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Neuropsychological function in patients with Gerstmann-Sträussler-Scheinker disease from the Indiana Kindred (F198S)

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Abstract

Three patients with Gerstmann-Sträussler-Scheinker disease (GSS) caused by a serine-for-phenylalanine substitution at codon 198 of the prion protein gene (PRNP) were compared to 9 age- and education-matched non-mutation-carriers from the same large Indiana kindred (GSS–IK) on a comprehensive neuropsychological test battery. Clinically significant impairments in intelligence, secondary memory, attention and cognitive processing speed, executive ability, and manual motor skills were noted in 2 patients. The wide range and the severity of the cognitive deficits indicated generalized cerebral dysfunction consistent with global dementia. One patient, symptomatic for less than 1 year, had more selective deficits involving memory, motor skills, and verbal fluency, suggesting early subcortical involvement. (*JINS*, 1997, **3**, 169–178.)

Keywords: Gerstmann-Sträussler-Scheinker disease, Dementia, Neuropsychological testing, Genetic disorder, Cognition

INTRODUCTION

Gerstmann-Sträussler-Scheinker disease (GSS) is an autosomal dominant disorder characterized by ataxia, variable pyramidal signs, extrapyramidal dysfunction, and cognitive deficits. The pattern of symptoms is variable within and across kindreds (Ghetti et al., 1995). The neuropathological hallmark of GSS is accumulation of prion protein (PrP) as amyloid in the brain; however, the regional pattern of amyloid deposition can be variable. Likewise, the degree of spongiform degeneration and the presence of neurofibrillary tangles (NFT) can also vary across GSS kindreds (Ghetti et al., 1995). Several different mutations in the prion protein gene (PRNP) have been associated with GSS (Ghetti et al., 1995; Young et al., 1995). In addition, a polymorphism at codon 129 may influence age at onset and rapidity of progression in GSS (Dlouhy et al., 1992; Young et al., 1995).

Over the past 10 years, patients from a large Indiana kindred with GSS (GSS–IK) have been studied clinically, genetically, biochemically, and neuropathologically (Azzarelli et al., 1985; Farlow et al., 1989; Ghetti et al., 1995). These investigations have revealed that a serine-for-phenylalanine substitution at codon 198 of PRNP likely causes the disease (Dlouhy et al., 1992; Hsiao et al., 1992). The mutation is on an allele that has valine at codon 129 (Dlouhy et al., 1992). Symptoms begin from the late 30s to early 60s with earlier age of onset associated with valine homozygosity at codon 129 (Dlouhy et al., 1992). Progressive gait ataxia, memory loss, nystagmus, and hypometria are early clinical signs. Later in the course of the disease, there are signs of rigidity, bradykinesia, and dementia (Azzarelli et al., 1985; Farlow et al., 1989, 1991; Ghetti et al., 1992; Yee et al., 1992). Neuropathologically, PrP-amyloid deposits are found throughout the cerebrum and cerebellum (Ghetti et al., 1989). Neurofibrillary tangles are present in the neocortex, hippocampus, and subcortical nuclei (Ghetti et al., 1989, 1995). Descriptions of the cognitive changes in the GSS–IK and other GSS kindreds have been limited to bedside mental status examinations. Comprehensive neuropsychological examination of affected and unaffected subjects from the GSS–IK was performed to further investigate cognitive and motor function in light of the known neuropathology of GSS-IK. The limbic

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pathology would be expected to produce significant recent memory and new learning dysfunction. Cerebellar involvement, in addition to producing deficits in voluntary movement, may influence executive (frontal lobe) function. Comprehensive clinical characterization of GSS and other hereditary prion diseases can advance our understanding of genotype–phenotype correlations and factors that modify clinical presentation. We report here the cognitive and motor functioning of 3 affected members of the IK and an age- and education-matched comparison group of family members free of the codon-198 mutation.

METHODS

Research Participants

The pedigree of the GSS–IK spans eight generations and includes over 3,000 individuals. Five living members are currently affected with GSS, 89 are known to be at-risk (children of affected members), and 228 are half-at-risk (children of at-risk individuals). Forty-four at-risk and half-at-risk members of the IK completed neurological and neuropsychological evaluations as part of a longitudinal study. The diagnosis of GSS was made by a neurologist based on history and clinical findings. The criteria for diagnosis were (1) history of progressive neurodegenerative disease in a parent, (2) evidence of progressive ataxia and/or parkinsonism, (3) mild cognitive changes, and (4) symptoms not explained by other medical or neurological disease or by current or past medication or substance abuse (Farlow et al., 1991).

