Multiplex Temporal Measures reflecting Neural Underpinnings of Brain Functional Connectivity under cognitive load in Autism Spectrum Disorder

Supplemental Information

Diagnosis of ASD

Diagnoses of Autism Spectrum Disorder (ASD) were confirmed using the Autism Diagnostic Observation Schedule-2nd Edition (ADOS-2) and Social Responsiveness Scale-2nd Edition (SRS-2). In ADOS-2, raw scores from two domains-Social Affect (ADOS_SA) and Restricted and Repetitive Behaviors (ADOS_RRB) were summed [1]. The interviewer engaged the participant in a series of interactive behaviors, which were observed and scored on the basis of a scoring algorithm (0= no concern with behavior, 1= mild concern with behavior, 2= concern with behavior). The total scores were fixed in a range of 1-12, where higher scores indicate greater severity. On this basis, if a severity score ≥ 6 is achieved, the participant was classified as having an ASD.

The SRS-2 is a parent-report evaluation of their child's ability to perceive social information and react pertinently in interactions with other persons [2]. This scale includes 3 items which cover the core deficits of autism, i.e., social deficits, interactive communication deficits, and reciprocal-repeated behavior pattern. In the present work, T-scores are used to mark the severity of the disorder in the participants. The total score of SRS involves the sum from five sub-scales: social awareness, social communication, social cognition, social motivation, and restricted-repetitive behavior. The T-scores ≥75 reflect a higher severity, in a range (66-75) reflects moderate, in 60-65 reflects mild and ≤59 represents a normal participant.

In the present paper, a Malin's Intelligence Scale for Indian Children (MISIC) [3] was utilized to determine the intelligence quotient (IQ). It is the Indian adaptation of Wechsler's Intelligence Scale for children. It gives a full IQ score based on two sub-domains: Verbal IQ and Performance IQ. Each sub-domain comprises 6 sub-tests: (i) Verbal involves vocabulary, information, general comprehension, arithmetic, analogy & digit span test.; (ii) Performance involves picture completion, block design, picture arrangement, object assembly, coding numbers, and tracing mazes. It is valid for the children in the age range of 6-15 years. It is conducted individually and lasts for approximately 2 to 2.5 hours.

The values of these diagnostic measures are provided in a tabular form in table S1. The normality of the data is checked using a test, namely the Shapiro-Wilk test. The parameters skewness (s)- a measure of the symmetry and kurtosis (k)- a measure of the probability of two tails. Here we attained- (i)negative values of 'k,' which reflects that the data distribution with flatter peak and light tails compared to normal distribution.; (ii)positive values of 's' which reflects longer right-hand tail than left-hand tail; (iii) negative values of 's' which reflects longer left-hand tail than the right-hand tail. The values among both group participants were compared using paired samples t-test at a significance level of 0.05.

Table S1: Mean values (Mean ± S.D.) of Demographic and Clinical Features for both ASD and TD participants.

Features		ASD (N=30)	TD (N=30)	Normality Test			t-test	p*
				p	k	s	df=58	
MISIC(IQ)	Verbal (Range)	102.0±8.3 (90-112)	113.5±13.9 (98-128)	0.41	-1.14	0.33	3.9	0.61
	Performance (Range)	105.6±10.1 (92-116)	108.4±12.2 (97-121)	0.61	-0.86	-0.11	1.6	0.45
	Full scale (Range)	109.2±10.2 (96-118)	112.1 ± 13.5 (100-126)	0.38	-0.56	1.25	3.4	0.09
ADOS-2 (Raw Score)	Total score (Range)	11.2 ±4.2 (6.4-12)	-	0.53	-1.21	-0.18	-	-
	ADOS_SA (Range)	7.7±3.3 (5-10)	-	0.28	-0.99	0.32	-	-
	ADOS_RRB (Range)	3.5±2.1 (1-6)	-	0.16	-1.01	0.46	-	-
SRS-2 (T-Score[a])	Total score (Range)	71.5 ±6.8 (62-80)	52.8 ± 6.3 (45-58)	0.52	-0.81	-1.18	13.2	0.001
	Social Awareness (Range)	70.6 ± 7.6 (59-82)	50.6 ± 5.8 (42-56)	0.08	-0.11	-1.32	12.8	0.03
	Social Cognition (Range)	69.3 ±6.5 (56-80)	42.7 ± 6.6 (35-49)	0.71	-0.65	-1.06	10.6	0.01
	Social Communication (Range)	72 ± 5.7 (65-81)	45.6 ± 7.1 (37-54)	0.23	-1.10	0.45	15.4	0.005
	Social Motivation (Range)	61.1 ± 8.1 (49-73)	47.3 ± 5.4 (40-54)	0.54	-0.04	0.98	9.9	0.02
	RRB (Range)	77.3 ± 4.6 (58-86)	43.4 ± 7.6 (34-51)	0.46	0.13	-0.84	16.5	0.001

