© JP 2020 J Psychology, 11(1-2): 1-11 (2020)
PRINT: ISSN 0976-4224 ONLINE: ISSN 2456-6292 DOI: 10.31901/24566292.2020/11.1-2.197

Working Memory as Endophenotypes in First-Degree Relatives of Children with Neurodevelopmental Disorders: An Indian Account

Kamlam Gopalkrishnan Iyer and S. Venkatesan

[1]Department of Studies (DOS), University of Mysore, Mysuru 570 006, Karnataka, India
E-mail: iyerkamlam@gmail.com
[2]Department of Clinical Psychology, All India Institute of Speech and Hearing, Manasagangotri, Mysuru 570 006, Karnataka, India
E-mail: psyconindia@gmail.com

KEYWORDS Cognitive. Executive Functions. Heritability. Parents. Probands. Tasks

ABSTRACT Few studies from India have undertaken research on neurocognitive endophenotypes in neurodevelopmental disorders (NDD). Hence, the researchers'objective was to assess one of the criterion of a neurocognitive endophenotype -- heritability. This study assesses an association between the children with neurodevelopmental disorders (NDD) and their first-degree relatives (FDR)--parents in working memory (WM) performance, using a framework of a unified definition of NDD. Additionally, differences in gender of parents in WM performance were assessed. A two-group cross-sectional design with 42 probands of NDD and their 54 parents (both mothers and fathers) were assessed on a similar WM battery of tests. Correlation between probands and parents and between mothers and fathers yielded no significant differences in their respective WM performance. The need for better statistical, methodological measures in the hands of an isolated researcher was highlighted along with the discussion in light of the concept of an endophenotype.

INTRODUCTION

Development refers to a period of rapid skill acquisition (Stoodley 2016). Neurodevelopment is defined as a dynamic link and interplay between many processes across one's developmental period. These processes are genetic, emotional, cognitive, behavioral in nature. Any powerful and continual disturbance to these processes--either through environmental and/or genetic risk factors can lead to neurodevelopmental disorders (NDD) and disability (Boivin et al. 2015). Many conditions of NDD are regarded as highly heritable (Thapar 2020).

Much evidence is contributed to such genetic studies with inputs from neuropsychology (Boivin et al. 2015). Neuropsychology has assisted in understanding the polygenic phenotypes and the endophenotypes (Kremen et al. 2016). Endophenotype is defined as a heritable subclinical trait associated with the disorder, present whether or not the illness is in an active state, existing in families, and observed in an unaffected family member rather than the general population (Gottesman and Gould 2003). The study of endophenotypes is essential as they help in identifying the "at-risk" individuals, understanding the genetic or biological pathophysiology of a disorder, and in demarcating the deficits in cognitive, behavioral, or physiological traits underlying polygenic phenotypes, but in the same diathesis (Park and Gooding 2014). Many criteria apart from that provided by Gottesman and Gould (2003) have been discussed (Bearden and Freimer 2006) in defining a neurocognitive function as an endophenotype. The following criteria as provided by Rommelse and colleagues (2008) could be considered vital for ascertaining a neurocognitive endophenotype:

1. It is associated with the disorder.
2. It is heritable and has a correlation between biological family members. Genetically, the same genes might influence both the phenotype and endophenotype.
3. It is observed in non-affected first-degree relatives (FDR) to a larger degree than the general population, as the FDR is more prone to bear some of the susceptible genes of the disorder.

Several studies have explored the use of neurocognitive endophenotype constructs in the area of NDD. Some such studies highlight how executive functions (EF) have shown considerable evidence of meeting the criteria of this construct as a practical domain (Rommelse et al. 2011).

Address for correspondence:
Ms. Kamlam Gopalkrishnan Iyer
Phone: 9632685294
E-mail: iyerkamlam@gmail.com

Working memory (WM) is understood as a core component of EF (Miyake et al. 2000). With the plethora of research come varied definitions of WM (Cowan 2017). Nevertheless, Baddeley (2010) theorizes WM as a "multi-component system" that holds, manipulates, and controls multi-dimensional information briefly. WM serves the basis for the entire learning and language development. Impairments of the same would be seen in many domains of development as well (Park and Gooding 2014).

The Rationale for the Present Study

The researchers attempted to understand if WM could be considered a neurocognitive endophenotype in the diathesis of NDD due to the following reasons.

1. The endophenotype approach towards understanding NDD has been studied numerous times in the western world. Indian studies using the same approach have been attempted for schizophrenia (Solanki et al. 2016; Holla et al. 2020), bipolar disorder (Kumar et al. 2015), and obsessive-compulsive disorder (Rao et al. 2008) but not for NDD, as per our current review.
2. Generally, a combination of cognitive functions has been addressed as an endophenotype (Doyle et al. 2005; Thissen et al. 2014; Van Eylen et al. 2017), barring a few studies.
3. Studies assessing candidate neurocognitive endophenotypes are extensive in the area of ASD and ADHD and highly limited to other disorders of neurodevelopment (Rommelse et al. 2011). Hence this study would look into the primary defining context of "functioning" in NDD, lumped together as a group.
4. NDD is approached in a unified way. That is if NDD is looked at as a dimensional trait, it offers more flexibility, both for research and clinical practice (Rutter and Pine 2015). Furthermore, the problems exist of co-morbidity and co-occurrence of many symptom patterns in NDD due to shared genetic risks and biological characteristics (Thapar and Rutter 2015). This might make it challenging to seek single patterns of symptoms of a disorder (Rutter and Thapar 2014). The same disorders can also give mixed patterns of symptoms in different children, which certainly goes against clarity and understanding, especially in research (Thapar and Rutter 2015).
5. Gender differences in cognitive performances in FDR has been noted to be sparse (Nigg et al. 2004; Losh et al. 2009). Hence examining the role of the parent (vis-a-vis their gender) could bring viability to the construct of endophenotype.