Three participants were diagnosed as being clinically affected with GSS (age at assessment ranged from 49 to 60 years, education ranged from 10 to 12 years, disease duration ranged from several months to 8 years). Forty-one subjects were found to be clinically unaffected. Allele-specific oligonucleotide hybridization was used to determine genotype at codon 198 and Mae II digestion was used to determine genotype at codon 129 (Dlouhy et al., 1992; Young et al., 1995). This genetic testing confirmed the clinical diagnosis in the 3 affected patients. All clinicians were kept blind to genotype among the unaffected participants. Fourteen of the 41 clinically unaffected participants carried the codon 198 mutation. Because of the possibility of presymptomatic cognitive dysfunction in these 14 individuals (Unverzagt et al., 1994, 1995), controls were selected from among the 27 subjects who were free of the mutation. Because age and education can affect performance on cognitive and motor tests, the project biostatistician (J.N.), who was unblinded to genotype, selected only controls who were older than age 40 years had less than 13 years of education. Nine women met these criteria and were selected to form the control group.

Neuropsychological Assessment

The neuropsychological test battery is listed in Table 1 with individual tests grouped according to the cognitive function

Table 1. Neuropsychological test battery

Domain of function	Test name
General cognition	Mini-Mental State Examination
Intellect	Wechsler Adult Intelligence Scale–Revised (WAIS–R)
	Barona IQ Formula
Memory	Temporal Orientation
	Wechsler Memory Scale–Revised (WMS–R)
	Logical Memory (I, II)
	Visual Reproduction (I, II)
	Selective Reminding Test
	7/24 Spatial Memory Test
Language	Boston Naming Test
Visuospatial	Judgment of Line Orientation
	Facial Recognition Test
Attention–Cognitive speed	WAIS–R Digit Span
	WAIS–R Arithmetic
	Symbol Digit Modalities Test
Executive	Trail Making Test Parts A & B
	Controlled Oral Word Association
	Wisconsin Card Sorting Test
Manual motor skills	Finger Tapping
	Grooved Pegboard
	Hand Dynamometer
Affect	Zung Self-Report Depression Scale

measured. All major domains of function were tested using standardized clinical instruments administered by trained technicians. The battery took approximately $3\frac{1}{2}$ hr to complete. All participants were tested at Indiana University Medical Center, with the exception of 2 GSS patients who were tested at home.

Analysis

For each GSS patient, narrative descriptions of the neurological and neuropsychological examinations are presented. In addition, transformed scores (standard scores for IQs, age-scaled scores for IQ subtests, and raw scores with percentile rank for all other tests) are presented in tabular form for each GSS patient (see Table 2). Transformed scores were derived from test manuals [Wechsler Adult Intelligence Scale–Revised (WAIS–R; Wechsler, 1981), Wechsler Memory Scale–Revised (WMS–R; Wechsler, 1987), Boston Naming Test (BNT; Goodglass & Kaplan, 1983), Judgment of Line Orientation (JLO; Benton et al., 1983), Facial Recognition Test (FRT; Benton et al., 1983), Symbol Digit Modalities Test (SDMT; Smith, 1973), Controlled Oral Word Association (COWA; Benton & Hamsher, 1976), and Wisconsin Card Sorting Test categories (WCST; Heaton, 1981)], published normative sources [Mini-Mental State Examination (MMSE; Ganguli et al., 1991), Trail Making Test (TMT; Heaton et al., 1991), WCST perseverative responses (Heaton et al., 1991), Finger Tapping (Heaton et al., 1991), Grooved Pegboard (Heaton et al., 1991), and Hand Dynamometer (Heaton et al., 1991)], or unpublished normative databases [Selective Reminding Test (SRT) and 7/24 Spatial Memory Test (7/24; Rao, personal communication, September 1991)].

T tests were used to determine group differences in demographic and neuropsychological performance. The clinical significance of the neuropsychological differences was determined by calculating the frequency of defective performance in each group. Defective performance was defined as a test score below the 5th percentile of normative reference values (sources listed above).

RESULTS

Patient VI-186

Background

Patient VI-186, homozygous for valine at codon 129, was a right-handed woman with a 10th-grade education and 20 years of work experience as a press operator in a television manufacturing plant. Medical and psychiatric history were unremarkable. First symptoms were ataxia and mild memory loss occurring at age 42 years. Neurological examinations at age 49 years revealed mild ataxia on finger-to-nose and heel-to-shin, and marked dysarthria, with high-pitched voice. The patient ambulated with a cane. Moderately severe Parkinsonism was present as evidenced by generalized bradykinesia and rigidity. Superior gaze and saccades on smooth pursuit were decreased. There was masked facies and some drooling, but no tremor.