([a]T-scores: moderate (60-75); severe (≥ 76); paired t-test (significance *p< 0.005)
(ADOS-2: Autism Diagnostic Observation Schedule (2nd edition); MISIC: Malin's Intelligence Scale for Indian children; RRB restricted and repetitive behaviors; SA: Social Affect; SRS-2: Social Responsivity Scale (2nd edition) k: Kurtosis; N= number of participants; p: significance value; s: Skewness)

Methodology

The multivariate time-series refers to the recording of the signals simultaneously from different brain regions. It can be represented as ($x(t) = \{x_1(t), x_2(t), ...x_M(t)\}$). The multiplex Visibility Graphs (VGs) are attained by converting each time series into a complex network called VG network. The procedure to convert time-series into VGs is explained as below:

STEP1: Consider each data sample points in the time-series as a node of the graph network- G (N, E). Let the time-series is $x_1(t_i) = \{x_1(t_1), x_1(t_2), ...x_1(t_N)\}$, where i: 1 to N. The graph-network will have N= (n_i) nodes (i = 1 to N) and E= (e_i) edges.

STEP2: Construct the edges between the nodes of graph-network by using the visibility criteria described by the equation, given as:

$$x(t_2) < x(t_1) + (x(t_3) - x(t_1))\frac{t_2 - t_1}{t_3 - t_1} \qquad (1)$$

where, $x(t_1)$, $x(t_2)$ and $x(t_3)$ are the data sample points at time instant t_1, t_2, t_3. Figure S1 illustrates the VGs of time-series data ($x(t)$) that represents the edge built upon the visibility among the nodes.

STEP 3: Determine the weight of the edge to attain more robust network using the equation, provided in [18], given as:

$$w_{ab} = \arctan\frac{n_b - n_a}{t_b - t_a} \qquad (2).$$

Where w_{ab} is the weight of the link connecting the node a (n_a) and b (n_b), and arctan function (*atan* in MATLAB) can detect the sudden variations in EEG signals.

STEP 4: Construct the Weighted VG as shown in Figure S1 (iv) based on the steps explained from Step1 to Step 4.

