

CASE STUDY

Neural correlates of adaptive working memory training in a glycogen storage disease type-IV patient

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Abstract

Glycogen storage disease type-IV has varied clinical presentations and subtypes. We evaluated a 38-year-old man with memory complaints, common symptoms in adult polyglucosan body disease subtype, and investigated cognitive and functional MRI changes associated with two 25-sessions of adaptive working memory training. He showed improved trained and nontrained working memory up to 6-months after the training sessions. On functional MRI, he showed increased cortical activation 1–3 months after training, but both increased and decreased activation 6-months later. Working memory training appears to be beneficial to patients with adult polyglucosan body disease, although continued training may be required to maintain improvements.

Introduction

Glycogen storage disease type IV (GSD-IV) is a rare autosomal recessive disease caused by *GBE1* mutations resulting in deficiency or lack of functional glycogen branching enzyme, and accumulation of abnormal glycogen (i.e., polyglucosan bodies).^{1,2} Polyglucosan bodies accumulate in many organs and cause diverse clinical manifestations³ with varying ages of onset.^{2,3} The childhood onset form presents with hepatomegaly, liver dysfunction, myopathy, and hypotonia, which may be progressive.^{2–4} The adult polyglucosan body disease (APBD) subtype generally appears in the fifth or sixth decade, with peripheral neuropathy, gait abnormalities, neurogenic bladder, and cognitive impairment; progression of symptoms often lead to functional deterioration and premature death.⁵ Memory impairments and dementia are present in approximately 50% of APBD patients.^{5–7}

We present a patient with a rare clinical variant, who had both the childhood nonprogressive hepatic subtype and later developed APBD. We aimed to elucidate his

cognitive deficit profile and to investigate whether working memory (WM) training might improve his cognitive function on WM tasks and functional MRI (fMRI).

Materials and Methods

The patient was a 38-year-old man, with a diagnosis of GSD-IV. He developed hepatosplenomegaly at age 2 and his liver biopsy showed cirrhosis with periodic-acid Schiff-positive staining, indicating polyglucosan body accumulation, with minimal activity on an indirect enzyme assay of skin fibroblasts. His symptoms improved; hence, he most likely had the nonprogressive hepatic subtype.

He presented with signs of APBD in his 30s, earlier than the typical course.⁵ Confirmatory genetic testing corroborated the abnormal enzymatic childhood tests. He inherited two mutations in *GBE1*: c.986A>C and c.2003delA. His symptoms included urinary hesitancy, mild lower limb weakness, gait disturbance, insomnia, fatigue, mild cognitive difficulties, and mood swings. He

participated in a clinical trial of triheptanoin for treatment of APBD symptoms, but stopped due to gastrointestinal side effects.

Additionally, he suffered a mild closed head injury, causing some transient seizure-like episodes, initially diagnosed as complex partial seizures with one episode of generalization. He was treated with levetiracetam, which he self-discontinued and had no seizure reoccurrence. He also reported worsening short-term memory problems and decreased concentration.

He was 70-inches tall, 180-lbs, had normal vital signs, physical examination and Mini-Mental State examination (MMSE, 30/30). Cranial nerve examination showed some horizontal nystagmus bilaterally at end gaze. Motor examination showed normal tone and strength, but increased rebound in his upper extremities bilaterally, with mild dysidiadochokinesia on his left side, and mild right-sided bradykinesia. He had some difficulty walking on his heels and instability with tandem gait. Deep tendon reflexes were symmetrical and normal.

Over 6 months, he completed computerized adaptive WM trainings, with Cogmed RM (www.cogmed.com), 25 sessions per training period \times 2 periods. Each session had eight verbal and visuospatial WM tasks; the difficulty level adjusted automatically and continuously based on daily task performance. He was evaluated before training (Week0), 1-month after first training (Week14), and 1-month (Week30) and 6-months (Week50) after his second training.

