit and spatial span; WMS-III letter–number sequencing; reading span (ascending/descending); AX-CPT; Hedden-Park (WM, interference)
Inhibitory control	AX-CPT; Hedden-Park; Stroop Color-Word (adjusted)
Other executive functions	Verbal fluency (letter, category, switching); D-KEFS Trail Making Test (switching adjusted for other conditions)
Processing speed	D-KEFS Trails scan and motor; Simple & Choice RT; Stroop Word
Episodic memory	WMS-III Visual Reproductions & Log. Memories; CVLT-II
Visual-spatial	Mental rotation; Gottschaldt hidden figures
Sustained attention	AX-CPT (signal detection perceptual sensitivity measure [d^1])
Circadian arousal	Morningness–Eveningness Questionnaire, time of day tests given

Note: WASI = Wechsler Abbreviated Scale of Intelligence; AFQT = Armed Forces Qualification Test; WMS = Wechsler Memory Scale; AX-CPT = AX Continuous Performance Test; WM = working memory; D-KEFS = Delis-Kaplan Executive Function System; RT = reaction time; CVLT = California Verbal Learning Test .

consisting of 100 multiple-choice items that was administered just prior to military induction (Bayroff & Anderson, 1963). The items equally represent the four domains of vocabulary, arithmetic word problems, knowledge of tools and of mechanical or electrical equipment, and spatial visualization, that is, matching folded and unfolded box patterns (Uhlaner & Bolanovich, 1952). Although it was intended as a measure of military trainability, the AFQT does appear to be a highly *g*-loaded test. For example, McGrevy et al. (1974) found a correlation of .84 (after correcting for restriction of range) between AFQT and Wechsler Adult Intelligence Scale (Wechsler, 1955) scores. VETSA investigators received permission from the United States Department of Defense to readminister a version of the AFQT that is similar to the AFQT versions that had been administered to VETSA subjects just prior to their induction into the military (1965–1975). This version has been used in previous research (Grafman et al., 1988). Scores from the time of induction are also available to VETSA investigators (see Previously Collected Data section).

A growing body of evidence suggests that the heritability of cognitive ability increases up to midlife and may then level off or decrease in older age (Finkel, Pedersen, et al., 1995; McClearn et al., 1997; McGue & Christensen, 2001). However, these conclusions are based essentially on cross-sectional findings. By readministering the AFQT as part of the VETSA test battery, we have a unique opportunity to prospectively examine stability and change in cognition from late adolescence to midlife, and to prospectively examine changes in heritability over a 35-year period.

Health and medical. Table 3 lists the VETSA health and medical measures. Health and medical conditions are, of course, important in their own right, but they may also influence neurocognitive and other dimensions of aging. The VETSA health and medical measures were selected on the basis of the existing literature for their potential relationship with cognitive aging. Because subjects are available for testing on only a single day, selection of measures was also determined by practical constraints concerning what assessments would be feasible in our laboratory. Health and medical conditions may negatively affect cognition in later life via their influence on the brain. Such conditions include blood pressure (Elias et al., 1998; Kilander et al., 1998; Swan et al., 1998), pulmonary function (Chyou et al., 1996; Emery et al., 1998), obesity, and head injury (Corkin et al., 1989). The health and medical measures are divided into those that are directly assessed at home or in the laboratory, and self-report measures.

As with any twin study, a major goal of the VETSA projects is to determine the heritability of various aging-related phenotypes. In addition, we collect 45 to 50 ml of blood from VETSA subjects for the purpose of genotyping and clinical chemistries. In

Table 3

Health and Medical Measures

Construct	Measurement technique
Direct assessment	
Cardiovascular	Systolic/diastolic blood pressures; Ankle-Arm Index
Pulmonary	Spirometry (FEV_1, FVC)
Height/weight	Scale measure: W/H Ratio; BMI
Genotyping	Lab Assay (APOE, GRK3, zygosity)
Vision/audition	Acuity; contrast sensitivity/audiometry
Motor function	Grip strength; rise from chair, walk speed
Self-report/interview	
Medical history	Medical history interview; SF-36
Head injury	Included in medical history interview

Note: FEV_1 = forced expiratory volume in one second; FVC = forced ventilatory capacity; W/H = body circumference at waist and hip; APOE = apolipoprotein E.