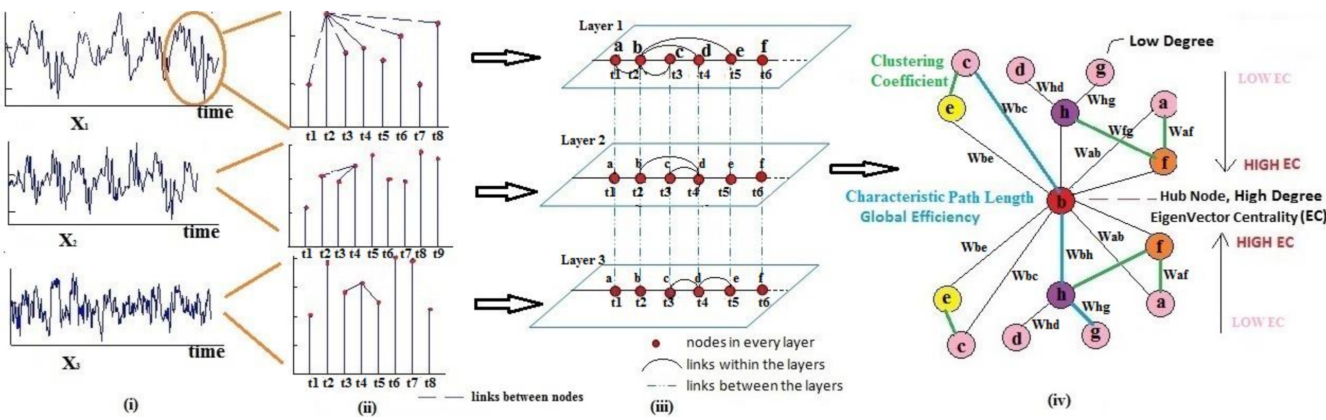

Figure S1: Schematic representation of converting multivariate time-series into multiplex Visibility Graphs (VGs). (i) first three series of a multivariate time-series (*M*-dimensional: $x_M(t) = \{x_1(t), x_2(t), x_3(t)\}$), (ii)mapping a portion of each time series into multiplex VG network in which nodes are the time events and edges are formed according to visibility between nodes, as described in [4, 5], (iii) multiplex VG with every layer corresponding to the respective time-series and every node of each layer is aligned, i.e., node *a* (relative to timestamp t) of layer 1 with node *a* (relative to timestamp t) of layer 2 , (iv) Diagrammatic Representation of the complex graph properties.

By following these steps, weighted VGs can be constructed for each of the time-series. In this manner, a multiplex VG network can be attained from a multivariate time-series. Figure S1 (iii) reflects the layers of VGs for different time-series. Every node of each layer is aligned, which means, node *b* (relative to timestamp t+1) of layer 1 will be aligned with node *b* (relative to timestamp t+1) of layer 2. Finally, a combination of different layers can generate a multiplex network. The different features need to compress the voluminous EEG data from all the channels are shown in Figure S1 (iv).

Statistical Analyses

The calculated mean and standard deviations for total group neural data were evaluated and compared to find significant differences. A paired samples t-test (with significance at a threshold of $p \leq 0.05$) is utilized for computing significant differences between the complex measures of ASD and TD participants.

Table S2 illustrates the comparison of Average weighted Degree (D_{avg}^{w}), Clustering Coefficient (CC), Global Efficiency (GE), Eigenvector Centrality (EC) in overall task connectivity with resting-state in ASD and TD participants. Similarly, a comparison of all these measures while transiting to 2-back task from the 0-back task is also elaborated for 19 electrodes. The values were shown at different levels of significance (p< 0.001; *p<0.005; **p<0.05). The differences in the Mutual Information (MI) parameter are illustrated in Table S3. The results reflected that intra-region connectivity is higher in ASD than inter-region connectivity. Although the MI magnitudes were higher in TD, the inter-region connectivity dominates over the intra-region connectivity, reflecting more direct exchange information over loner connections. The results truly support that ASD individuals have densely segregated network with short local functional reach, compared to TDs.

Table S2: Comparison of complex graph measures in overall task connectivity with resting-state connectivity and 2-back with 0-back level for each group (p< 0.001;*p<0.005;p<0.05).**