Objectives of the Study

The main objective is to evaluate the criterion of heritability using WM as an endophenotype in parents and their children with NDD. Additionally, we seek to evaluate the WM performance of each parent (vis-a-vis their gender).

Research Questions

The following research questions have been formulated in the background of the aforementioned rationale:

1. Is there a correlation between the probands and their parents in WM performance, thereby constituting a cognitive endophenotype?
2. Are there any gender differences in the WM performance, in parents?

Operational Definitions

1. NDD is any impairment in the developing brain and/or the CNS originating during the developmental period and characterized by delay by three or more months or disturbance in the acquisition of skills in at least two domains such as motor, sensory, speech, and language, social, cognition, play and academics as measured on valid tools.
2. WM is the ability to store and manipulate information for brief periods. It covers verbal and visuospatial facets as measured by N-back and spatial span tasks.
3. FDR is the parents of the NDD probands.

METHODOLOGY

A two-group cross-sectional study was designed and the sample was recruited, only with the written consent of the parents. The data included in the manuscript is compliant with all the ethical rules as necessary for bio-behavioral research (Venkatesan

2009a). The period of collection of the data was from August 2019 to January 2020.

Participants

A non-probability purposive technique was used to collect the sample. The sample consisted of NDD probands (N = 42) in the age group of 6 to 8 years with both boys and girls included; their parents (N = 54) in the age group of 25 to 48 years, with both mothers and fathers, included. The families were of Indian origin, right-handed with no visual-hearing impairment.

Recruitment of NDD Probands and Their Parents

Families who approached the multispecialty clinics/hospitals/speech therapy clinics/special education centers were contacted and invited to participate in the study. Criteria for the inclusion of the probands and their parents were according to Table 1. A flow diagram depicting the recruitment of the final sample is given in Figure 1. NDD probands consisted of 32 boys (76.2 %) and 10 girls (23.8 %). Though the efforts were toward including both the parents, only a few families consented, and so the final target group consisted of 42 mothers (77.8 %) and 12 fathers (22.2 %).

Tasks and Procedure

The investigators used a computer coded and amenable data intake and record sheet for every child to facilitate ease of scoring and administration of the measures. Complete obstetric, behavioral and developmental history was taken. The results of the same have been discussed elsewhere (Gopalkrishnan and Venkatesan 2020). The probands and their parent/s were assessed in well-lit rooms of either the clinics/centers or their homes in two or three sessions of 50 minutes each by the investigator who has a Rehabilitation Council of India (RCI) approved pre-doctoral qualification in clinical psychology. The investigators were not blind to the diagnosis of the probands while assessing their parents. The details of the tasks presented are provided in the following interrelated sections.

1. ***Assessment of background variables in probands:*** They were assessed on the following measures of development and intellectual ability.
   (a) Assessment of development was done using the Activity Checklist Developmental Disabilities (ACPC-DD) (Venkatesan 2004). The number of items in each of the eight child development domains is fixed at 50 items. On each item, the child receives a score from 0 to 5 depending on the level of assistance required to perform that given item. Children with delays of three or more months and in at least two domains were included.
   (b) Intellectual ability was assessed using the Binet Kamat Intelligence Scale (BKIS; Kamat 1967; Venkatesan 2002). It is a normatively indexed age-scale. Many sets of tasks combining both speed and power in its verbal, numerical, and visuospatial components are included. Scoring is in the form of credits for partial or complete successful completion of each task. Basal, Ceiling and Mental

Table 1: Inclusion criteria for probands and parents

S. No.	*Probands*	*Parents*
1.	In the ages of 6 to 8 years	Proband child staying together
2.	Having a delay of 3 months or more in at least any of the 2 developmental domains	Absence of any other medical/mental illness
3.	IQ of equal or above 70	Of Indian origin, speaking Tamil, English, Kannada or Hindi
4.	Staying with biological parents	Absence of any major life event/chronic illness/on psychotropic medication/head injury since the past 6 months
5.	Children not on medication for NDD	Formal education of graduation or above
6.	No other medical condition associated with NDD	Belonging to middle or upper socioeconomic status
7.	-	Biological parents/parent only
8.	-	Family size of 4 or 5, including themselves