Neuropsychological examination

Patient VI-186 was 49 years old when examined neuropsychologically. On questioning, the patient reported mild depression. She scored in the *moderately depressed* range on a self-report questionnaire (Zung Depression Scale; Zung, 1965). However, her cooperation and effort during the testing were very good and the results were believed to be reliable estimates of her functioning. Neuropsychological test results for Patient VI-186 are presented in Table 2. Summary IQ scores were in the *defective* to *borderline defective* range (Verbal IQ = 69, Performance IQ = 72, Full Scale IQ = 69) and clearly below estimated premorbid ability based on demographic data (Barona estimated Full Scale IQ = 94; see Barona et al., 1984). Marked intra-subtest scatter on Vocabulary and Comprehension strongly suggests that this patient had experienced significant acquired cognitive impairment (Mittenberg et al., 1989). Memory processes were also impaired as evidenced by mild temporal disorientation (errors on day of month and time of day) and very poor registration and delayed recall of the paragraph-length stories from the Logical Memory (LM) subtest of the WMS–R. Immediate recall of the geometric figures from the Visual Reproduction (VR) subtest of the WMS–R was very impaired, with loss of figure elements (failure to draw any part of the half-circle and triangle in Design 4) and perseveration (repetition of the "X" shape of Design 1 to reproductions of Designs 2, 3, and 4). Recognition testing of VR (Hanger et al., 1991) was at a chance level (1 of 5 correct). The patient's performance on tests of new learning suggested little benefit from repeated exposure. For example, on the SRT, a 12-item multitrial word list learning task, only 3 words were entered into long-term storage after 12 trials, 2 of 12 words were recalled after a 60-min delay interval, and recognition testing was very poor, at 15 of 24 words correctly identified. Nonverbal new learning as assessed by the 7/24, a task in which the subject is presented with a seven-dot array within a 24-square grid for five learning trials and a delayed recall trial, indicated poor initial registration of the pattern, with haphazard attempts at encoding the design over the five learning trials (number correct at each trail: 3, 3, 4, 5, and 3) and marginal delayed recall (3 of 7 correct). Evidence of the degradation of semantic knowledge suggested in the Verbal IQ was found in the patient's very poor performance on confrontation naming of objects (BNT). Visuoconstructional performance on the WAIS–R Block Design was very impaired. The problem appeared to be caused by more than psychomotor slowing, as she passed Item 1 in 19 s but was unable to correctly position any of the four blocks for Items 2 and 4. Marked impairment of visuospatial skills not requiring a motor response was noted on perception of line angles (JLO) and complex visual discrimination (FRT). Clear evidence of slowed cognition was revealed on the oral administration of

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Table 2. Neuropsychological performance of GSS patients

Variable	Patient					
	VI-186 Score (%)		VI-63 Score (%)		VI-98 Score (%)	
General cognition						
Mini-Mental State Exam [30]	21	(<5%)	22	(<5%)	25	(>10%)
Intellectual ability						
Est. Premorbid IQ [121]	94	(34%)	95	(37%)	107	(68%)
WAIS–R Verbal IQ [150]	69	(2%)	75	(5%)	90	(25%)
WAIS–R Performance IQ [150]	72	(3%)	73	(4%)	91	(27%)
WAIS–R Full Scale IQ [150]	69	(2%)	73	(4%)	90	(25%)
Memory						
WMS–R, LM immediate [50]	4	(1%)	8	(2%)	4	(1%)
WMS–R, LM delay [50]	1	(1%)	0	(1%)	1	(1%)
WMS–R, VR immediate [41]	8	(1%)	17	(4%)	21	(9%)
WMS–R, VR delay [41]	3	(1%)	6	(1%)	12	(9%)
SRT, long-term store [144]	21	(1%)	20	(1%)	59	(1%)
SRT, delay [12]	2	(1%)	0	(1%)	5	(1%)
SRT, recognition [24]	15	(2%)	14	(1%)	23	(53%)
7/24, sum recall [35]	18	(1%)	14	(1%)	28	(19%)
Language						
Boston Naming Test [60]	34	(1%)	50	(2%)	54	(25%)
Visuospatial						
WAIS–R Block Design, AS [19]	4	(2%)	4	(2%)	7	(16%)
Judgment Line Orient. [30]	20	(9%)	17	(1%)	24	(40%)
Facial Recognition [54]	32	(1%)	37	(3%)	46	(59%)
Attention–Cognitive speed						
WAIS–R Digit Span, AS [19]	3	(1%)	7	(16%)	7	(16%)
WAIS–R Arithmetic, AS [19]	4	(2%)	5	(5%)	7	(16%)
Symbol Digit, oral [110]	12	(1%)	27	(1%)	48	(45%)
Executive						
Controlled Oral Word	9	(1%)	18	(2%)	24	(6%)
Trail Making, Part A, sec	95	(1%)	100	(1%)	53	(12%)
Trail Making, Part B, sec	300	(1%)	300	(1%)	148	(14%)
WCST, no. categories [6]	3	(7%)	4	(21%)	1	(5%)
WCST, persev. resp. [128]	46	(4%)	18	(39%)	68	(1%)
Motor examination						
Finger Tapping, R, no. taps	16	(1%)	23	(1%)	16	(1%)
Finger Tapping, L, no. taps	13	(1%)	21	(1%)	21	(1%)
Grooved Pegboard, R, sec	416	(1%)	119	(3%)	255	(1%)
Grooved Pegboard, L, sec	300	(1%)	127	(1%)	137	(1%)
Hand Dynamometer, R, kg	15	(2%)	51	(63%)	30	(7%)
Hand Dynamometer, L, kg	13	(1%)	53	(83%)	35	(22%)