EXPERIMENT		Overall Task Connectivity- Resting State connectivity								2-back – 0-back							
Elect	Group	D_{avg}^{w}		CC		GE		EC		D_{avg}^{w}		CC		GE		EC	
		Mean	t-value	Mean	t-value	Mean	t-value	Mean	t-value	Mean	t-value	Mean	t-value	Mean	t-value	Mean	t-value
Fp1	ASD	-24.33*	-58.73	0.06**	26.67	0.09*	83.07	0.21*	10.11	22.11	19.70	0.17*	28.56	-0.09*	-25.41	0.15	18.31
	TD	16.09*	44.46	0.11**	13.72	0.13**	39.21	0.29**	15.17	16.54	13.93	0.07	20.08	0.10	23.86	0.17**	15.24
Fp2	ASD	20.82*	51.92	-0.21	-18.21	x	x	0.15	17.31	18.30*	23.16	x	x	x	x	0.18	12.34
	TD	14.71*	41.61	x	x	x	x	0.32*	63.45	12.93	31.63	x	x	x	x	0.14*	16.72
F7	ASD	x	x	x	x	-0.06*	-35.11	0.09*	18.42	x	x	x	x	0.04*	x	0.12	13.11
	TD	x	x	x	x	x		0.35**	69.21	x	x	x	x	x	x	x	x
F3	ASD	x	x	0.03	13.41	-0.03*	-24.97	0.22*	26.73	x	x	0.18**	52.63	-0.19*	-29.68	0.14**	9.67
	TD	-5.33*	-18.9	0.13**	14.85	0.14**	64.19	x	x	-13.78**	-7.41	0.08*	26.65	0.15	33.08	-0.23	-19.21
Fz	ASD	-26.39*	-73.9	0.04	38.06	x	x	x	x	-42.31*	-36.01	0.21	44.16	-0.01	x	0.06	4.32
	TD	-3.67	-10.78	0.06	3.94	x	x	x	x	20.92	43.54	x	x	x	x	x	x
F4	ASD	x	x	0.04**	28.36	-0.05	-35.04	0.24**	18.14	x	x	x	x	-0.14	-35.82	0.12	25.00
	TD	-7.01*	-29.24	x	x	x	x	x	x	-8.27*	-17.24	0.09	27.02	x	x	-0.31	-28.91
F8	ASD	-30.04*	-102.3	x	x	x	x	0.19*	39.02	19.14	25.97	x	x	x	x	0.04**	3.69
	TD	x	x	x	x	0.14	78.74	0.25	49.00	x	x	-0.05*	-17.38	0.11**	25.92	x	x
T3	ASD	x	x	x	x	x	x	0.13*	27.43	x	x	x	x	x	x	0.05**	8.69
	TD	8.01*	-28.7	x	x	x	x	0.28	11.16	-13.69**	-35.05	x	x	x	x	0.14*	29.01
C3	ASD	10.32*	25.14	x	x	x	-28.52	0.18*	29.21	29.16*	52.81	x	x	x	x	-0.68	-34.21
	TD	-19.86*	-53.88	-0.30*	-22.71	x	x	x	x	-32.64*	-82.58	0.03*	9.44	0.11	34.93	x	x
Cz	ASD	x	x	x	x	x	x	0.08	17.06	x	x	x	x	x	x	-0.11**	-14.65
	TD	x	x	-0.11	-43.52	0.12**	92.02	-0.23*	-9.41	x	x	x	x	0.08*	19.37	x	x
C4	ASD	x	x	x	x	-0.03	-42.67	-0.15	-34.51	x	x	x	x	x	x	x	x
	TD	x	x	x	x	0.02	71.72	-0.2	-33.32	x	x	x	x	x	x	0.05**	8.98
T4	ASD	5.99	22.62	0.03**	30.01	x	x	x	x	x	x	x	x	x	x	-0.07*	-4.75
	TD	-5.75*	-22.6	0.04*	1.82	x	x	x	x	11.43*	38.56	x	x	x	x	x	x
T5	ASD	x	x	x	x	x	x	x	x	-28.02	-36.37	x	x	x	x	-0.18	-32.21
	TD	x	x	x	x	x	x	0.35*	13.52	x	x	x	x	x	x	0.13*	8.33
P3	ASD	21.1**	46.55	0.09*	59.61	-0.03*	-18.60	-0.19	-20.04	25.24	30.31	-0.23	44.77	-0.12	-30.51	x	x
	TD	-7.95*	-46.75	-0.14**	-65.19	0.13**	66.19	-0.52**	-63.10	-44.75*	-110.8	-0.16*	-26.54	0.11*	24.14	-0.15	-10.33
Pz	ASD	22.82*	133.7	-0.15	x	-0.07*	-40.61	x	x	x	x	0.15**	48.24	0.15	x	0.12**	15.30
	TD	10.4**	34.9	0.12*	39.29	0.09**	56.45	-0.57	-16.52	x	x	x	x	0.19	28.08	x	x
P4	ASD	x	x	0.08**	58.39	0.19**	83.07	-0.19*	-22.03	x	x	0.18*	27.96	0.21**	22.47	0.18	21.34
	TD	x	x	-0.12*	-59.76	0.05*	52.89	0.31**	61.59	x	x	-0.11*	-31.49	0.08	14.41	0.14	29.00
T6	ASD	9.87	x	0.05*	27.05	0.09*	67.64	x	x	x	x	0.21**	44.16	0.17*	27.83	-0.03	-27.81
	TD	-5.7**	-35.12	0.16	58.46	0.1**	50.77	-0.33**	-67.00	x	x	0.14	13.27	x	x	-0.15*	-31.43
O1	ASD	x	x	x	x	-0.13*	-23.59	0.12*	13.21	-38.92	-93.65	-0.13*	-26.27	0.08**	22.38	0.04	4.11
	TD	x	x	0.12*	62.60	0.01	5.08	0.29	14.52	19.50	-4.01	x	x	-0.10	-45.16	0.11*	7.66
O2	ASD	12.87*	63.7	0.08	6.02	x	x	-0.9	-37.65	19.47*	16.16	-0.07	-14.99	x	x	0.02**	5.32
	TD	10.64*	37.3	-0.31*	-25.21	-0.01*	-7.51	-0.24**	-12.12	x	x	0.05	17.69	-0.12*	-45.16	0.10*	13.65