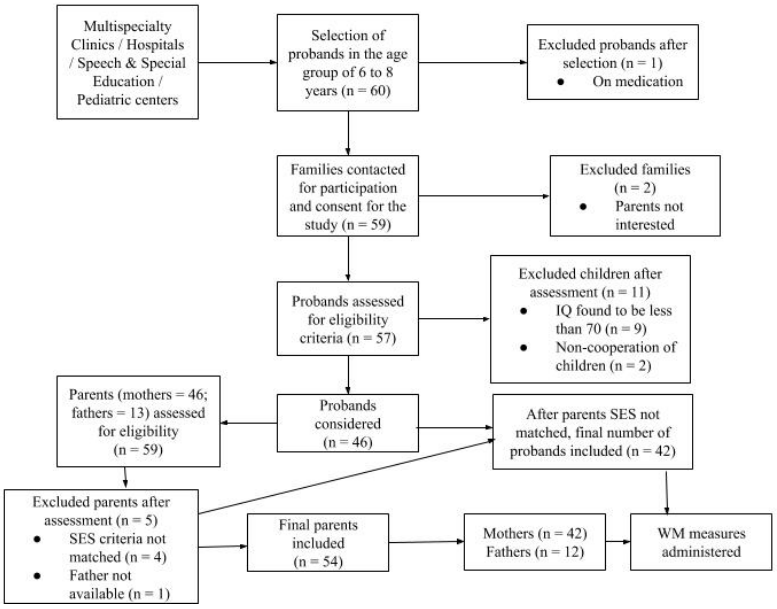

Fig. 1. Flow diagram depicting the recruitment of the sample

ages are computed to derive intelligence quotient (IQ) accordingly. All children above an IQ score of 70 were included.

2. ***Assessment of background variables in parents:*** Parents were assessed for the following variables using the measures as given below.
   (a) Socioeconomic Status: The family's SES was assessed using NIMH-SES readapted version (Venkatesan 2009b), as direct questions might elicit vague or inappropriate answers. A family SES score of 16 and above are included.
   (b) Screening for any current psychiatric morbidity: This was assessed using the Self Report Questionnaire (SRQ) (Kumbhar et al. 2012). A positive score of 10 and above is considered to be an indicator of psychiatric morbidity.
   (c) Screening for current cognitive functioning: This was assessed using the Hindi Mental Status Examination (HMSE) (Ganguli et al. 1995). This tool was used to obtain a clinical examination of higher mental functions and to rule out any cognitive impairments in the participants. A score of 17 and above is considered adequate cognitive ability.
3. ***WM measures:*** The measures of WM were administered to both the groups in random order as provided from the table of random sets generated using computer software (Urbaniak and Plous 2007). N-back and Spatial span tasks were incorporated to measure verbal and visuospatial components of WM for both probands and parents. The tasks for probands are from the NIMHANS Child Neuropsychological Battery (Kar et al. 2004) and for parents from NIMHANS Neuropsychological Battery (Rao et al. 2004) respectively. Verbal 1-back was presented for both probands and parents consisting of 30 consonants from Indian languages. The participant is to tap his hand on the table if the consonant gets repeated consecutively. The 2-back task for the probands consisted of 54 consonants while for their parents a list of 30 consonants was presented. The participant responds by tapping the table if the consonant gets repeated after an intervening

consonant. Visual 1 and 2 back tasks for both probands and their parents consisted of 36 cards of the same dimensions, with a black dot placed randomly on the card, again of the same dimension throughout. In the 1-back task, the participant is to respond by tapping the table, if the dot repeats itself in the same location, consecutively. In the 2-back task, the participant responds if the dot is seen at the same place after one intervening random card. The number of accurate responses and errors in both the verbal and visual tasks form a score (Rao et al. 2004).

The span task for the probands consisted of 1-inch cubes of 4 are arranged in a row with 1 inch in between, with the examiner tapping using the fifth cube for different sequences as provided in the NIMHANS Child Neuropsychological Battery (Kar et al. 2004). The child should repeat the sequence exactly like the examiner. Both forward and backward sequence is provided, and the accuracy scores are the number of correct sequences tapped for both the conditions. For the parents, the visuospatial task was assessed using the spatial span task (Milner 1971). It has a baseboard of 10 cubes of 3 cm each fixed to the board. The examiner taps the cubes in a particular sequence which increases in length at the successful completion of each trial. The forward and backward tests are both used in this study. Scoring is either 1 or 0 depending on the success or failure of the trial. The total score being the scores obtained on all the successful trials.

Data Analysis and Statistics

All analysis proper was conducted using the Statistical Package for Social Sciences (SPSS version 23.0) (IBM Corp 2014). Data were screened for normality using Shapiro Wilk's test, and depending on the obtained results, parametric (normal distribution) and non-parametric (skewed distribution) tests were conducted to infer appropriately.

RESULTS

The study's findings are presented in the following four distinct but interrelated headings: (a) Sample demographic characteristics (b) Distribution of WM scores in probands and parents (c) Correlational analysis and (d) Distribution of WM scores and gender differences (e) Additional analyses.

(a) Sample Demographic Characteristics

A perusal of demographic characteristics of the sample is provided in Table 2. It shows the probands (N: 42) were on average in the early childhood of development and studying in mostly senior kindergarten and grade I schooling. Table 2 depicts their mean level of intellectual functioning was in the below-average category with a marked delay in development. The age group of their parents (N: 54) ranged from 25 to 48 years. The parents belonged to high SES, with nil psychiatric morbidity and cognitive impairments at the time of assessment.

