Co-Variations among Cognition, Cerebellar Disorders and Cortical Areas With Regional Glucose-Metabolic Activities in a Homogeneous Sample with Uner Tan Syndrome: Holistic Functioning of the Human Brain

Uner Tan

ABSTRACT

Patients with Uner Tan syndrome (UTS) exhibit habitual quadrupedal locomotion (QL), intellectual disability, dysarthric speech and truncal ataxia. Examination of cognitive ability in this syndrome has not yet been demonstrated in the scientific literature. Aims: (i) To analyze the cognitive abilities of the siblings with UTS; (ii) to assess the grade of their ataxia in relation to cerebellar disorders; (iii) to measure the metabolic activities of various cerebral regions in comparison with healthy individuals; (iv) to detect the interrelationships among all of the measured variables (IQ test scores, ataxia scores, cerebro-cerebellar areas and their metabolic activity levels) to reveal the holistic activity of the brain. The Minimental State Examination (MMSE) and Wechsler Adult Intelligence Scale (WAIS-R) were applied to the affected cases and healthy subjects. Cerebellar disorders were assessed by the International Cooperative Ataxia Rating Scale (ICARS). Brain MRI scans were performed and cerebro-cerebellar areas were measured on MRI scans, including their metabolic activities (SUV), measured by positron emission tomography (PET) scanning. MMSE and WAIS-R scores both correlated with cerebro-cerebellar areas. Cerebello-vermial areas and their metabolic activities were significantly smaller in patients than in normal controls; areas of the remaining structures were not significantly different between patients and healthy subjects. Brain areas significantly inter-correlated: ICARS negatively correlated with WAIS-R, MMSE scores, SUV, and cerebro-cerebellar areas, which significantly correlated with each other. The results suggested (i) ICARS may not only be a test for cerebellar disorders, but also may be related to global functioning of all of the cerebro-cerebellar regions; (ii) ICARS, WAIS-R and MMSE may be measures of emergent properties of the holistic activity of the brain; (iii) the psychomotor disorders in UTS may be related to decreased brain metabolism.

Key Words: Uner Tan syndrome, ataxia, intelligence, neural network, holistic brain

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Introduction

In 1917, W. J. Childs described in his book "Across Asia Minor on Foot" a man who walked on all fours. Childs (1917) described this case (p. 29) as follows: "He went on all fours and showed a number of antics, imitating a dog and goat and other animals to admiration. Then I saw he was without thighs; that the knee-joint was at the hip, the leg rigid, and only half the usual length."

About 100 years later, Tan first described six siblings who presented a novel syndrome with habitual QL, intellectual disability, and impaired speech accompanied by truncal ataxia (Tan, 2005). Among cerebellar ataxias, this is a unique syndrome with substantial differences from other balance disorders such as dysequilibrium syndrome (DSE), Cayman ataxia, and Joubert Syndome (Tan, 2010).

Corresponding author: Author name
Address: Cukurova University, Medical School, Department of Physiology, Adana, Turkey; Honorary Member of the Turkish Academy of Sciences, Ankara, Turkey.
e-mail ✉ unertan37@yahoo.com
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Guertin (2012) emphasized the uniqueness of UTS as a "*recently identified and uniquely different neurological disorder, called Uner Tan syndrome.*" This syndrome showed genetic heterogeneity: nonsense mutations were found in the WDR81 gene in the the patients of the Iskenderun family (Gulsuner, 2011), presented in this work, the VLDLR gene was affected in the Gaziantep and Canakkale families (Ozcelik *et al.,* 2008), and the ATP8A2 gene in the Adana family (Onat *et al.,* 2012), suggesting no single gene was responsible for the emergence of this syndrome.

Considering the brain function in human beings, the neural control systems consist of two major controls: inside-out (from bottom to top) and outside-in (from top to bottom). The outside-in concept is a holistic approach consistent with the idea that an entity's properties or behaviors are more than the sum of its parts. Aristotle (384-322BC) concisely summarized this holism: "*the whole is more than the sum of its parts.*" The noted scientist with important original contributions to holism in motor control was the Russian physiologist Nikolai Bernstein (1896-1966) (Stuart, 2005), who considered movement as a holistic action, which cannot be produced in isolation (Thelen & Smith, 1994).

Contemporary scientific thinking assumes that cognitive functions may result from an orchestrated activity of multiple cortical regions. In this context, Deacon (1989) stated "*mental activities are processes of the whole brain... mental events cannot be localized into specific structures (anti-localizationism).*" It was also reported that the regions of the cerebral cortex might be functionally coupled with each other (Fox *et al.,* 2006). There is also evidence that functional and structural networks within the brain may be closely associated with each other (Zemanova *et al.,* 2006); *"many cognitive disorders are associated with the localized or global failure of brain networks"* (Sporns, 2011). In this context, the cognitive functioning in UTS cases was never analyzed in detail. Intellectual disability, one of the main symptoms of UTS, was previously reported, but only using the MMSE test (Tan *et al.,* 2012), which superficially assesses the cognitive ability of patients in clinical sessions. A more comprehensive IQ test to gain more accurate information about their cognitive abilities, such as WAIS-R, was never applied to UTS cases. On the other hand, another major symptom, ataxia, was assessed only by inspection, without using an internationally recognized ataxia scale such as ICARS. MRI and PET scans were also previously performed and compared with healthy subjects (Tan *et al.,* 2008), but without studying their quantitative relations to ataxia and cognition.