Scores are number correct except where indicated. Maximum possible score is presented in brackets next to each test. Raw scores, standard scores (for IQs), and percentile rank are presented for each test by patient. Estimated Premorbid IQ = Barona formula, WAIS–R = Wechsler Adult Intelligence Scale–Revised, WMS–R = Wechsler Memory Scale–Revised, LM = Logical Memory, VR = Visual Reproduction, SRT = Selective Reminding Test, 7/24 = 7/24 Visual Memory Test, Judgment Line Orient. = Judgment Line Orientation, AS = age scaled score, WCST = Wisconsin Card Sorting Test, persev. resp. = perseverative responses, R = right hand, L = left hand.

the SDMT, where the patient made only 12 correct responses in 90 s (an average score for a woman of her age and education is 54 ± 10). Sequential tracking was grossly slow on Trail Making Part A (1 min 35 s) while the shifting between sets required in Trail Making Part B resulted in even more impairment (9 circles were connected with 4 errors in 5 min). Phonemic fluency was also defective, with a total of only 4 words generated to the letters "C," "F," and "L" (COWA). Clear difficulty with conceptual reasoning was revealed on the WCST, as only 3 categories were obtained, although the

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number of perseverative responses was within the normal range. The motor examination was grossly abnormal, with severe bilateral deficits in manual speed (Finger Tapping) and strength (Hand Dynamometer), and very severe impairment in dexterity (Grooved Pegboard).

Patient VI-63

Background

Patient VI-63, heterozygous at codon 129, is a right-handed man with 11 years of education who was employed as a production worker in an automobile factory. Prior medical history was unremarkable. At age 46 years, he developed difficulty in operating complicated machinery at work. This progressed over 12 months until he was unable to do simple tasks at home. He was frequently unable to remember where he had placed items around the home. Neurological examination at age 49 years revealed mild ataxia in the lower extremities (unable to tandem walk and unsteady gait) and minimal ataxia in the upper extremities. Mild Parkinsonism was revealed in generally increased tone, with some cogwheeling in the upper extremities and masked facies. There was no tremor. Jerky saccades were seen on smooth pursuit.

Neuropsychological examination

Patient VI-63 was 49 years old when examined neuropsychologically. The patient was receptive to the test procedures, but would frequently digress from the task to talk of other matters. The patient was taking antidepressants but did not appear particularly dysphoric. Depression and anxiety were within normal limits on self-report questionnaires. The patient did have great difficulty mastering the movements involved in executing the Wisconsin Card Sorting Test, in that he constantly tried to place the stimulus cards on top of one of the four reference cards or off to the side. Cooperation and effort during the examination procedures were good. Neuropsychological test results for Patient VI-63 are presented in Table 2. The overall IQ scores were in the *borderline defective* range (Verbal IQ = 75, Performance IQ = 73, Full Scale IQ = 73) which is significantly below estimated premorbid ability based on demographic data (Barona estimated Full Scale IQ = 94). The subtest scores appeared to be fairly uniformly depressed. Performance on memory tests was quite poor. The patient was significantly disoriented to time (incorrect by 13 days on Day of Month, and by 1 day on Day of Week). On the WMS–R LM subtest, he recalled a total of 8 units of information (4 from each story) out of a total possible of 50, immediately after presentation. He was unable to recall any parts of either story after a delay of 30 min. For WMS–R VR, the patient tended to produce incomplete and somewhat dyspraxic figures immediately after presentation, and recalled only 1 of 4 figures after 30 min. New learning skills were also severely impaired. Only 2 words were entered into long-term storage after 12 trials on the SRT, no words were recalled at 60 min delay, and only 15 of 24 were correctly recognized. Spatial design learning on the 7/24 was similarly impoverished, with essentially no learning over trials (3, 3, 1, 3, and 4 correct placements on the five trials) and no items recalled at delay. Mild dysnomia was evidenced on the Boston Naming Test, with errors primarily semantic. Visuoconstructional ability was markedly impaired. On the WAIS–R Block Design, the patient passed the first item in 15 s and then went on to consecutive failure on the next three items. Errors were notable for two rotations and, on testing the limits with Item 4 (the chevron) a breakdown in the square configuration, with three blocks placed in a line horizontally, the fourth block centered below the others. Perception of angles (JLO) and complex visual discrimination (FRT) were also defective. Significant cognitive slowing was present on oral Symbol Digits. Deficits in sequential tracking were noted in both parts of the Trail Making Test in a manner similar to Patient VI-186. Verbal fluency was defective on the COWA. Despite the patient's inability to master the movements of the WCST, he was able to achieve 4 categories and was not overly perseverative, although he did have 3 failures to maintain set. The motor examination was grossly abnormal, with bilateral impairments in manual speed (Finger Tapping) and dexterity (Grooved Pegboard) but normal strength (Hand Dynamometer).