Cognition was evaluated with Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV)⁸ and tests assessing seven cognitive domains (Table 1).^{9,10} Additionally, at each visit, near-transfer effects were assessed with Digit Span and Letter-Number Sequencing tasks (WAIS-IV),⁸ and far-transfer tasks with Logical Memory (Story A), Spatial Span, and Word List (Wechsler Memory Scale-Third Edition).¹¹

The MR scans were performed using a protocol approved by our institutional ethics committee and after informed consent was obtained; other measures were not considered research and exempt from ethical review [45 CFR 46. 102(d)]. All scans were performed on a Siemens 3-Tesla Trio scanner. Structural MRI included a T1-weighted 3-D magnetization-prepared rapid gradient-echo sequence (TR/TE/TI 2200/4.47/1000 msec; $256 \times 256 \times 160$ matrix) and T2-weighted axial fluid attenuated inversion-recovery sequence (TR/TE 9100/84 msec; $204 \times 256 \times 44$ matrix). Blood-oxygen-level-dependent (BOLD)-fMRI was performed using single-shot gradient-echo EPI time series (TE/TR 3000/30 msec, 3 mm slices, typically 46 axial slices, 3 mm in-plane resolution, 124 time points), with a 1-back WM task (e.g., B-C-D-D; second D as target) with block design (alternating 30 sec

Table 1. Baseline neuropsychological assessment.

Cognitive domain subtests	Raw Score	Z-score*
Fluency		-0.67
Verbal fluency test: letter fluency (number of correct responses) ¹⁵	29	-0.79
Design fluency test (number of correct designs) ¹⁵	30	-0.55
Executive function		-0.65
Color-word interference: inhibition and inhibition/switching (seconds to complete) ¹⁵	47/67	-0.86
Trail making test: number-letter switching (seconds to complete) ¹⁵	67	-0.43
Speed of information processing		-1.58
Symbol digit modalities test ¹⁶	36	-2.26
Color-word interference: color naming (seconds to complete) ¹⁵	37	-2.15
Trail making test: number sequencing (seconds to complete) ¹⁵	24	-0.32
Attention/working memory		-0.74
Digit span (number of correct responses) ¹⁴	26	-1.09
Letter-number sequencing (number of correct responses) ¹⁴	19	-0.82
Arithmetic (number of correct responses) ¹⁴	14	-0.26
Paced auditory serial addition test (number of correct responses) ¹⁶	35	-0.78
Learning		-1.31
Rey auditory verbal learning test: 5th trial (number of words recalled) ¹⁶	12	-0.34
Rey-Osterreith Complex Figure: Immediate Recall (number of items correctly reproduced) ¹⁶	8	-2.29
Memory		-1.68
Rey auditory verbal learning test: delayed recall (number of words recalled) ¹⁶	6	-1.31
Rey-osterreith complex figure: delayed recall (number of items correctly reproduced) ¹⁶	9.5	-2.05
Fine motor function		-2.32
Grooved pegboard: dominant hand (seconds to complete) ¹⁶	90	-2.21
Grooved pegboard: nondominant hand (seconds to complete) ¹⁶	112	-2.43

*Z-scores are normalized to healthy individuals from published norms (adjusted by age and education).

control and 30 sec activation periods, including 3 sec instruction; total 6 min). fMRI time series were analyzed using SPM8 software (Wellcome Department of Cognitive Neurology, London, UK). The MNI152 atlas was used for spatial normalization of fMRI scans, using 8 mm isotropic smoothing. Brain activation maps (1-back task) and changes in BOLD signals at the various time points relative to the baseline visit were calculated with a fixed effects model. Statistical analyses thresholds were set at a

cluster-wise extent of >100 contiguous voxels with $P < 0.05$ false discovery rate corrected peak-level.

Results

At baseline, the patient had normal intelligence quotient (IQ, 92, 95% CI [88, 96]) and scored within normal limits for Attention/WM (-0.74 SD), Fluency (-0.67 SD) and Executive Function (-0.65 SD) domains, but below normal performance in Information Processing Speed (-1.58 SD), Learning (-1.31 SD), Memory (-1.68 SD), and Fine Motor Function (-2.32 SD) (Table 1).

His index of improvement on Cogmed RM was 57 for the first, and 39 for the second training period (normal range: 18–42).¹² The participant performed better on all

tasks at the final visit than at baseline, except for Word List Immediate Recall (Fig. 1A–D). Greatest gains were at Week30 for Auditory WM far-transfer tasks: Logical Memory (remembering a story) Immediate and Delayed, and Word List Delayed. However, scores were not maintained at Week50. Additional improvements were observed after the second training period on several auditory WM tasks (Fig. 1A–B). Improvements were less pronounced, but maintained across visits for near-transfer tasks at Week50: Digit Span, Letter-Number Sequencing, Spatial Span (Fig. 1C–D).