Table S3: Comparison of mean MI values in overall task connectivity with resting-state connectivity, and 2-back with 0-back level for each group.

Group	ASD			TD		
Experiment	Electrode	Mean Difference	t-test	Electrode	Mean Difference	t-test
Overall-resting	F8-O1	-0.47	-8.2	Fp1-P3	-0.89*	-28.99
	F3-O2	0.62*	10.74	T5-P3	0.54**	-34.97
	Fp1-Fz	0.52**	10.95	P3-P4	-0.48	-32.00
	P3-O1	-1.54*	-11.21	P3-T4	-0.58*	-20.62
	F3-T5	0.53	7.62	P4-O2	0.32	8.60
	FP2-P4	0.11**	72.83	P4-T6	-0.36*	-21.27
	T5-P3	0.48*	48.92	C3-P3	-0.30	-14.56
	T3-T4	-1.43	-29.55	C4-O2	-0.33**	-31.43
	Fp1-P3	-0.27*	-37.82	F7-C3	-0.39*	-63.50
	O1-O2	-0.26**	-36.95	Fp2-T4	0.31	20.17
	F7-F8	-1.49*	-33.04	F7-Fz	0.57	13.40
	T4-O2	1.22**	61.04	T3-T4	0.45*	56.41
	P3-T4	-1.04*	-44.67	T4-P4	0.56*	17.12
	P4-O2	1.12	117.95	T4-O2	0.32**	27.20
	P4-T6	1.49*	79.61	F8-P3	0.20*	12.42
	P3-P4	-0.13	-54.27	T3-O1	0.53	21.43
	F3-F4	1.25**	19.21			
	F8-P4	1.54	24.56			
2-back – 0-back	Fp1-P3	0.41	12.46	T4-P4	-0.31*	-22.81
	Fp1-Fz	0.73	9.56	T6-O2	-0.28	-14.08
	T5-P3	-0.12	-11.13	T3-O1	-0.39**	-14.26
	P3-Pz	0.27**	20.85	T4-O2	-0.32	-16.49
	Fp1-T5	0.11	21.04	Fp2-T3	0.53	32.23
	Fp1-F4	0.56*	13.45	T3-P4	0.74	50.63
	Fp2-T6	-0.08	-19.26	C3-F3	0.72*	17.18
	F7-Fz	0.43**	17.82	C4-Cz	1.01	46.76
	Fp2-F3	-0.12*	-32.54	F3-T5	0.73*	30.54
	F3-Fz	0.42	29.32	Fp1-F7	1.00**	24.26
	F3-F7	0.31**	15.62	T4-Cz	-0.42	-13.35
	F4-T6	0.27*	65.32	F3-F4	-0.12*	-28.92
	F8-Fp1	-0.25	-72.32	Fp2-C3	0.34	25.45
	F8-T6	-0.11*	-31.98	T3-F7	1.31	17.21
	F8-P4	-0.52	-29.03	P3-O2	-0.87	-19.81
	C4-T6	-1.02**	-10.05	C4-F8	-0.65*	-22.93
	T6-P4	-0.49	-35.92	P4-Cz	-1.47*	-21.34
	P4-O1	0.43**	42.25	T5-O1	-0.83**	-33.54
	T4-O2	-0.52	-39.67	F3-Fz	-0.88	-42.81
	T5-T6	-0.09	-20.93	T6-Cz	0.32	-29.47
	P4-P3	0.13*	34.87			
	T5-O1	-0.13**	-11.92			

(p< 0.001;<0.005;**p<0.05)

Supplemental References

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