Patient VI-98

Background

Patient VI-98, heterozygous at codon 129, is a right-handed man with 12 years of education who worked as a grain farmer. Prior medical and psychiatric history was unremarkable. He first noted symptoms at age 59 years, consisting of difficulties with speed, balance, and coordination. There was some memory loss as he would forget to do tasks around the house. Neurological examination at age 60 years revealed mild Parkinsonism (mild generalized bradykinesia, rigidity in all extremities, masked facies, and a shuffling gait). There was no tremor. The patient's voice was mildly nasal and high-pitched. Minimal ataxia was seen in his gait and on finger-to-nose and heel-to-shin maneuvers.

Neuropsychological examination

Patient VI-98 was 60 years old when examined neuropsychologically. The patient reported increased anxiety throughout the preceding year but was taking no medications. Effort was good, and he was generally cooperative with the testing procedure; however, toward the end of the session he became frustrated and ultimately refused to complete some of the tests. Neuropsychological test results for Patient VI-98 are presented in Table 2. Overall IQ scores were within the *average* range (Verbal IQ = 90, Performance IQ = 91, Full Scale IQ = 90), though perhaps slightly below estimated premorbid ability based on demographic data. Despite the equality in verbal and nonverbal IQ, the freedom from distractibility index was lower than the verbal comprehension

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and perceptual organization quotients. There was no intrasubtest scatter of note on the WAIS–R. Temporal orientation was normal; however, recall for paragraph-length stories was very impaired, with minimal information recalled immediately after presentation or after a 30-min delay. Visual memory was better preserved, as it rated in the *low average* range. Most of what was initially registered was recalled at delay on the WMS–R VR. New learning on the SRT was impaired, but less so in this patient than in the others. He was able to put 7 of the 12 words into long-term storage by the 12th trial, he recalled 5 of 12 words at 60-min delay, and had normal recognition. Spatial design learning on the 7/24 was normal. There was no dysnomia on the BNT. Visuoconstructional skill on the WAIS–R Block Design rated as *low average* overall, with one design rotated. Other tests of visuospatial ability were normal (JLO, FRT). Speed of processing was normal on the SDMT while sequential tracking on the Trail Making Test was *low average*. Verbal fluency was *borderline defective* on COWA. The patient completed only one category, and was highly perseverative on the WCST before refusing to complete the test three-quarters of the way through (he quit on the 96th of a possible 128 cards, and his scores on this test were prorated). Bilateral manual motor deficits were apparent in speed and dexterity, while grip strength was normal.

GSS *Versus* Normal Controls

Demographic and affective comparisons

Demographic matching was successful, as there were no significant group mean differences in age [53.0 ± 6.1 years for the GSS patients, 51.1 ± 12.1 years for the controls, $t(10) = 0.27$, $p > .10$] or education [11.0 ±1.0 years for patients, 10.7 ± 1.3 years for controls, $t(10) = 0.39$, $p > .10$]. Additionally, the level of self-reported depression was not significantly different as measured by the Zung scale [Zung, 1965; raw score = 43.5 for patients. *vs*. 40.6 for controls, $t(8) = 0.56$, $p > .10$]. Data were missing for 1 control and 1 patient.

Cognitive and motor comparisons

Not unexpectedly, global cognitive function was different on the MMSE, with GSS patients scoring significantly lower ($M = 22.7 \pm 2.1$) than the normal controls [$M = 28.0 \pm 1.5$, $t(9) = 4.75$, $p = .001$]. Data were missing for 1 control. Table 3 shows neuropsychological performance of the GSS and normal controls groups. As can be seen, the patients have a fairly broad range of cognitive and motor dysfunction. Despite equivalence in estimated premorbid IQ, the GSS group had currently measured IQ in the *borderline defective* range, indicating a mean decline of approximately 20 IQ points. The GSS patients had deficits relative to normal controls in secondary memory, including immediate and delayed recall of prose (WMS–R LM) and geometric figures (WMS–R VR) and word list learning and delayed recall (SRT). The GSS patients showed deficits in other domains including attention (WAIS–R Digit Span and Arithmetic), cognitive processing speed (Symbol Digit), verbal fluency (COWA), and visuomotor skills (WAIS–R Block Design and Trail Making, Parts A and B). Simple manual motor speed (Finger Tapping) and dexterity (Grooved Pegboard) were also significantly worse in the GSS group. Interestingly, primary memory as measured by forward digit span was not significantly different between groups. No differences were noted in spatial design learning (7/24), confrontation naming (BNT), novel problem solving (WCST), or complex visual discriminations (JLO and FRT), although in each case the mean score from the GSS group was lower than that of the normal controls.