The structural MRI (Fig. 2A) showed confluent and diffuse white matter hyperintensities, mostly in the frontal and parietal regions bilaterally. Brain atrophy was evident with moderate to severe thinning of the corpus callosum,

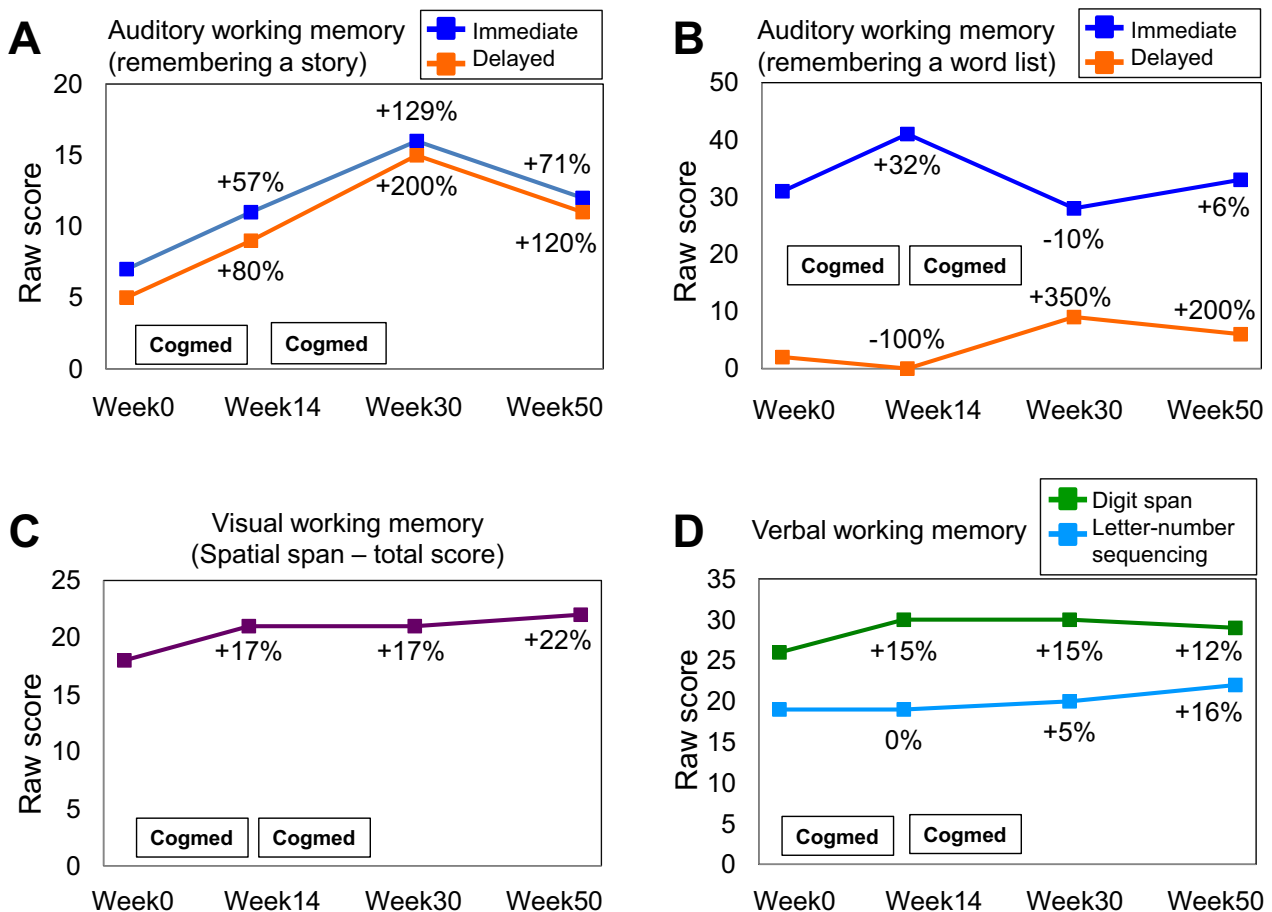


Figure 1. Neuropsychological test scores before and after completing two training periods of a working memory training program. Percent changes of scores were calculated to determine differences between baseline and post training scores. (A–B) Changes in performance on Auditory Working Memory tasks at each time point (Week14, Week30, Week50) relative to the baseline (Week0) for the immediate and delayed recall (Panel A: Logical Memory; Panel B: Word List; Wechsler Memory Scale-Third Edition). (C) Total scores on a visual working memory task (Spatial Span; Wechsler Memory Scale-Third Edition) at baseline and at follow-up visits. (D) Scores on verbal working memory tasks (Digit Span) and Letter-Number Sequencing total scores; Wechsler Adult Intelligence Scale-Fourth Edition) at baseline and at follow-up visits. Abbreviations: Week0: before training; Week14: 1-month after first training; Week30: 1-month after second training; Week50: 6-months after second training.

and moderately enlarged anterior and posterior horns of the lateral ventricles. These structural brain abnormalities did not change over time.