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Table 4

Personality and Psychosocial Measures

Construct	Measure
Personality	
Attachment/ interpersonal function	Experience in Close Relationships Inventory; Relationship Questionnaire; MPQ Communion, Social Closeness
Resiliency	Ego-Resiliency Questionnaire; Rosenberg Self-Esteem Scale
Coping style	Ways of Coping Questionnaire
Personality traits	MPQ
Adaptive functioning/ well-being	Ryff Well-Being Scale; CES-D; MPQ Well-Being; Life Complexity Inventory ('Dissatisfaction'); social adjustment
Psychosocial indicators	
Social support	MOS Social Support Survey
Life events	Modified Holmes-Rahe Scale
Lifestyle and activities	Life Complexity Inventory
Family environment	Modified Moos Family Environment Scale

Note: MPQ = Multidimensional Personality Questionnaire; CES-D = Center for Epidemiologic Studies–Depression Scale; MOS = Medical Outcomes Study.

Table 5

Previously Collected Data

Information category	Years data collected
Alcohol and cigarette consumption	1987, 1990
Major medical illnesses	1987,1990
Cardiovascular and pulmonary disease	1990
Dietary habits	1990
Vitamin and aspirin use	1990
Type A personality, social support	1987
Level of regular physical activity	1990
Sleep habits	1990
DSM-III-R psychiatric disorders and substance abuse	1992
Height, weight	1970, 1987, 1990, 1992
Hip, waist circumference	1990
Cognitive (AFQT)[a]	1965–1975
Age, education, parental education at the time of induction into the military	1965–1975

Note: [a] Collected once, as part of the military induction evaluation.

DSM-III-R = *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed., rev.), published by the American Psychiatric Association in 1987.

the primary VETSA project, we are examining the apolipoprotein E (APOE) genotype because of the association that has been observed between the APOE-ε4 allele and cognitive deficits associated with dementia (Blesa et al., 1996; Bondi et al., 1999; Henderson et al., 1995). In the VETSA Cortisol study, we are examining the G protein-coupled receptor kinase 3 (GRK3) genotype because GRK3 plays a role in regulating corticotropin-releasing-factor (CRF_1) receptors (Dautzenberg et al., 2001; Dautzenberg et al., 2002), which is important in cortisol and hypothalamic-pituitary-adrenal axis function. DNA is regularly processed and stored for additional genotyping. A portion of the blood samples is also stored for clinical chemistries that will be carried out as well.

Personality and psychosocial measures. Personality and psychosocial factors are likely to influence brain and cognitive aging through their effects on health and adaptive functioning. For example, aspects of personality, or a sedentary lifestyle may increase risk for cardiovascular problems, which in turn may increase risk for cognitive deficits. On the other hand, personality and psychosocial factors may be important determinants of stress reduction, sense of well-being, health maintenance (e.g., diet), and activity level, and so should be associated with better adaptive functioning that promotes health and cerebral integrity.

These measures are divided into three categories in Table 4: (1) personality, (2) adaptive functioning and well-being, and (3) psychosocial indicators. Although the measures are listed in this way, resiliency (flexible coping) and attachment (quality of close relationships with others) are two overarching personality and psychosocial constructs that we believe are important for successful aging.

Previously collected data. Because VET Registry twins have participated in several research projects over the years, the VETSA projects are in the unique position of being able to examine data longitudinally, even at the Wave 1 assessment. The VETSA consent form specifically informs subjects that the investigators will be utilizing these previously collected data for this purpose. Table 5 lists the already collected data that are available and the approximate years when the data were obtained. Only data that are available for all, or nearly all, of the VETSA twins are included in Table 5.

It is noteworthy that some of these data go back to the time of subjects' induction into the military when their average age was 19.9 years. Height and weight are available from the time of induction and at other times. These data enable us to examine genetic and environmental influences on body mass index, changes in body mass index over time, and the relationship between body mass index and other VETSA measures. As mentioned previously, we also have access to scores on the AFQT. Individuals scoring in the lowest 10 percentile ranks were excluded from the military, and thus not eligible for inclusion in VETSA. Exclusion of those scoring below the 10th percentile results in a mean percentile score above 50 in the more recent Vietnam era sample.