Trial-by-trial analysis of long-term storage on the SRT in GSS and normal control subjects revealed significant differences beginning at Trial 2 that was maintained through all subsequent trials (all ps $< .01$). As can be seen in Figure 1, the controls showed very rapid acquisition on Trials 2, 3, 4, and 5, and then appear to reach an asymptote at Trial 8. On average, they lost approximately 2 words from Trial 12 to delay. On the other hand, the GSS subjects show no burst of learning on the early trials, and they appear to reach asymptote earlier, around Trial 6. Like the controls, the GSS patients lost approximately 2 words between the last learning trial and delayed recall. Performance of both groups improves at recognition, though the baselines are clearly different. We also examined the rate of forgetting on the WMS–R by dividing delayed recall by immediate recall. GSS patients had significantly higher rates of forgetting on both Logical Memory ($M = 17\%$ *vs*. 80% in GSS and controls respectively, $t(10) = 5.67$, $p = .002$] and Visual Reproduction [$M = 43\%$ *vs*. 80% in GSS and controls respectively, $t(10) = 2.44$, $p = .034$].

Clinical significance

The univariate comparisons indicate statistically significant group differences on many of the neuropsychological tests. It is also of interest to determine whether these statistical differences are clinically important. To this end, Table 3 shows the frequency of defective test performance, defined as a score below the 5th percentile of normative reference samples, in each group. As can be seen, the affected patients had high rates of clinically significant impairment in memory, motor, and executive domains. In contrast, fairly low rates of test failure were noted in the normal control group with no more than 1 or 2 participants below the cutoff except on BNT and WCST. The apparent difficulty for the controls on these two tests is probably related to their low level of education relative to the normal reference samples, rather than occult brain damage.

DISCUSSION

Three patients from the GSS-IK were examined neuropsychologically from 3 months to 7 years after onset of symp-

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Table 3. Neuropsychological test performance by group

	Control ($N = 9$)			GSS ($N = 3$)		
Measure	*M*	*SD*	Fail[a]	*M*	*SD*	Fail
Intellect						
Est. Premorbid IQ	95.9	(4.7)	0/9	98.6	(7.0)	0/3
WAIS–R Verbal IQ	94.2	(5.7)	0/9	78.0	(10.8)**	1/3
WAIS–R Performance IQ	94.7	(6.0)	0/9	78.7	(10.7)**	2/3
IQ Decline	−2.0	(6.3)	0/9	−21.2	(4.2)***	2/3
Primary memory						
Digits Forward	6.7	(1.1)	0/9	5.3	(1.1)	1/3
Secondary memory						
WMS–R, LM immediate	21.1	(3.0)	0/9	5.3	(2.3)***	3/3
WMS–R, LM delay	16.9	(4.3)	0/9	0.7	(0.6)***	3/3
WMS–R, VR immediate	30.4	(5.2)	0/9	15.3	(6.7)**	2/3
WMS–R, VR delay	24.9	(9.0)	1/9	7.0	(4.6)**	2/3
SRT, long-term store	110.5	(14.9)	1/9	33.3	(22.2)***	3/3
SRT, delay	9.7	(2.4)	1/9	2.3	(2.5)**	3/3
SRT, recognition	23.5	(1.3)	0/9	17.3	(4.9)**	2/3
7/24, sum recall	24.9	(10.7)	3/9	20.0	(7.2)	2/3
Language						
Boston Naming Test	50.9	(5.8)	4/9	46.0	(10.6)	2/3
Visuospatial						
WAIS–R Block Design (AS)	8.3	(2.3)	1/9	5.0	(1.7)*	2/3
Judgment Line Orient.	20.4	(5.8)	2/9	19.0	(3.6)	1/3
Facial Recognition	42.1	(5.9)	1/9	38.0	(6.6)	2/3
Attention/Cognitive speed						
WAIS–R Digit Span (AS)	9.9	(1.6)	0/9	5.7	(2.3)**	1/3
WAIS–R Arithmetic (AS)	9.1	(1.8)	0/9	5.3	(1.5)**	1/3
Symbol Digit, oral	50.1	(7.7)	1/9	29.0	(18.1)*	2/3
Executive						
Trail Making, Part A (T)	52.0	(6.9)	0/9	26.7	(9.9)***	2/3
Trail Making, Part B (T)	47.2	(9.0)	1/9	25.0	(12.3)**	2/3
Cont. Oral Word Assoc.	35.9	(9.9)	0/9	11.7	(7.1)**	2/3
WCST, no. categories	3.9	(2.1)	5/9	2.7	(1.5)	2/3
WCST, persev. resp.	23.8	(15.6)	1/9	44.0	(25.1)	2/3
Motor						
Finger Tapping, R (T)	50.4	(11.9)	0/9	15.3	(4.2)***	3/3
Grooved Pegboard, R (T)	44.8	(13.0)	2/9	16.7	(14.0)**	3/3
Grip Strength, R (T)	48.2	(11.4)	2/9	39.0	(12.5)	1/3