In light of the above considerations, the present work was aimed (i) to examine the cognitive abilities of the UTS cases in detail using WAIS-R and MMSE, (ii) to analyze the cerebellar ataxia disorders quantitatively using ICARS, and (iii) to analyze the interrelationships between ICARS, WAIS-R, MMSE and cerebro-cerebellar regions and their metabolic activities, to have an idea about the origins of the UTS in relation to a possible holistic functioning of the brain. In this context, the interconnectedness among the levels of cognitive abilities, ataxia scores, cerebro-cerebellar areas and their regional metabolic activities were subjected to correlation analysis in light of the complex systems theory with regard to holistic brain functions.

Materials and Methods

Participants

The UTS patients (n = 6; five consistently QL plus one with transition from QL to ataxic bipedal locomotion, BL) were recruited from a family with 17 consanguineous siblings resident in a small village near Iskenderun, in Southern Turkey (Tan, 2005). The group consisted of two men and four women, ranging in age from 29 to 40 years. None had any school experience or literacy. One woman was ambidextrous, two women were left-handed, two women and one man were right-handed, according to the hand used for everyday activities.

Informed and written consent was obtained from the father on behalf of all of the patients. The study was approved by the ethics committee of the Medical School, Cukurova University, Adana, Turkey, in accordance with the Helsinki declaration.

Wechsler adult intelligence scale revised (WAIS-R)

The cognitive ability was assessed using the Turkish version of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Epir & Iskir, 1972), which was standardized on a sample of 1880 adult Americans (Wechsler, 1981). This test has high reliability and was

considered to be a core intelligence test in clinical practice. The raw scores were converted to standard scores, which were then converted to IQ scores (Wechsler, 1981). The raw scores were labeled borderline for 5 and below, low average for 6-7, average for 8-11, high average for 12-13, superior for 14-15, and very superior for 16 and up. IQ scores are classified as follows: above 130 superior or gifted, 120-129 very high, 110-119 bright normal, 90-109 average, 85-89 low average, 70-84 borderline cognitive ability, 50-69 intellectual disability, 35-49 moderate intellectual disability, 20-34 severe intellectual disability, and below 20 to 25 profound intellectual disability.

Magnetic resonance imaging (MRI)

The participants were scanned using magnetic resonance imaging (MRI) to measure the areas of the cerebro-cerebellar structures. Briefly, the participants' brains were scanned using a Siemens 1.5 T MRI scanner with a standard head coil and a tilted T1-weighted coronal and sagittal sequence. The cerebro-cerebellar regions were traced manually three times by a radiologist, who was unaware of the clinical data and diagnosis. The workstation from Sun Microsystems Inc. Mountain View CA USA, and commercially available software (Magic View 1000) were utilized in the measuring process. Total areas (mm^2) of the cerebellar vermis and corpus callosum were measured on the sagittal section, whereas the areas of the cerebrum and cerebellum were traced on the coronal sections, excluding the vermis, cerebellar pedunculi, and the fourth ventricle. The areas of the frontal, parietal, and temporal cortices, thalamus, gyrus cingulatus, and basal ganglia were measured on the coronal sections, taking the average of three measurements.

International Cooperative Ataxia Rating Scale (ICARS)

As a standard method, ICARS is frequently used to evaluate the cerebellar ataxia symptoms on a semi-quantitative scale with high inter-rater reliablility, test-retest reliability, and internal consistency. The semi-quantitative 100-point ICARS consists of four subscales: posture and gait disturbances (items 1-7, 34 points), limb kinetic functions (items 8-14, 52 points), speech disorders (items 15 and 16, 8 points), and oculomotor disorders (items 17-19, 6 points), with a total ataxia score of 100. Higher ICARS scores indicate greater degrees of impairment. The posture/gait and limb-kinetic subscales show the highest reliability (Storey *et al.,* 2004). The internal consistency has been found to be rather high (r = .93) (Schoch *et al.,* 2007).

Mini Mental State Examination (MMSE)

The MMSE standardized for illiterate Turkish adults was used to evaluate the cognitive status of the patients. This test has high inter-rater reliability (r = .99) and validity for the diagnosis of dementia in the Turkish population (Güngen *et al.,* 2002). Scores within the range of 0-23 (out of 30) indicate degrees of mental disturbance. The test attempts to assess the cognitive abilities in five fields: orientation (time, date and location), registration (immediate recall of three words), attention and calculation (count backwards), recall (recall three items), language (naming a pencil and a watch), repetition (repeating a given phrase), and complex commands (drawing shown figure, paper folding, etc.). Individuals with normal cognition score greater than or equal to 25, while 21-24 points indicate mild cognitive impairment, 10-20 points moderate, and scoring less than or equal to 9 points indicates severe cognitive impairment (Mungas, 1991).