(b) Distribution of WM Scores in Probands and Parents

Table 3 provides the distribution of WM scores for both probands and parents. N back task parameters are defined as follows. An accuracy score is a correct response given by the participant.

Table 2: Demographic information on the descriptive variables of the study

Demographic variables	*N*	*Mean*	*SD*	*Range*
Number of probands seen	42	-	-	-
Boys to girls ratio	32:10	-	-	-
Age of probands	42	6.72	0.83	5.1-8.30
IQ	42	82.50	9.98	69-105
Developmental Score	42	1314.05	273.21	817-1862
The education level of probands	42	2.86	1.10	1-5
Number of parents seen	54	-	-	-
Number of mothers seen	42	-	-	-
Number of fathers seen	12	-	-	-
Age of mothers	42	35.17	4.77	25-48
Age of fathers	12	37.50	4.23	27-43
SES of parents	54	19.65	1.40	19-20
The score on SRQ in parents	54	18.72	0.98	17-20
The score on HMSE in parents	54	29.57	1.11	27-31

Table 3: Distribution of scores of probands and parents and in WM tasks

WM tasks	*Parents (n=54)*			*Probands (n=42)*		
	Median	*Mean ranks*	*IQR*	*Median*	*Mean ranks*	*IQR*
Verbal 1-back Accuracy scores	7.00	35.31	2.00	2.00	22.64	2.00
Verbal 1-back Omission errors	2.00	64.69	2.00	7.00	62.61	2.00
Verbal 1-back Commission errors	0.00	52.19	1.00	1.00	46.46	2.00
Verbal 2-back Accuracy scores	6.00	40.49	2.25	1.00	22.95	2.00
Verbal 2-back Omission errors	3.00	59.11	2.00	17.00	62.61	2.00
Verbal 2-back Commission errors	1.00	55.68	1.00	1.00	50.71	3.00
Visual 1-back Accuracy scores	6.00	39.88	2.00	1.00	29.32	1.25
Visual 1-back Omission errors	3.00	60.54	2.00	8.00	55.86	1.25
Visual 1-back Commission errors	1.00	56.70	1.00	2.00	42.75	3.25
Visual 2-back Accuracy scores	4.00	50.37	2.00	0.00	28.08	1.00
Visual 2-back Omission errors	5.00	49.33	2.00	9.00	57.35	1.00
Visual 2-back Commission errors	2.00	49.56	3.00	1.00	38.21	3.00
Spatial Forward Accuracy scores	5.00	52.31	2.00	2.00	25.86	1.00
Spatial Backward Accuracy scores	4.00	48.19	2.00	0.00	28.06	0.25
Spatial Total Accuracy scores	9.00	50.59	2.00	2.00	25.18	2.00

Omission errors are noted when the participant is unsuccessful to provide a correct response at the presentation of the correct stimulus. Commission errors are noted when the participant provides a response inaccurately at the presentation of a false stimulus. The distribution for WM scores presented across span tests forward and backward, 1-back as well as 2-back task conditions for both the probands and their parents depict similarities in the range of mean accuracy scores for all of the tasks. The highest mean rank was for the visual 1 task, and the lowest was observed for the verbal 1 task. The interquartile range (IQR) for verbal 1 and 2 tasks and for total spatial span tasks indicated higher variation as compared to the other tasks. Parents' profile of IQR for the tasks were almost similar to that of probands indicative of similar variation in accuracy scores. The mean ranks for visual 2 and spatial span tasks were the highest as compared to the verbal 1 and 2 and visual 1 tasks. The next level of analysis pertains to the errors. The mean ranks of omission errors have been consistently higher for the probands except for the visual 2 tasks. On the contrary, the commission errors have been consistently higher for the parents.

(c) Correlational Analysis

Table 4 depicts the correlational analysis of WM performance between the probands and their parents. Probands were assessed for their association in WM performance on all the tasks with their mothers and fathers, respectively. None of the correlations have yielded any significant associations ($p<0.05$). Also, there seems to be an inverse relationship between the probands and parents on many task accuracy scores. This refutes the criterion on the heritability of WM as a cognitive endophenotype in parents of probands.

The next analysis of errors, as provided in Table 5 has also not yielded any significant correlations on all the tasks ($p<0.05$). Again, the inverse relationship between the probands and parents on errors could be observed. The results on accuracy scores and errors support the researchers' first research question negatively.