Est. Premorbid IQ = Barona Equation, IQ decline = (current Full Scale IQ) - (estimated premorbid IQ), WAIS–R = Wechsler Adult Intelligence Scale–Revised, WMS–R = Wechsler Memory Scale–Revised, LM = Wechsler Memory Scale–Revised (WMS–R), LM = Logical Memory, VR = Visual Reproduction, SRT = Selective Reminding Test, AS = age scaled score, Judgment Line Orient. = Judgment of Line Orientation, persev. resp. = perseverative responses, T = T-score (Heaton et al., 1991), R = right hand. [a] = number of subjects failing a test over number given the test with failure defined as score below the 5th percentile of normative values. *$p < .05$, **$p < .01$, *** $p < .001$.

toms and compared to normal controls from the same kindred, matched for age and education. The largest group differences were noted on tests of secondary memory and manual motor skills. Significant, though less pronounced, dysfunction was present in Verbal and Performance IQ, phonemic fluency, attention and cognitive processing speed, and visuomotor tasks. The statistical differences were also clinically important as reflected in the frequency of test failure in each of these areas (defined as a score below the 5th percentile of normative reference values).

There was correspondence between disease duration and cognitive dysfunction. Specifically, the GSS patient with the longest disease duration (Patient VI-186, affected 7 years at the time of neuropsychological testing) had significant deficits in all aspects of cognition consistent with global dementia. The patient who had been symptomatic for 3 years (Patient VI-63) had a similar but less severe pattern of impairment also consistent with global dementia. On the other hand, the 3rd patient, symptomatic for less than 1 year (Patient VI-98), had more selective impairments in memory,

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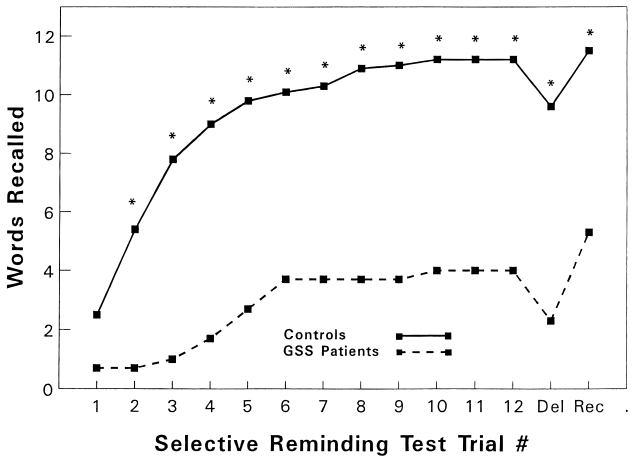

Fig. 1. Long-term storage in normal controls and GSS patients.

executive, and manual motor skills suggestive of subcortical dysfunction. The patient who was homozygous at codon 129 for valine had the youngest age of onset, but did have a fairly protracted course.

Ataxia is a consistent early feature of GSS–IK (Farlow et al., 1989) so it is not surprising that the GSS patients scored very significantly below the controls on tests of finger tapping speed and manual dexterity. The finger tapping test puts a premium on rapidly alternating movement, while the grooved pegboard requires speed, fine dexterity, and visuomotor coordination. Impairment on these tests would be consistent with cerebellar dysfunction. This interpretation is supported by MRI (Farlow et al., 1990), eye movement (Yee et al., 1992), and autopsy studies (Azzarelli et al., 1985; Ghetti et al., 1989; Hsiao & Prusiner, 1990; Farlow et al., 1991) in this kindred showing the cerebellum as a major locus of involvement.

The largest group differences were found in the memory domain. All GSS patients showed severe secondary memory impairment with clinically important deficits in recall of stories, geometric figures, and word lists. While depression was present in 1 and possibly another of these GSS patients, the level of cooperation and effort put forth during the testing was good; therefore, it is unlikely that motivational deficits associated with depression significantly affected these test results. Primary memory capacity, as measured by forward digit span, was comparable between groups, suggesting that this is not the cause of the memory problem. The GSS group was significantly worse than controls in the area of attention and cognitive processing speed, and it might be argued that some of their secondary memory deficit was due to inability to integrate information fast enough to allow registration. Data from the early-stage patient argues against this interpretation, since he scored in the broadly normal range on Digit Span, Arithmetic, and Symbol Digit, and yet still evidenced a severe secondary memory deficit. In addition, the learning curve for the GSS patients is not just depressed but also shortened in the trial-by-trial analysis of Selective Reminding Test recall; not a phenomenon predicted by attentional or speed-of-processing defects alone. Third, rate of forgetting of prose and geometric figures on the WMS–R was greater in GSS than control participants, suggesting a consolidation defect. Lastly, recognition on the Selective Reminding Test was also impaired, arguing against a simple retrieval deficit hypothesis. Thus, it would appear that these GSS patients suffer from dysfunction of processes intrinsic to memory itself.