Positron emission tomography (PET)

The method for obtaining PET scans was previously described in detail elsewhere (Tan *et al.,* 2008). PET was performed using a dual-modality PET/CT system. The participants received an intravenous injection of 362.6 ± 59.2 MBq ^{18}F-FDG (fluorodeoxyglucose) in a quiet, dimly lit room. Their blood glucose levels prior to injection of FDG were 104 ± 17.7 mg/dl. The mother's level was 310.0 mg/dl, and she was consequently excluded from the PET scan. PET/CT measurement was started 60 min after the FDG injection. The cranial CT was performed first to correct attenuation and for anatomical localization, and then the PET was performed. PET slices were evaluated visually and semi-quantitatively on the transaxial, coronal, and sagittal planes. Brain glucose utilization was expressed by SUV, the standardized uptake value of FDG.

Statistical analysis

Relations between variables (IQ scores, ICARS, cerebro-cerebellar areas and SUV) were revealed using Pearson two-tailed bivariate correlation analysis, considering the normality and constant variance tests. The power of the

performed tests was also evaluated. For the regression coefficients, values of $p < .05$ were taken as significant. The following software programs were used for statistical analysis and drawings: SPSS 17.0 (IBM, USA), Systat 13 (Version 13.00.05, Chicago, IL), and SigmaPlot 12.5 (Chicago, IL).

Results

All of the patients exhibited the main symptoms of UTS, such as dysarthric speech, intellectual disability, and QL, except the late-onset ataxic BL in one case. Table 1 presents the main characteristics of the patients recruited to this study.

Table 1. Main clinical characteristics of the patients.

Cases	Age	WAIS-R	MMSE	Main symptoms
Case 1	37	10	14	Early-onset QL, late-onset ataxic BL, mild intellectual disability, dysarthric speech
Case 2	32	4	10	Habitual QL, severe intellectual disability, dysarthric speech
Case 3	22	2	8	Habitual QL, severe intellectual disability, dysarthric speech
Case 4	27	3	8	Habitual QL, severe intellectual disability, dysarthric speech
Case 5	31	1	2	Habitual QL, severe intellectual disability, dysarthric speech
Case 6	39	0	1	Habitual QL, severe intellectual disability, dysarthric speech

Cognitive abilities (WAIS-R and MMSE) and ICARS

The minimum, maximum, mean, SE, and SDs for WAIS-R, MMSET, and ICARS with their subscales are presented in Table 2. The raw WAIS-R scores were borderline (four and below) for five of the six patients, while the sixth score was average (10). This patient used ataxic bipedal locomotion after habitually walking on all four extremities until adulthood. MMSET in not a measure for intellectual disability but only for cognitive impairment showed severe intellectual disability in four (1/30 to 8/30), and moderate intellectual disability (10/30 and 14/30) in two affected individuals. Age was not significantly associated with ICARS, WAIS-R or MMSE test scores ($r = -.31$ to $+.24$, $p = .55$ to $.64$).

WAIS-R and MMSE test scores *vs* cerebro-cerebellar areas

The WAIS-R and MMSE test scores linearly correlated with each other ($r = .90$, Rsqr = .81, SE = 1.74, $t = 4.11$, $p = .02$; normality test (Shapiro-Wilk) passed ($p = .72$), constant variance test passed ($p = .06$), power of performed test with alpha = 0.05: 0.72. The ratio of cerebral area to body weight, and the areas of the cerebellum, basal ganglia, corpus callosum, frontal cortex, gyrus cingulatus, parietal cortex, temporal cortex, thalamus, and cerebellar vermis were significantly correlated with WAIS-R and MMSE test scores (see Table 3). The correlation coefficients were significantly greater for the WAIS-R scores than those for the MMSE test scores. Namely, the power of the performed test was always greater for WAIS-R than for MMSE; regression coefficients were always greater in WAIS-R than those in the MMSE test scores.

ICARS *vs* cognitive abilities (WAIS-R, MMSE)

Table 4 presents the interrelationships among IQ test scores (WAIS-R and MMSE) and various cerebro-cerebellar areas (cerebrum, cerebellum, basal ganglia, corpus callosum, cerebellar vermis, thalamus, and frontal, temporal, cingular, and parietal cortices). All of the variables were significantly interrelated at .05 to .000 levels. Higher ICARS, including the postural, kinetic, speech, and oculomotor disorders subscales, indicate greater degrees of impairment. The total ICARS between 36 and 85 for the total sample was remarkably high, with the higher figure being close to the maximal ICARS of 100. Similarly, the upper score for the postural disorder of between 13 and 32 was also close to the full score 34, which would indicate completely disordered postural functions. The scores for the kinetic, speech, and oculomotor dysfunctions were also close to the maximal values, being 52 points for kinetic, 8 points for speech and 6 points for oculomotor disorders. The total ICARS scores in four control siblings ranged from 1 to 8.

Cerebellar disorders (ICARS) *versus* WAIS and SMMT scores

Table 5 presents the Pearson two-tailed bivariate correlations for the WAIS scores, SMMT scores, and the degrees of the cerebellar disorders, including ICARS, postural, kinetic, speech, and oculumotor disorders. WAIS and SMMT scores were positively correlated.

Table 2. Range, mean, minimum, maximum, SE and SDs for WAIS-R and MMSE scores.