Table 4: Correlation analysis between probands and mothers/fathers on WM tasks

WM tasks	*rho**	
	Probands - Mothers (n=42)	*Probands - Fathers (n=12)*
Verbal 1-back Accuracy Scores	-0.097	0.394
Verbal 2-back Accuracy Scores	0.024	0.078
Visual 1-back Accuracy Scores	-0.156	0.184
Visual 2-back Accuracy Scores	0.006	-0.175
Span Forward Scores	0.041	-0.134
Span Backward Scores	-0.129	-0.084
Span Task Total Scores	0.006	-0.111

[rho* obtained using Spearman's correlation test]

Table 5: Correlation analysis between probands and mothers/fathers on N-back Task Errors

N back task errors	*rho**	
	Probands - mothers (n=42)	*Probands - fathers (n=12)*
Verbal 1-back Omission errors	-0.066	0.394
Verbal 1-back Commission errors	0.270	0.048
Verbal 2-back Omission errors	0.026	0.112
Verbal 2-back Commission errors	0.155	0.367
Visual 1-back Omission errors	-0.140	0.184
Visual 1-back Commission errors	0.253	-0.304
Visual 2-back Omission errors	0.000	-0.175
Visual 2-back Commission errors	0.122	0.091

[rho* obtained using Spearman's correlation test]

(d) Distribution of WM Scores and Gender Differences

Table 6 denotes distribution of WM scores vis-a-vis parental status (gender). It depicts no significant differences between mothers and fathers in WM performance. This answers the researchers' second research question negatively.

(e) Additional Analysis

An additional analysis of assortative mating (Wong et al. 2006) was conducted to rule out the possible dependence of the scores in the mothers and fathers in WM performance from the same families. This was done to understand if other factors are influencing the pattern of results in gender. Table 7 depicts no significant mother-father correlations on the accuracy scores or the errors, except for the verbal 1 task accuracy scores ($r = 0.529$; $p < 0.05$) and verbal 1 omission errors ($r = 0.529$; $p < 0.05$). This association of significance depicts the mothers' and fathers' performance is similar in verbal 1 task and their omission errors committed.

DISCUSSION

This study assessed the performance of probands with NDD and their FDR (parents) across a set of tasks assessing verbal and visuospatial WM. Based on the research questions raised, it was found that (a) WM performance in probands is not correlated with parents and (b) No gender differences were found between mothers and fathers in WM performance. In the following sections, we researchers' these two findings.

Table 6: Distribution of scores between mothers (n=12) and fathers (n=12) in WM tasks

WM tasks	*Mothers (n = 12)*			*Fathers (n = 12)*			*Probability**
	Median	*Mean ranks*	*IQR*	*Median*	*Mean ranks*	*IQR*	
Verbal 1-back Accuracy scores	7.00	11.79	1.50	7.00	13.21	1.75	0.607
Verbal 1-back Omission errors	2.00	13.21	1.50	2.00	11.79	1.75	0.607
Verbal 1-back Commission errors	0.00	12.33	1.00	0.00	12.67	1.00	0.889
Verbal 2-back Accuracy scores	6.00	10.79	2.00	7.00	14.21	1.75	0.225
Verbal 2-back Omission errors	3.00	14.21	2.00	2.00	10.79	1.75	0.225
Verbal 2-back Commission errors	1.00	14.00	2.50	0.00	11.00	1.75	0.254
Visual 1-back Accuracy scores	6.00	11.29	2.00	6.50	13.71	1.75	0.386
Visual 1-back Omission errors	3.00	13.71	2.00	2.50	11.29	1.75	0.386
Visual 1-back Commission errors	2.00	13.29	1.75	2.00	11.71	1.75	0.565
Visual 2-back Accuracy scores	4.00	10.71	3.00	4.50	14.29	2.75	0.203
Visual 2-back Omission errors	4.50	14.08	3.00	4.50	10.92	2.75	0.259
Visual 2-back Commission errors	2.50	13.67	2.50	2.00	11.33	2.00	0.410
Spatial Span Forward scores	5.00	11.21	2.00	5.50	13.79	1.75	0.348
Spatial Span Backward scores	4.00	10.33	1.75	5.00	14.67	1.75	0.111
Spatial Span Total	9.00	10.42	2.75	10.00	14.58	3.25	0.140

[Probability* using Mann-Whitney non-parametric test]

Table 7: Correlational analysis of scores between mothers (n=12) and fathers (n=12) in WM tasks

WM tasks	*Mothers- Fathers (n=12) rho**
Verbal 1-back Accuracy scores	0.529ψ
Verbal 1-back Omission errors	0.529ψ
Verbal 1-back Commission errors	-0.154
Verbal 2-back Accuracy scores	-0.099
Verbal 2-back Omission errors	0.340
Verbal 2-back Commission errors	-0.307
Visual 1-back Accuracy scores	-0.138
Visual 1-back Omission errors	-0.138
Visual 1-back Commission errors	0.492
Visual 2-back Accuracy scores	0.366
Visual 2-back Omission errors	0.457
Visual 2-back Commission errors	0.336
Spatial span Forward scores	0.331
Spatial span Backward scores	0.101
Spatial span Total	0.439

[*rho using Spearman's Correlation; ψp < 0.05]

(a) Is there a correlation between the probands and their parents in WM performance, thereby constituting a cognitive endophenotype?