Similar brain regions were activated on fMRI during the 1-back task, with 100% performance accuracy, at all visits (Fig. 2B). However, the spatial extent of activation increased at 7 and 11 weeks postadaptive WM training. Conversely, 6-months after both training sessions (Week50), activation in the dorsolateral prefrontal and posterior parietal cortices became more localized, suggesting greater neural efficiency. BOLD signals at Week14 were increased compared to baseline in frontoparietal regions including the right superior frontal, middle frontal, and postcentral gyri (Fig. 2C; $P < 0.0001$;

Week14 > baseline contrast). Greater activation was also observed at Week30 in the left fusiform gyrus ($P < 0.0001$), and at Week50 in the left fusiform, right middle frontal and the left inferior frontal gyri ($P < 0.001$). However, activation tended to decrease relative to baseline in the left cuneus ($P = 0.07$) and left precentral gyrus ($P = 0.07$) at Week50.

Discussion

Approximately 50% of APBD patients exhibit memory problems or dementia,⁵⁻⁷ but few studies investigated cognitive changes over time.¹³ Our patient had an earlier age of onset for neurological signs of APBD,⁵ which

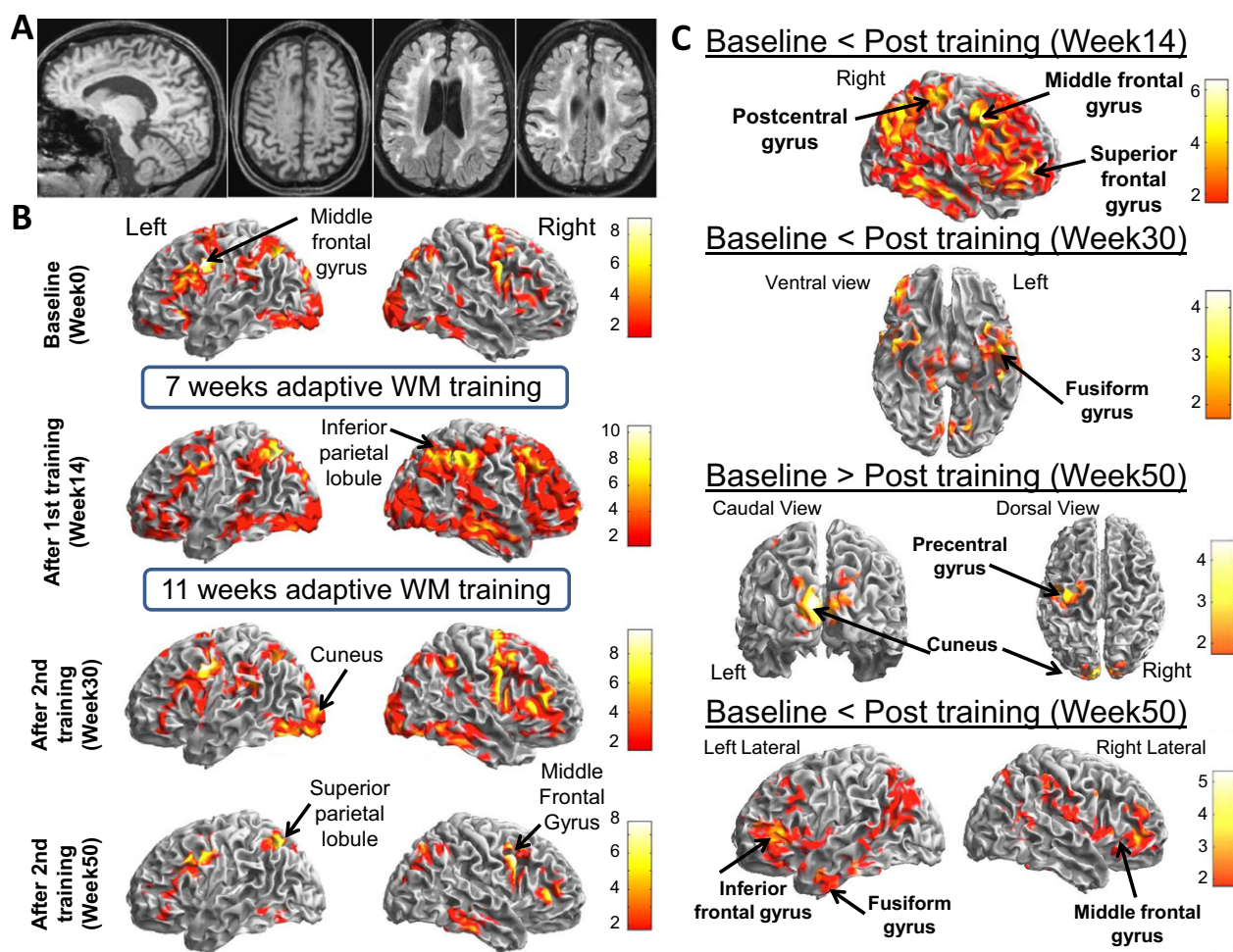


Figure 2. Brain Structure Abnormalities and Brain Activation Changes at Baseline and After Working Memory Training. (A) Structural MRI showing significant atrophy (left two panels of T1-weighted MPRAGE sequence) and white matter abnormalities (right two panels of T2-weighted FLAIR images). (B) Brain surface activation during the 1-back visual working memory task at baseline and at three follow-up visits. (C) Brain regions showing significantly greater activation at each of the follow-up visits relative to the baseline scans. Brain activation showed trends for increases at Week50. 1-back task performance accuracy was 100% at each visit. Abbreviations: Week0: before training; Week14: 1-month after first training period; Week30: 1-month after second training period; Week50: 6-months after second training. Color bars indicate T-scores.

might have resulted from his childhood manifestation of GSD-IV with residual brain injury and lesser cognitive reserve. Baseline neuropsychological results confirmed the patient's subjectively reported deficits (processing speed, motor function and memory). Prior studies of APBD patients typically reported learning and motor function deficits, as well as memory problems, but not processing speed.^{6,7,13} Comprehensive testing in APBD patients should be considered since a simple clinical evaluation (e.g., Folstein MMSE) failed to identify cognitive impairment in our patient and in a prior case.¹³

One to 6-months after training, our patient's cognitive scores were at or above baseline levels for almost all WM tasks, indicating maintained improvements from the WM training. He showed cumulative improvement after the second training, even on far-transfer auditory memory tasks, whereas most WM studies evaluated effects of a single training period. Importantly, tasks with the most severe initial deficits showed the greatest gains, although some of the improvement could be practice effects. Previous studies in healthy adults also showed increases in WM capacity with WM training.^{14–16}