IQ TESTS	N	RANGE	Minimum	Maximum	Mean	SEM	SD
WAIS-Verbal	6	4.0	6.0	10.0	7.2	0.601	1.5
WAIS-Performance	6	2.0	5.0	7.0	5.8	0.401	1.0
WAIS-Full scale	6	6.0	11.0	17,0	13.0	0.894	2.2
WAIS-Verbal IQ	6	4.0	46.0	50.0	47.5	0.619	1.5
WAIS-Performance IQ	6	9.0	40.0	49.0	44.2	1.579	3.9
WAIS-Full scale IQ	6	6.0	41.0	47.0	42.8	1.046	2.6
MMSE	6	13.0	1.0	14.0	7.2	2.011	4.9

Table 3. Linear relations of WAIS-R and MMSE test scores to cerebro-cerebellar areas.

Areas	R	Rsqr	t	P	Normality	Variance	Power
Cerebrum to:							
WAIS-R	.98	.96	10.07	< .001	Passed (p = .44)	Constant (p = .06)	.98
MMSE	.93	.86	4.92	<.008	Passed (p = .33)	Constant (p = .06)	.81
Cerebellum to:							
WAIS-R	.99	.98	13.81	< .001	Passed (p = .11)	Constant (p = .06)	.99
MMSE	.90	.81	4.07	< .01	Passed (p = .06)	Constant (p = .06)	.72
Basal ganglia to:							
WAIS-R	.96	.92	6.75	<.005	Passed (p = .61)	Constant (p =.06)	.92
MMSE	.95	.91	6.29	<.005	Passed (p = .06)	Constant (p = .06)	.90
Corp.callosum to:							
WAIS-R	.99	.99	20.01	< .001	Passed (p = .98)	Constant (p = .06)	.99
MMSE	.91	.82	4.25	< .01	Passed (p = .58)	Constant (p = .06)	.74
Frontal to:							
WAIS-R	.98	.96	9.36	< .001	Passed (p = .45)	Constant (p = .06)	.97
MMSE	.86	.74	3.40	< .05	Passed (p = .60)	Constant (p = .06)	.62
Cingulate to:							
WAIS-R	.99	.99	19.10	< .001	Passed (p = .82)	Constant (p = .06)	.99
MMSE	.86	.74	3.34	< .05	Passed (p = .29)	Constant (p = .06)	.61
Parietal to:							
WAIS-R	.97	.94	8.23	< .001	Passed (p = 47)	Constant (p = .06)	.96
MMSE	.87	.76	3.56	< .05	Passed (p = .90)	Constant (p = .06)	.64
Temporal to:							
WAIS-R	.98	.96	9.29	< .001	Passed (p = .18)	Constant (p = .06)	.97
MMSE	.89	.80	4.00	<.01	Passed (p = .76)	Constant (p = .06)	.71
Thalamus to:							
WAIS-R	.99	.97	11.53	< .001	Passed (p = .75)	Constant (p = .06)	.99
MMSE	.84	.71	3.11	< .05	Passed (p = .40)	Constant (p = .06)	.57
Vermis to:							
WAIS-R	.94	.89	5.73	<.005	Passed (p = .32)	Constant (p = .06)	.87
MMSE	.84	.71	3.11	< .05	Passed (p = .40)	Cosntant (p = .06)	.57

Table 4. Interrelationships among WAIS-R and MMSE test scores, and various cerebro-cerebellar areas: Pearson two-tailed bivariate correlations with *p* values.

VARIANTS	WAIS	MMSE	CER	CRB	BG	CC	FR	GYR	PAR
WAIS		.899*	.981**	.990**	.959**	.995**	.978**	.995**	.972**
P		.015	.001	.000	.003	.000	.001	.000	.001
MMSE	.899*		.926**	.897*	.953**	.905*	.862*	.858*	.872*
P	.015		.008	.015	.003	.013	.027	.029	.024
CER	.981**	.926**		.963**	.932**	.979**	.954**	.967**	.942**
P	.001	.008		.002	.007	.001	.003	.002	.005
CRB	.990**	.897*	.963**		.973**	.996**	.981**	.985**	.989**
P	.000	.015	.002		.001	.000	.001	.000	.000
BG	.959**	.953**	.932**	.973**		.964**	.938**	.937**	.955**
P	.003	.003	.007	.001		.002	.006	.006	.003
CC	.995**	.905*	.979**	.996**	.964**		.988**	.991**	.988**
P	.000	.013	.001	.000	.002		.000	.000	.000
FR	.978**	.862*	.954**	.981**	.938**	.988**		.988**	.994**
P	.001	.027	.003	.001	.006	.000		.000	.000
GRY	.995**	.858*	.967**	.985**	.937**	.991**	.998**		.978**
P	.000	.029	.002	.000	.006	.000	.000		.001
PAR	.972**	.872*	.942**	.989**	.955**	.988**	.994**	.978**	
P	.001	.024	.005	.000	.003	.000	.000	.001	
TEMP	.978**	.894*	.989**	.958**	.915*	.979**	.976**	.977**	.956**
P	.001	.016	.000	.003	.011	.001	.001	.001	.003
THAL	.985**	.841*	.974**	.970**	.906*	.984**	.984**	.994**	.967**
P	.000	.036	.001	.001	.013	.000	.000	.000	.002
VER	.944**	.913*	.976**	.947**	.912*	.955**	.915*	.923**	.921**
p	.005	.011	.001	.004	.011	.003	.010	.009	.009

*: Correlation is significant at the 0.05 level (2-tailed), **: Correlation is significant at the 0.01 level (2-tailed), CER: cerebrum, CRB: cerebellum, BG: basal ganglia, CC: corpus callosum, FR: frontal cortex, GYR: gyrus cingulatus, PAR: parietal cortex, TEMP: temporal cortex, THAL: thalamus, VER: vermis

Table 5. Pearson two-tailed bivariate correlations among WAIS, SMMT and ICARS scores with subscales.