Studies have reported mixed findings concerning familiarity or heritability using correlational analysis. Nyden et al. (2011) conducted a similar sample study with multiple incidence families of ASD, in order to decipher the neurocognitive deficits as endophenotypes. Eighteen families (18 fathers and 18 mothers) and 37 children, along with their affected and unaffected siblings were included. Results suggested no significant associations between parents and the children on the whole. On EF assessment, only planning accurate task responses were correlated significantly between fathers and children ($p<0.01$). Similar same task correlations were performed on ADHD probands and their parents and siblings in another large scale study (Nigg et al. 2004). This study recruited 176 mothers, 131 fathers, and 79 siblings of ADHD probands. The probands were categorized into combined ADHD, predominantly inattentive ADHD, and non-ADHD control groups. Many neuropsychological assessments encompassing EF were administered. No significant correlation was seen for WM tasks and therefore dropped for further analysis as candidate endophenotypes. Again another small scale study such as this, with 40 parents of children with a learning disability (LD), depicted no familial correlations between verbal working memory tasks along with reading skills (Bonifacci et al. 2014). These data between parent-child pairs lend some confidence to the methodology and statistical analysis of this study.

Numerous studies point to the differences between parents and NDD probands in comparison to the other control groups (Wong et al. 2006). Nevertheless, one large scale study on high-risk substance abuse families (376 parents and 434 children aged 12-17 years) were evaluated on IQ and EF abilities. This study conducted an elaborate factor analysis and family correlations were computed using statistical packages for genetic studies (S.A.G.E. 2004) on the data. Significant correlations were found on both the preliminary and advanced statistical analyses between mothers-children and fathers-children. This depicted the inter-transmission of EF in the family (Jester et al. 2009). In most of the studies reviewed, age and IQ have been covariates of the study.

In one recent study on EF (cognitive flexibility and response inhibition) on both probands with ASD and their unaffected parents, significant inter-correlations were observed, suggesting the presence of a dominant endophenotype in NDD (Schmitt et al. 2019).

The results obtained in the present study, could be discussed with a variety of possibilities. First, high SES indicating higher education and income levels of parents might be indicative of better IQ in them. This could have made the parents perform better on WM tasks in comparison to the probands. Friedman and his colleagues (2006) found a strong relation between WM capacity and intelligence, in comparison to the other EF abilities. The difference in the WM performance of probands with their control group TD children can be found elsewhere (Doyle et al. 2005). Second, the small size of the probands and parents could have limited the statistical power to detect a significant resemblance between the groups (Murphy and Barkley 1996). Although when an endophenotype is identified in a given disorder in a population, it is linked as a causal factor rather than as the effects of the disorder (Cannon and Keller 2006). Appropriate samples and rich analytic strategies are required to establish causal-pathway and heritability of an endophenotype. This approach is also noted to be not in the scope of many

investigators, especially working in isolation (Miller and Rockstroh 2013). Nevertheless, if a significant resemblance was established in this study, further research along the same lines of hypothesizing WM as a neurocognitive "biomarker" of NDD and their unaffected relatives in this study's population could be pursued. In this context, another possibility is the lack of information on the deficit in WM performance of the parents of NDD probands vis-a-vis a control group of parents of TD children. Only this would help the researchers' explain the heritability criterion and help the researchers' better explain the non-association between the parents and probands of the present study.

Thirdly, Kendler and Neale (2010) suggest that endophenotypes should be assessed using either of the mediational or the liability-risk models along with the best of statistical genetics, to ascertain the role of endophenotypes in any psychiatric disorder strongly. While this study could be considered a macro attempt based somewhat on the liability-risk model using pairs of relatives, many design parameters could be bettered for the heritability or familiarity factor to emerge.

Fourthly, an aspect that requires a check could be measurement errors in the study. Varied settings of home/clinic were utilized based on the convenience of the participants for the administration of the tasks. This could have resulted in the participants getting affected by many state effects, albeit temporarily. Multiple sessions and their different timings contributing to ambient noise, temperature, transient changes in mood due to stressors of everyday living/consumption/withdrawal from the caffeine in parents could be a reason for no relationship between the probands and parents in WM performance (Iacono 2018).

A fifth possibility of importance in such family studies is the environmental variables (Bonifacci et al. 2014). Since neuropsychological studies have become strategic points of research in understanding NDD, controlling environmental factors would be pertinent (Boivin et al. 2015). Endophenotypes could reflect the environmental etiological factors (Kendler and Neale 2010), which if accounted for in a study, could bring a better possibility of indexing the heritability/familiarity criterion in an endophenotype.

Endophenotypes were conceptualized to be disorder-specific (Gottesman and Shields 1972), but psychiatric illnesses are widely heterogeneous in nature (Iacono 2018). Comorbidity with symptom overlap in NDD (Thapar et al. 2017) may be reflected in multiple endophenotypes, making them transdiagnostic (Iacono 2018). Still, the further possibility could be that genetic heterogeneity is as complex as phenotypic heterogeneity in NDD. This is due to the current unified definition of NDD used in this study. It needs to be reinstated that better research facilities in our country would bring in better design and a larger sample. This might help us to bring out cognitive traits underlying such polygenic phenotypes with the one diathesis of NDD.

(b) Are there any gender differences on the WM performance in parents of probands with NDD?

Consistent with the researchers' findings, Wong et al. (2006) included evaluations of EF on the gender of parents in their study on ASD families. On assessing WM tasks, no significant differences in gender were observed for the same. Additional analyses of assortative mating depicted no effects were attributable to the non-significant results. Only a few studies have explored such gender differences in parents of probands of NDD. Still further in gender evaluations concordant with such family studies, there is an under-representation of unaffected fathers of probands. This study's small sub-sample size could be a reason why specific gender patterns could not be delineated. The researchers evaluated the additional effects of the assortative mating of these parents. That is if they are interdependent on each other on these abilities. The researchers found no significant association in all tasks and their errors except for the verbal 1 task and its omission errors. This explains the results obtained for the verbal 1 task but not the others.