Dramatic memory loss of the kind documented in these GSS patients is similar to that reported in Alzheimer's disease (AD). Rapid rate of forgetting is characteristic of AD, as it differentiates AD, from normal elderly (Butters et al., 1988; Welsh et al., 1991) and other dementing conditions including Huntington's disease (Butters et al., 1988; Delis et al., 1991) and Parkinson's disease (Stern et al., 1993); however, there is some controversy in this area (Kopelman, 1985; Becker et al., 1987; Robinson-Whelen & Storandt, 1992). The characteristic memory impairment of AD is believed to be related to neuronal cell loss and NFT in the perforant pathway of the entorhinal cortex as well as CA1 and subiculum of the hippocampus itself (Hyman et al., 1984, 1986). Pathological studies of GSS–IK using immunohistochemistry reveal lesioning in some of the same areas. For example, PrP-amyloid plaques and NFT are found in CA1 and subiculum (Ghetti et al., 1995) and in parahippocampal cortices (Ghetti et al., 1989). The commonality in the regional distribution of pathology in the mesial temporal lobes of AD and GSS–IK may be the basis for similarities in secondary memory dysfunction in the two diseases. Direct comparison of AD and GSS–IK patients on tests of memory would be informative in this regard.

The lexical fluency deficit, like the memory impairment, was present in all the GSS–IK patients including the patient with shortest disease duration, who was not globally demented. Fluency deficits have been reported in many other diseases with subcortical pathology, e.g., multiple sclerosis (Rao et al., 1991), Huntington's disease (Butters et al., 1987), Parkinson's disease (Litvan et al., 1991; Stern et al., 1993), progressive supranuclear palsy (Milberg & Albert, 1989), and cerebellar atrophy (Appollonio et al., 1993). In Patient VI-98, the fluency deficit occurred in conjunction with impairment in conceptual reasoning (WCST), suggesting a possible dysexecutive syndrome. Since autopsy of an asymptomatic codon 198 serine carrier indicates that the cerebellum is an early site of pathology in GSS–IK (Farlow et al., 1991; Ghetti et al., 1992), it may be that the cerebellar dysfunction is contributing to the cognitive as well as the motor deficits of Patient VI-98. Some have suggested that a cerebellar–thalamic–frontal network may bring the equivalent of mental dexterity to cognitive operations (Leiner et al., 1986). Disruption at any point in this system could lead to "dysexecutive" behavior (Grafman et al., 1992). In fact, recent evidence suggests that the cerebellum contributes to executive abilities such as verbal fluency (Appollonio et al., 1993), cognitive planning (Grafman et al., 1992), and initiation–perseveration (Appollonio et al., 1993). Mem-

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ory impairment in cerebellar patients is correlated with executive dysfunction (Appollonio et al., 1993). Our sample size was too small to pursue correlations between memory and executive performance, although this would be informative. It may well be that some of the cognitive deficits seen in GSS–IK are related to cerebellar involvement. Neuropsychological testing of asymptomatic mutation-carriers from the IK could provide a means of measuring the effects of slowly progressive cerebellar disease on cognition.

Interpretation of the findings for Performance IQ, Block Design, and Trail Making are complicated by the presence of significant motor dysfunction in the GSS group, which could adversely impact performance on these tests. The Judgment of Line Orientation and Facial Recognition tests measure visuoperceptual ability but, unlike Block Design, are not timed and have minimal motor demands. Patients VI-186 and VI-63 scored in the impaired range on these tests, suggesting the possibility of a visuoperceptual deficit in GSS–IK. Some Parkinson's disease patients appear to have specific impairment on the Facial Recognition Test (Levin et al., 1991) suggesting a role for the nigrostriatal system in this function. The GSS-IK is characterized by significant nigrostriatal involvement clinically (rigidity and bradykinesia on neurological examination; Farlow et al., 1989), on imaging (decreased signal in the basal ganglia and substantia nigra; Farlow et al., 1990), and on pathological examination (nerve cell loss, iron deposition, PrP amyloid deposits in the substantia nigra, caudate, and putamen; Ghetti et al., 1989, 1995). Thus, the visuoperceptual deficit may be related to nigrostriatal involvement in these affected patients.

In summary, the GSS–IK patients with disease duration of 3 years or more had deficits in secondary memory, motor skills, intelligence, visuoperceptual skill, attention, speed of processing, and executive ability. This broad array of cognitive deficits is consistent with global dementia, and suggested generalized brain dysfunction. A more selective pattern of deficits involving disturbance of secondary memory, executive dysfunction, and manual motor impairment characterized the patient with briefest disease duration. This restricted pattern of impairment could be consistent with subcortical and possibly cerebellar disease. Our analyses suggested that memory impairment in GSS–IK is not simply a function of limited primary memory capacity, poor attention, slowed information processing, or depression. Instead it appears to be related to deficits intrinsic to memory, including encoding and consolidation processes. Further study of this family may help to elucidate the role of the cerebellum in cognition, while comparison to other diseases (AD, PD, and focal cerebellar disease) and functional neuroimaging would be helpful in localizing the deficits and clarifying the role of the cerebellum in cognitive functioning.

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