TESTS		WAIS	MMSE	ICARS	Posture	Kinetic	Speech	Oculomo.
WAIS	Pearson Corr.	1	+,899*	-,965**	-,969**	-,967**	-,881*	-,921**
	Sig. (2-tailed)		,015	,002	,001	,002	,020	,009
	N	6	6	6	6	6	6	6
MMSE	Pearson corr.	+,899*	1	-,923**	-,926**	-,887*	-,951**	-,982**
	Sig. (2-tailed)	,015		,009	,008	,018	,004	,000
	N	6	6	6	6	6	6	6
ICARS	Pearson corr.	-,965**	-,923**	1	1,000**	+,996**	+,961**	+,908*
	Sig. (2-tailed)	,002	,009		,000	,000	,002	,012
	N	6	6	6	6	6	6	6
POSTURE	Pearson corr.	-,969**	-,926**	1,000**	1	+,996**	+,959**	+,914*
	Sig. (2-tailed)	,001	,008	,000		,000	,003	,011
	N	6	6	6	6	6	6	6
KINETIC	Pearson corr.	-,967**	-,887*	+,996**	+,996**	1	+,936**	+,877*
	Sig. (2-tailed)	,002	,018	,000	,000		,006	,022
	N	6	6	6	6	6	6	6
SPEECH	Pearson corr.	-,881*	-,951**	+,961**	+,959**	+,936**	1	+,898*
	Sig. (2-tailed)	,020	,004	,002	,003	,006		,015
	N	6	6	6	6	6	6	6
OCULOMOT	Pearson corr.	-,921**	-,982**	+,908*	+,914*	+,877*	+,898*	1
	Sig. (2-tailed)	,009	,000	,012	,011	,022	,015	
	N	6	6	6	6	6	6	6

*: Correlation is significant at the p < .05 level (2-tailed).
**: Correlation is significant at the p < .01 level (2-tailed).

The total ICARS scores, including the subscale scores of the postural, kinetic, speech, and oculomotor disorders, were negative linearly correlated with WAIS and SMMT scores. The scores for the cerebellar disorders showed a positive linearly correlation with each other. The negative linear relations among the scores for the cerebellar disorders (ICARS, posture, speech and oculomotor), WAIS-R, and SMMT (MMSE) scores, including positive linear correlations among cerebellar disorders, and MMSE *vs* WAIS-R scores are illustrated in Figure 1, which shows near-perfect correlations.

PET in healthy controls and UTS cases

The mean SUVs (standardized uptake values for FDG) in PET for the healthy control (CON) subjects (n = 5) and the patients with UTS (n = 5) are presented in Table 6. One patient, with late onset bipedal ataxic gait, rejected this investigation. As can be seen in Table 6, the SUVs from the cerebellum and vermis were significantly less in patients than in healthy normal; the remaining cerebral structures exhibited no significant differences between healthy normal and patients.

The intercorrelations among SUVs of the cerebro-cerebellar structures, gyrus cingulatus, thalamus, basal ganglia, temporal cortex, occipital cortex, cerebellum, vermis, frontal cortex and parietal cortex, are illustrated in Figure 2. SUVs of these cerebro-cerebellar structures showed significant positive linear correlations with each other (r = .91 to .99, p < .01 to .0001).

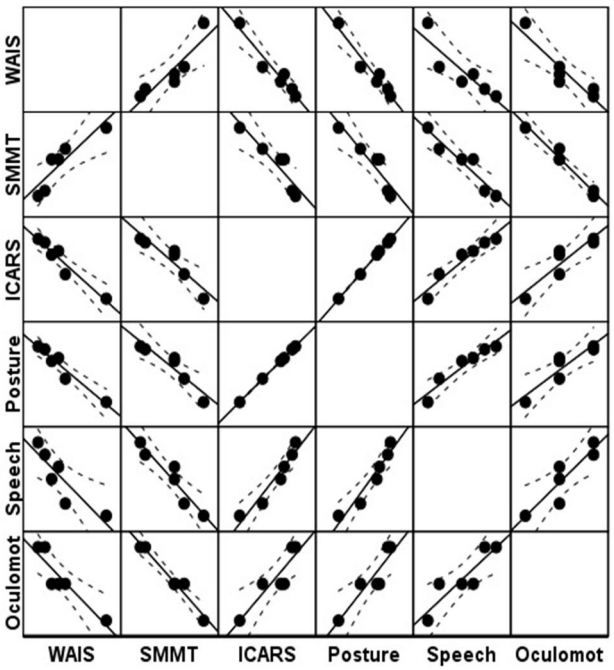

Figure 1. Correlations among scores for ICARS, WAIS, MMSE (SMMT), and cerebellar disorders (postural, kinetic, speech and oculomotor) in cases with UTS.

Table 6. Mean SUV in cerebro-cerebellar structures of the healthy controls (CON) and patients, with t-test results for differences.