Integration of assessment domains. VETSA investigators plan to identify health, psychosocial, personality, and lifestyle factors that may exert influences on outcomes of interest. For example, multiple studies have linked cardiovascular functioning to age-related changes in cognition (e.g., Elias et al., 1998; Emery et al., 1998; Guo et al., 1997; Kilander et al., 1998; Kuo et al., 2005; see Anstey & Christensen, 2000, for review), and both genetic and environmental factors contribute to

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variability in cardiovascular functioning (e.g., Emery et al., 1998; Evans et al., 2003; Feinlab et al., 1977; Finkel et al., 2000). The inclusion of multiple interrelated health measures relevant to cognitive aging — such as blood pressure, pulmonary functioning, medication usage, health problems, head injury, and motor/sensory functioning — allows for investigation of complex relationships between these variables and cognitive decline. Similarly, data collection includes detailed measures of relationship quality and life satisfaction, well-being, depression, involvement in activities, spirituality, and personality indicators (control, mastery, positive and negative emotion) found in other research to mediate/moderate health or cognitive outcomes.

Neuroendocrine and Neuroimaging Studies

As noted, grants supporting two additional VETSA projects are closely integrated with the primary VETSA project. Because all subjects participating in these two additional projects will have also participated in the primary VETSA project, all data collected in the primary study are available. Thus, there is an extensive range of phenotypes that are available to characterize these subjects. These studies, funded by the National Institute on Aging (Principal Investigator: Dr. Kremen), each recruit subsamples from the primary VETSA sample. The VETSA Cortisol Study (AG 22982) began in 2005 and the VETSA MRI Study (AG 22381) began in 2003.

VETSA Cortisol Study

One major factor underlying individual differences in cognitive and other aspects of aging is the cumulative effect of exposure to life stress and changes in the regulation of the hypothalamic–pituitary–adrenal (HPA) axis (Sapolsky et al., 1986). These effects can be observed in the regulation of glucocorticoids (GCs) and other hormones. Research linking cortisol regulation with cognition has focused primarily on episodic memory. However, based on evidence that cognitive aging most strongly reflects a kind of 'frontal-subcortical syndrome' (Pugh & Lipsitz, 2002), and that there are high concentrations of GC receptors in prefrontal cortex as well as in the hippocampal formation (Lupien & Lepage, 2001; Sanchez et al., 2000; Sarrieau et al., 1986), the investigators extend that focus to frontal-executive functions in VETSA. Elevated cortisol levels are also associated with depression and components of the metabolic syndrome, including diabetes, hypertension, and central obesity (Litchfield et al., 1998; Reynolds et al., 2001; Rosmond, 2005; Tsigos & Chrousos, 2002; Walker et al., 1998). Therefore, health outcomes are another area of emphasis in the VETSA Cortisol Study.

In the cortisol study, we assess diurnal variation of basal cortisol, and examine HPA response to acute and sustained stressors and its association with chronic stressors in VETSA via comparisons of at-home and in-lab measurements. Because there is a regular diurnal variation in cortisol levels, the regulation or responsivity of the system is likely to be reflected in differences in that variation ('cortisol slope') rather than just simple mean level differences. In addition to cortisol, the anabolic steroids, testosterone and dehydroepiandrosterone (DHEA) are also measured in this study. Inclusion of these other steroids leads to some interesting hypotheses. For example, testosterone has an opposing (counteracting) effect on cortisol. Since testosterone levels decrease with age, it may be that the same cortisol level later in life would, in effect, constitute a functional hypercortisolemia because the counteracting influence of testosterone would be reduced. We will also genotype the GRK3 gene; GRK3 is important is stress-related responses and it plays a role in regulating corticotropin-releasing-factor (CRF_1) receptors (Dautzenberg et al., 2001; Dautzenberg et al., 2002). In addition, we plan to genotype other genes that are relevant to HPA axis functioning.

As of June 2006, 295 subjects have been enrolled in the VETSA Cortisol Study. These subjects provide five saliva samples per day on 2 week days at home (Tuesday and Thursday). Times are specified depending on the subject's usual time of awakening. The project also provides each subject with a 'medication reminder' watch that is programmed to go off at the specified sampling times. Samples are stored by the subject in a small plastic container with a track cap that digitally records the date and time whenever it is opened.