Bonifacci et al. (2014) in their study found no significant correlation amongst the fathers and mothers of children with LD on verbal WM tasks. And no significant difference was reported between them on the verbal WM task of digit span. Contrary to the researchers' findings, Hughes et al. (1997) found a significant difference in the performance between mothers and fathers of children with ASD on the planning tasks. Fathers performed poorly in comparison to mothers on further evaluation.

CONCLUSION

WM is important for day-to-day activities and is highly essential for a developing child. Its implications are imperative to all the domains of development.

The present study does not support the heritability of WM as a cognitive endophenotype in parents of children with NDD. This study's attempt of using a unified definition of NDD in endophenotype research currently has only been able to provide a macro outlook. This could be due to the transdiagnostic nature of both the NDD and endophenotypes. Furthermore, no differences in WM performance is noted in the mothers and fathers of children with NDD.

RECOMMENDATIONS

An appropriate methodology with rich strategies for analyses is required in order to establish the familiarity and/or heritability of an endophenotype. Therefore, a multivariate and multilevel approach to such studies from our subcontinent would help us contribute significantly to the other research studies across the globe.

ACKNOWLEDGMENTS

We are indebted to all the parents and children without whom, this study would not have been possible.

REFERENCES

Baddeley A 2010. Working memory. *Curr Biol*, 20: R136-140. DOI:10.1016/j.cub.2009.12.014.

Bearden CE, Freimer NB 2006. Endophenotypes for psychiatric disorders: Ready for primetime? *Trends Genet*, 22: 306-313. DOI: 10.1016/j.tig.2006.04.004.

Boivin MJ, Kakooza AM, Warf BC, Davidson LL, Grigorenko EL 2015. Reducing neurodevelopmental disorders and disability through research and interventions. *Nat*, 527: S155. DOI:10.1038/nature16029.

Bonifacci P, Montuschi M, Lami L, Snowling MJ 2014. Parents of children with dyslexia: Cognitive, emotional, and behavioral profile. *Dyslexia*, 20: 175-190. DOI:10.1002/dys.1469.

Cannon TD, Keller MC 2006. Endophenotypes in the genetic analyses of mental disorders. *Annu Rev Clin Psychol*, 2: 267-290. DOI:10.1146/annurev.clinpsy.2.022305.095232.

Cowan N 2017. The many faces of working memory and short-term storage. *Psychon Bull* Rev, 24: 1158-1170. DOI: 10.3758/s13423-016-1191-6.

Doyle AE, Faraone SV, Seidman LJ, Willcutt EG, Nigg JT, Waldman ID et al. 2005. Are endophenotypes based on measures of executive functions useful for molecular genetic studies of ADHD? *J Child Psychol Psychiatry*, 46: 774-803. DOI: 10.1111/j.1469-7610.2005.01476.x.

Friedman NP, Miyake A, Corley RP, Young SE, DeFries JC, Hewitt JK 2006. Not all executive functions are related to intelligence. *Psychol Sci*, 17: 172-179. DOI:10.1111%2Fj.1467-9280.2006.01681.x.

Ganguli M, Ratcliff G, Chandra V, Sharma S, Gilby J, Pandav R et al. 1995. A Hindi version of the MMSE: The development of a cognitive screening instrument for a largely illiterate rural elderly population in India. *Int J Geriatr Psychiatry*, 10: 367-377. DOI:10.1002/gps.930100505.

Gopalkrishnan IK, Venkatesan S 2020. Risk factors associated with neurodevelopmental disorders in high socioeconomic families: A brief Indian analysis. *Innovare J of Educ,* 8: 1-11.

Gottesman II, Gould TD 2003. The endophenotype concept in psychiatry: Etymology and strategic intentions. *Am J Psychiatry*, 160: 636-645. DOI:10.1176/appi.ajp.160.4.636.

Gottesman II, Shields J 1972. *Schizophrenia and Genetics. A Twin Study Vantage Point*. New York: Acad Press.

Hughes C, Leboyer M, Bouvard M 1997. Executive function in parents of children with autism. *Psychol Med*, 27: 209-220. DOI: 10.1017/S0033291796004308.

Holla B, Dayal P, Das A, Bhattacharya M, Manjula V, Ithal D, Dalachander S, Mahadevan J, Nadella RK, Sreeraj VS, Benegal V 2020. Transdiagnostic neurocognitive endophenotypes in major psychiatric illness. *medRxiv*. DOI: 10.1101/2020.02.14.20022863.

Iacono WG 2018. Endophenotypes in psychiatric disease: Prospects and challenges. *Genome Med*, 10: 11. DOI:10.1186/s13073-018-0526-5.

IBM Corp 2014. *IBM SPSS Statistics*, Version 23.0.

Jester JM, Nigg JT, Puttler LI, Long JC, Fitzgerald HE, Zucker RA 2009. Intergenerational transmission of neuropsychological executive functioning. *Brain Cogn*, 70: 145–153. DOI:10.1016/j.bandc.2009.01.005.