Structures	N	Mean±SD	t	DF	p
Cerebellum					
CON	5	19.00±0.57			
Patients	5	8.74±1.44	14.81	8	< .0001
Vermis					
CON	5	8.94±0.50			
Patients	5	4.04±0.46	16.14	8	< .0001
Thalamus					
CON	5	22.6±1.60			
Patients	5	25.0±3.31	1.46	8	= .18 (NS)
Basal ganglia	5	23.6±1.81			
CON	5	26.0±3.21	1.50	8	= .17 (NS)
Patients					
Caudate nucleus	5	22.6±2.11			
CON	5	24.7±3.11	1.28	8	= .24 (NS)
Patients					
Occipital cortex	5	25.0±1.22			
CON	5	28.1±5.11	1.32	8	= .22 (NS)
Patients					
Frontal cortex	5	24.0±2.41			
CON	5	22.8±4.11	0.57	8	= .59 (NS)
Patients					
Parietal cortex	5	21.2±2.61			
CON	5	20.9±4.11	0.14	8	= .89 (NS)
Patients					
Temporal cortex	5	21.3±1.66			
CON	5	20.0±4.01	0.68	8	= .52 (NS)
Patients					

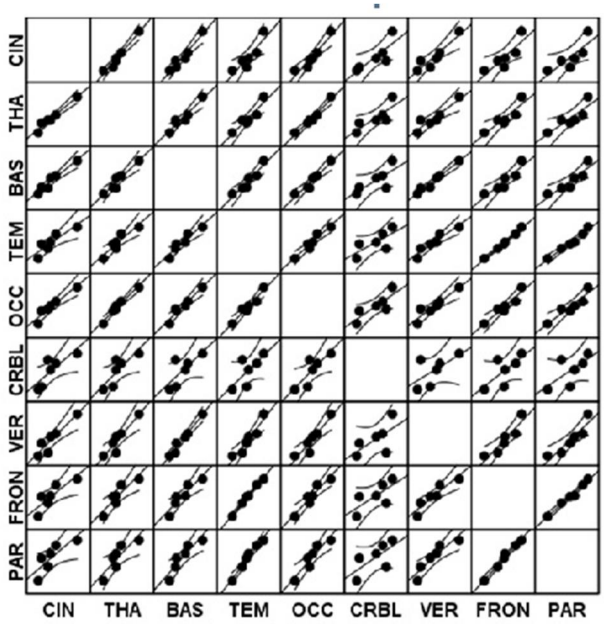

Figure 2. Linear intercorrelations with 95% confidence limits among SUVs for gyrus cingulatus (CIN), thalamus (THA), basal ganglia (BAS), temporal cortex (TEM), occipital cortex (OCC), cerebellum (CRBL), vermis (VER), frontal cortex (FRON) and parietal cortex (PAR).

The intercorrelations among SUVs of the cerebro-cerebellar structures and cerebro-cerebellar areas are illustrated in Figure 3**.** SUVs of the cerebro-cerebellar structures and the areas of the cerebro-cerebellar structures were positive linearly correlated, as well as the holistic correlations among all of the variables with each other (r = .84 to .99, p < .05 to 0.0001).

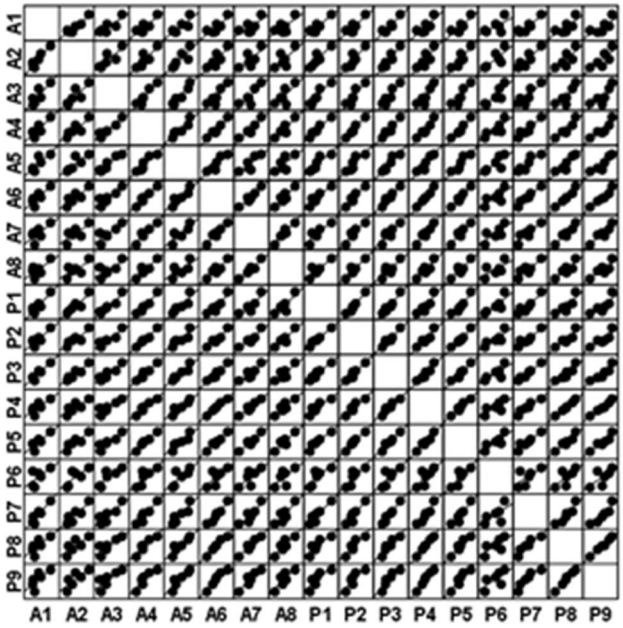

Figure 3. Positive linear intercorrelations among SUV and cerebro-cerebellar areas in patients with UTS. SUVs from cingulate gyrus (P1), thalamus (P2), basal ganglia (P3), temporal cortex (P4), occipital cortex (P5), cerebellum (P6), vermis (P7), frontal cortex (P8), parietal cortex (P9; Areas from cingulate gyrus (A1), vermis (A2), cerebellum (A3), thalamus (A4), basal ganglia (A5), frontal cortex (A6), parietal cortex (A7), temporal cortex (A8).