Salivary samples provide accurate neuroendocrine measures. Saliva samples have two advantages over blood samples: (1) they reduce the likelihood of a cortisol elevation due to the stress of the needle stick itself, and (2) saliva contains only unbound (free) cortisol, making it a more pure measure of the bioactive form of the hormone. Additional saliva samples are collected on the day of testing, at awakening and at bedtime, after the subject has left the laboratory. Thus, samples are collected under both normative (at-home) and stressful (in-lab) conditions in order to examine prospectively the regulation of HPA activity and its relationship to extensive cognitive and health data. For the purposes of the study, the entire day of testing is conceptualized as a sustained stressor. Because the cortisol baseline — like that of VETSA at large — is established at midlife, the data are of enormous potential value for risk identification as developmental trajectories turn toward the potentially stressful challenges of retirement, increased chronic health problems, care giving for parents and spouses, and bereavement.

VETSA MRI Study

To our knowledge, the VETSA MRI Study is the first longitudinal, neuroimaging twin study. Examining genetic and environmental influences on brain aging is a logical next step, given the strong focus on cognitive aging in the primary VETSA project. The VETSA MRI project includes: (1) brain morphometry based on three-dimensional structural MRI, (2) diffusion tensor

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imaging, and (3) analysis of resting metabolism based on T2* signal in the hippocampal formation. The VETSA investigators hypothesize that cognitive and brain aging strongly involves changes in distributed neural circuits regulating working memory and cognitive inhibition (prefrontal cortex [PFC]-striatal), and episodic memory (PFC-hippocampal; Alexander & Crutcher, 1990; Buckner et al., 1998; Goldman-Rakic, 1987; Park et al., 1996). Although PFC volume has the strongest correlation with age of any parenchymal region (Raz, 2000), there is virtually no volumetric analysis of its subdivisions in the aging literature. Despite its importance in aging and memory, hippocampal volume has been inconsistently correlated with memory and much less consistently correlated with age than PFC (Raz, 2000). We seek to address these and other issues in the VETSA MRI study by parcellating PFC, that is, measuring volumes of subcortical regions comprising a distributed neural circuit linked to PFC. We are performing volumetric and shape analyses of the hippocampal formation. In addition, we measure cortical thickness and other regional gray matter, white matter, and ventricular volumes.

Diffusion tensor imaging provides microstructural indices of white matter integrity that can be used to make inferences about functional connectivity in the brain. This method measures the diffusion of water molecules. Although water molecules can move in any direction, they tend to flow in a direction parallel to the longitudinal axes of axons. A greater degree of directional flow parallel to the longitudinal axes (i.e., less random flow) implies greater efficiency, and therefore, greater functional connectivity. The VETSA MRI team also works closely with the Biomedical Informatics Research Network (BIRN). The BIRN is a multisite project supported by the United States National Institutes of Health/National Center for Research Resources. The overall BIRN principal investigator is Dr. Bruce Rosen; the principal investigator of the morphometry BIRN is Dr Anders Dale, who is also a co-investigator on the VETSA MRI Study at the University of California, San Diego. Part of the collaborative VETSA-BIRN effort is the development of state-of-the-art tractography for delineating brain white matter tracts with diffusion tensor imaging data.

VETSA MRI consultant, Dr Scott Small at Columbia University, has developed a paradigm for measuring T2* signal in the hippocampal formation in both normal elderly and those with dementia (Small et al., 2000). Because the hippocampus is a key brain region with regard to both normal and pathological aging, we are implementing a modification of this paradigm with the help of Dr Dale to longitudinally examine T2* signal beginning earlier in life (i.e., middle age). Increased brain metabolism results in relatively decreased deoxyhemoglobin. The para-magnetic properties of deoxyhemoglobin suppress T2*, which in turn, results in areas with greater metabolism having higher signal intensity. As such, T2* provides an index of neuronal dysfunction by virtue of its reflection of chronic, resting metabolism.

As of June 2006, 417 subjects from the primary VETSA study have stayed a second day to undergo neuroimaging in the VETSA MRI study. The VETSA MRI study is creating a unique normative neuroimaging database from which it will be possible to identify genetic and environmental determinants of individual differences in neuroanatomy during midlife, and assess relationships among brain structure/metabolic variables, cognitive functioning, and health/medical characteristics within individuals. Continuation studies for longitudinal MRI data are also planned so that we can understand genetic and environmental influences on brain aging.