The abnormal cerebral atrophy and extensive white matter lesions on MRI are typical of APBD patients.^{5,17} The increased cortical activation on fMRI after the first training period suggest recruitment of additional neural networks, but the activated brain regions became more localized afterward. Re-organization of neural networks after WM training was previously reported with increased activation of prefrontal and parietal regions,¹⁴ but decreased activation in other brain regions.^{15,16}

In particular, the left middle frontal gyrus appears to be important for WM training, and increased activity in this region was correlated with better WM performance in healthy controls.¹⁴ However, our patient had increased activation in the right middle frontal gyrus, which might be due to the greater white matter injury in his left frontal region.

Our results should be interpreted with some limitations. First, these findings are based on a single patient and may not be generalizable to other APBD patients. Second, these results may not represent WM training efficacy, but may be due to expectancy effects¹⁸ and non-specific training factors (e.g., increased computer use). Although a recent meta-analysis of Cogmed[®] studies concluded it was effective,¹⁹ another meta-analysis questioned the clinical utility of WM trainings including Cogmed.²⁰

In conclusion, improved neuropsychological performance across visits indicated WM training was beneficial to this APBD patient. These improvements may be due to increased neural efficiency and recruitment of additional neural resources as shown on the fMRI. However, multiple WM training sessions may be needed to maintain the

improved performance in APBD patients or others with white matter disease.

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Author Contributions

L.C. planned and supervised all aspects of the case study, evaluated the patient clinically, reviewed all data for accuracy and co-wrote the paper. T.E. supervised the acquisition and processing of the functional MRI studies. G.L. designed, supervised and interpreted the cognitive assessments and Cogmed training procedures. K.L. coordinated the study, administered the cognitive assessments and working memory training, and completed the first draft of the manuscript. X.Z. was involved in the fMRI analyses. All authors participated in data interpretation, and critical revisions and approval of the final version of the manuscript.

Conflict of Interest

None of the authors have any disclosure of potential conflicts of interest (regarding the 5 items listed in the International committee of Medical Journal Editors Form) for the information reported in this article.

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