The intercorrelations among the various cerebro-cerebellar structures (gyrus cingulatus, thalamus, basal ganglia, temporal cortex, occipital cortex, cerebellum, vermiş, frontal cortex and parietal cortex), ICARS with its subscales (postural, kinetic, speech and oculomotor disorders), WAIS and MMSET scores, are illustrated in Table 7**.** The scores of ICARS and its subscales were negative linearly correlated with the SUVs of the cerebro-cerebellar structures. The scores from WAIS-R and MMSET were positive linearly correlated with the SUVs of the cerebro-cerebellar structures.

Table 7. Intercorrelations among SUVs for various regions of the brain with WAIS, MMSET, and ICARS, including its subscales posture (POST.), kinetic (KIN.), speech, and oculomotor disorders. r: Pearson correlation coefficient; p: significance level.

BRAIN REGIONS		ICARS	POST.	KIN.	SPEECH	OCULO	WAIS	MMSET
CING.	r		-.915*	-.893*	-.950**	-.896*	+.939**	+.880*
	p		.011	.016	.004	.016	.006	.021
THAL.	r	-.890*	-.896*	-.892*	-.969**	-.952**	+.946**	+.911*
	p	.018	.016	.017	.001	.003	.004	.012
BASAL G.	r	-.969**	-.983**	-.959**	-.967**	-.928**	+.970**	+.953**
	p	.001	.000	.002	.002	.008	.001	.003
TEMPORAL	r	-.877*	-.915*	-.884*	-.951**	-.940**	+.916*	+.950**
	p	.022	.010	.019	.004	.005	.010	.004
OCCIPITAL	r	-.900*	-.915*	-.906*	-.958**	-.965**	+.935**	+.934**
	p	.014	.011	.013	.003	.002	.006	.006
CEREBEL.	r	-.900*	-.894*	-.880*	-.971**	-.956**	+.945**	+.912*
	p	.020	.017	.022	.001	.003	.004	.012
VERMIS	r	-.970**	-.984**	-.971**	-.981**	-.942**	+.987**	+.985**
	p	.001	.000	.001	.001	.005	.000	.000
FRONTAL	r	-.843*	-.887*	-.855*	-.927**	-.928**	+.885*	+.935**
	p	.035	.018	.030	.008	.008	.019	.006
PARIETAL	r	-.858*	-.900*	-.869*	-.900*	-.912*	+.872*	+.938**
	p	.029	.015	.025	.014	.011	.023	.006

*: Correlation is significant at the 0.05 level (2-tailed);
**: Correlation is siginificant at the 0.01 level (2-tailed).
CING: cingulate gyrus, THAL: thalamus, BASAL G: basal ganglia, TEMPORAL: temporal cortex, OCCIPITAL: occipital cortex, CEREBEL: cerebellum, VERMIS: vermis, FRONTAL: frontal cortex, and PARIETAL: parietal cortex

Discussion

This study presented a detailed analysis of the cognitive abilities (WAIS-R and MMSE) and ataxia scores (ICARS) in relation to the cerebro-cerebellar structures' size and metabolism in a homogeneous group of UTS-patients for the first time in the scientific literature to my knowledge. The interrelationships among these variables were also examined as an attempt to approach the global networking within the human brain with regard to structure and function.

The MMSE, a test to superficially assess the cognitive abilities of patients in clinical sessions, showed positive linear correlation with WAIS-R, a comprehension intelligence test. This correlation was used to evaluate the cognitive status of individuals in more detail in regard to health and disease. The positive linear correlation between the WAIS-R and MMSE scores suggests that WAIS-R, a detailed intelligence test, may be predicted from MMSE, a relatively simple test measuring cognitive abilities. This is the first report with regard to WAIS-R *versus* MMSE correlation in a homogeneous group of UTS cases. The relation of MMSE to WAIS-R was also previously studied in different samples with different results. Homogeneity of the samples would play a role in consistency of the results reported by different research groups. For instance, MMSE score significantly correlated with WAIS-R scores in patients with dementia, stroke, schizophrenia, depression, psychomotor delay, Alzheimer's disease, and elderly individuals (Folstein *et al.*, 1975). However, Faustman et al. (1990) reported only modest correlation between WAIS-R and MMSE test scores, suggesting MMSE may not reliably estimate the cognitive decline in psychiatric patients, thus being an inappropriate method to assess the cognitive deficit in these cases. MMSE and WAIS-R are indeed different instruments, which evaluate different functions. Namely, MMSE, being a quantitative cognitive test, evaluates cognitive impairment in normally developing individuals, while WAIS-R evaluates intelligence and measures different levels of intellectual disabilities.

The raw WAIS-R scores showed a borderline cognitive state in five of the six patients, with the other being of moderate intelligence. This was more or less consistent with the MMSE test results: severe cognitive impairment in four and moderate cognitive impairment in two affected individuals. Interestingly, the man with a late-transition from QL to BL showed moderate intelligence, contrary to the other patients with consistent QL exhibiting severe intellectual disability. These different gaits with different cognitive abilities suggest that gait may be related to cognition, individuals with BL being better than those with QL in cognitive abilities. Unfortunately, there are no reports with regard to this argument. We only know, in general,

that the non-human primates with habitual QL are inferior in cognition to human primates with habitual BL. In this context, Tobias (1992) noted that, "*human uprightness is among the most striking characteristics that distinguish living man from the great apes of Africa and Asia.*" Accentuating the prominent role of posture in the emergence of the human quadrupedalism seen in UTS, Ivanenko et al. (2013) argued: "*any reflection of the nature of human quadrupedalism should include a consideration of the mechanisms determining the choice of unconscious habitual posture.*" On the other hand, the results suggested a relation between posture and cognition in humans, upright being better than quadruped posture. Moreover, the degrees of the postural and kinetic disorders were found in this work to be negative linearly correlated with the WAIS-R and MMSE scores, and this is the first report in the UTS-literature. Although a similar correlation analysis has not been performed for these variables in ataxias other than UTS, the cognitive dysfunctions were frequently reported in various types of spinocerebellar ataxias (e.g., Schmahmann, 1991).