Potential Limitations

The VETSA sample constitutes a highly valuable resource, but it must be acknowledged that it includes men only. The number of women in military service during the Vietnam War era was small, and therefore female twin pairs were not sought as meaningful female twin analyses would not have been possible. The primary reason for this is that the probability of serving in the United States military during the Vietnam era was only about .01% or less for any single female, and the joint probability that both members of a female-female twin pair would have served would be even lower. Also, married women may change their last names; thus, there would have been bias against detecting female twin pairs in which one or both parties changed her name.

In addition, our sample is mostly Caucasian–American. It is unfortunate that the percentage of minority participants in VETSA is low. However, all ethnic groups are included, and the racial composition of our sample is relatively similar to that of the overall population of Vietnam Era veterans.

It has already been noted that socioeconomic or health differences in Vietnam era veteran versus nonveterans are unlikely to be very substantial, although this issue still warrants consideration. It is also possible that because VETSA subjects are asked to travel to the study sites, healthier subjects may be more likely to participate. On the other hand, health measures to date appear to be generally consistent with those of population or census data.

It is also possible that combat exposure is one military experience that could particularly influence physical or cognitive measures. Indeed, in the first publication based on VETSA data (first 236 twins), we showed that twins who had served in Vietnam had lower lifetime educational attainment than their cotwins who had not been in combat (Lyons et al., 2006). This effect was small but significant, even after controlling for several potential confounders. Although the VETSA sample was drawn from individuals who had been members of the military, it is important to note that two thirds were never deployed to Southeast Asia,

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thereby permitting the researchers to assess and control for possible effects of combat exposure. Moreover, research suggests some benefits to military service (Elder & Clipp, 1989).

Because all of the VETSA subjects are in an extremely narrow age range, the study design precludes examination of cohort effects. Of course, it is not possible to address all issues in any single study. We believe, however, that this limitation is offset by some of the benefits of the VETSA design. These include benefits gained by having all of our subjects being middle-aged at the baseline assessment, and by the increased power to examine within-person change over time that is afforded by this very narrow age range.

Future Directions

As already noted, VETSA was conceptualized as both a cross-sectional and longitudinal study. As our subjects enter into a stage of greater physical, social, and environmental change, we plan to reassess them every 5 years for as long as possible in order to ascertain the extent to which the relative influence of genetic and environmental factors on cognition, health, personality, and psychosocial functioning changes from middle to later life, and to examine predictors of more or less successful aging in the various domains under study. All VETSA subjects have already participated in at least one VET Registry study. The fact that these subjects have demonstrated an interest and willingness to return for subsequent research is a cause for some optimism about future recruitments.

We currently offer to travel to a subject's hometown for testing if he wishes to participate but does not wish to travel to one of the study sites. Fortunately, many of the study protocols are portable. For future waves of the VETSA projects, we expect that we will need to increase off-site testing as it may become difficult for some subjects to travel. Doing so will help to reduce attrition as well as bias regarding which subjects continue to participate in follow-up assessments. The VET Registry also regularly updates information from the United States National Death Index, so the investigators will have information about date and cause of death. The study plan is to continue to assess twins whose co-twins have died during the course of the study again so as to avoid bias toward healthier or longer-living twins in follow-up assessments.

Although the VETSA projects are genotyping only two specific genes at this time (APOE and GRK3), plans are underway for extensive genotyping in order to examine polymorphisms that are associated with cognitive and brain aging, health-related aging, aging-related personality and psychosocial factors, and longevity. Other potential avenues for research include studies of gene expression and other epigenetic processes (e.g., methylation) that capture individual differences in the biological effects of genes. One intriguing component of these latter approaches is that, unlike polymorphisms, they will vary even within monozygotic twin pairs.

We plan to utilize the VETSA blood samples for clinical chemistries, including variables such as fasting glucose and insulin concentration, lipids, triglycerides, hematocrit, thyroid stimulating hormone, and C-reactive protein. In future waves of the study we also plan to obtain blood samples in order to examine age-related change in these measures. In particular, we are interested in a subset of clinical chemistries as a way of assessing the metabolic syndrome or subsyndromal manifestations of the metabolic syndrome.

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