The study of the relations between structure and function found that the cerebro-cerebellar areas showed significant correlations with cognitive test scores, WAIS-R and MMSE, but we did not measure the regional volumes of the cerebro-cerebellar areas, which could be taken as an index for the gray matter volumes (Feczko *et al.,* 2009). On the other hand, the cortical areas also reflect the number of columns within a cortical region (Rakic, 1988). That is, a correlation between IQs assessed by WAIS-R and MMSE and the size of the regional cerebro-cerebellar areas may suggest a positive correlation between the number of the cortical columns and IQ scores, and high IQ may be associated with a greater number of regional cortical columns. The mental retardation in UTS cases may be related to fewer cortical columns developing in these cases than in healthy subjects. The metabolic activity in the regional cerebro-cerebellar regions correlated with IQ scores may also be explained by this argument: less glucose metabolism of the cortical regions may also be associated with smaller cortical areas (volumes) including fewer cortical columns, and resulting in lower IQ scores, i.e. various degrees of intellectual disabilities. On the other hand, ICARS and its subscales negative linearly correlated with IQ scores, cerebro-cerebellar areas and the regional glucose metabolic activities. Considering again the number of the cortical columns, ICARS may be associated with this: the lower the number of regional cortical columns, the higher the ICARS ataxia scores with subscales.

The results showed, for the first time, that the metabolic activity of the cerebello-cerebral areas inversely correlated with WAIS-R and MMSE and ICARS scores with subscales. This may be accounted for by the relation of the columnar size to the regional metabolic activities of the cerebral cortex: the larger the cortical column, the higher its metabolic activity (Woolsey *et al.,* 1996). It can thus be concluded that lower metabolic activity in the cerebro-cerebellar areas may be associated with smaller cortical columns with lower metabolic activities in UTS cases. This may, in turn, be associated with higher ICARS scores and lower WAIS-R and MMSE test scores.

Interestingly, all of the variables studied in this work showed highly significant linear interrelationships with each other, such as cerebro-cerebellar areas with their PET-measured glucose-metabolic activities (cerebellum, basal ganglia, corpus callosum, cerebellar vermis, thalamus, and frontal, temporal, cingular, and parietal cortices), WAIS-R and MMSE test scores, and ICARS including cerebellar disorders (postural, kinetic, speech, and oculomotor). This suggests that none of these variables can be considered as an independent entity, emerging without the influence of the brain as a whole. This also suggests that the brain may be formed by the highly interconnected dynamical units, with psychomotor outcomes in health and disease. This web-like structure of the brain "*is capable to coordinate and integrate distributed brain activities in a unified neural process*" (Boccaletti *et al.,* 2006). However, this kind of neuronal wiring needs to be related to function. In this context, the results of the present work seem to be able to fill this gap, since it relates the structure to function.

In accordance with the holistic nature of brain functions in health and disease—as shown in the present work—there is evidence that the human cerebral cortex may be considered as an ensemble of the reciprocally coupled cortical areas holistically interconnected to form a large-scale cortical circuitry. In such a holistic system, the neuronal connections may continuously change following the

environmental conditions, establishing new connections within the system. Therefore, the holistic interactions may be highly dynamic, allowing the emergence of the coherent global dynamics yielding an efficient holistic communication within the brain. This may play a role in the emergence of UTS in addition to the epigenetic mechanisms triggered by the extremely poor living conditions. Conclusions from this specific disease may be that environmental factors may play a role in the emergence of some pathological conditions by the epigenetic mechanisms.

Conclusions

In the present work, the cognitive abilities, ICARS ataxia scores, MRI-measured cerebro-cerebellar areas and their glucose-metabolic activities were subjected to a correlational analysis in a homogeneous group of patients (n = 6) with UTS, living within the same family with 17 consanguineous siblings. A detailed IQ test, WAIS-R, could be predicted from a simple cognition screening method, the MMSE test. These cognitive ability test scores highly correlated with all of the cerebro-cerebellar areas, regional glucose-metabolic activity levels, and ICARS with subscales; there were dynamic intercorrelations among all of these variables. For instance, ICARS, a test to traditionally assess the ataxia level in cerebellar disorders, associated with cognitive tests, the size of the cerebro-cerebellar areas and their glucose-metabolic activities, suggesting that this ataxia score may be indicative not only for the cerebellar disorders, but it may also be related to all brain structures and functions. These dynamic intercorrelations among these variables suggest that the brain may not function in discrete entities, but rather that the human brain may show a collective behavior of neural networks, common to all complex systems. The results are also consistent with notion that the brain is a quantum system, both exhibiting holistic properties (Tarlaci, 2010).

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Conflict of interest

The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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