Kamat VV 1967. *Measuring Intelligence of Indian Children.* Oxford University Press.

Kar BR, Rao SL, Chandramouli BA, Thennarasu K 2004. *NIMHANS Neuropsychological Battery for Children-Manual*. Bangalore: NIMHANS Publication Division.

Kendler KS, Neale MC 2010. Endophenotype: A conceptual analysis. *Mol Psychiatry*, 15: 789–797. DOI:10.1038/mp.2010.8.

Kremen WS, Panizzon MS, Cannon TD 2016. Genetics and neuropsychology: A merger whose time has come. *Neuropsychol*, 30: 1-5. DOI: 10.1037%2Fneu0000254.

Kumar A, Solanki R, Satija Y, Gupta S, Singh P 2015. Neurocognitive endophenotypes in first degree relatives of bipolar affective disorder: an Indian experience. *Eur Psychiatr*y, 30: 179. DOI: 10.1016/S0924-9338(15)30145-0.

Kumbhar UT, Dhumale GB, Kumbhar UP 2012. Self Reporting Questionnaire as a Tool to Diagnose Psychiatric Morbidity. Natl J Med Res, 2: 51-54. From <https://scholar.google.com/scholar_url?url=http://njmr.in/home/download/42andhl=enandsa=Tandoi=gsb-ggpandct=resandcd=0andd=3367515704363736058andei=DUVsXq_QMIK5yQSPr7i4CQandscisig=AAGBfm2hXtMfVII6sNks-BjNKpXN9o_8wA> (Retrieved on 11 March 2020).

Losh M, Adolphs R, Poe MD, Couture S, Penn D, Baranek GT et al. 2009. Neuropsychological profile of autism and the broad autism phenotype. *Arch Gen Psychiatry*, 66: 518-526. DOI: 10.1001/archgenpsychiatry.2009.34.

Miller GA, Rockstroh B 2013. Endophenotypes in psychopathology research: Where do we stand? *Annu Rev Clin Psychol*, 9: 177–213. DOI:10.1146/annurev-clinpsy-050212-185540.

Milner B 1971. Interhemispheric differences in the localization of psychological processes in man. *Br Med Bull*. DOI: 10.1093/oxfordjournals.bmb.a070866.

Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD 2000. The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. *Cognit Psychol*, 41: 49-100. DOI:10.1006/cogp.1999.0734.

Murphy KR, Barkley RA 1996. Parents of children with attention-deficit/hyperactivity disorder: Psychological and attentional impairment. *A J Ortho Psychiatr*, 66: 93-102. DOI:10.1037/h0080159.

Nigg JT, Blaskey LG, Stawicki JA, Sachek J 2004. Evaluating the endophenotype model of ADHD neuropsychological deficit: results for parents and siblings of children with ADHD combined and inattentive subtypes. *J Abnorm Psychol*, 113: 614-625. DOI: 10.1037/0021-843X.113.4.614.

Nydén A, Hagberg B, Goussé V, Rastam M 2011. A cognitive endophenotype of autism in families with multiple incidences. *Res Autism Spectr Disord*, 5: 191-200. DOI: 10.1016/j.rasd.2010.03.010.

Park S, Gooding DC 2014. Working memory impairment as an endophenotypic marker of a schizophrenia diathesis. *Schizophr Res: Cognit*, 1: 127-36. DOI:10.1016/j.scog.2014.09.005.

Rao NP, Reddy YJ, Kumar KJ, Kandavel T, Chandrashekar CR 2008. Are neuropsychological deficits trait markers in OCD? *Prog Neuro-Psychopharmacol Biol Psychiatry*, 32: 1574-1579. DOI: 10.1016/j.pnpbp.2008.05.026.

Rao SL, Subbakrishna DK, Gopukumar K 2004. *NIMHANS Neuropsychology Battery- Manual*. Bangalore: NIMHANS Publication Division.

Rommelse NN, Altink ME, Oosterlaan J, Buschgens CJ, Buitelaar J, Sergeant JA 2008. Support for independent familial segregation of executive and intelligence endophenotypes in ADHD families. *Psychol Med*, 38: 1595-1606. DOI: 10.1017/S0033291708002869.

Rommelse NN, Geurts HM, Franke B, Buitelaar JK, Hartman CA 2011. A review of cognitive and brain endophenotypes that may be common in autism spectrum disorder and attention-deficit/hyperactivity disorder and facilitate the search for pleiotropic genes. *Neurosci Biobehav Rev*, 35(6): 1363-1396. DOI: 10.1016/j.neubiorev.2011.02.015.

Rutter M, Pine DS 2015. Diagnosis, diagnostic formulations, and classification. In: Anita Thapar, Daniel Pine, James F Leckman, Stephen Scott, Margaret J Snowling, Eric A Taylor (Eds.): *Rutter's Child and Adolescent Psychiatry.* 6th Edition. West Sussex, UK: John Wiley and Sons Ltd, pp. 17-30.

Rutter M, Thapar A 2014. Genetics of Autism Spectrum Disorders. In: Fred R Volkmar, Sally J Rogers, Rhea Paul, Kevin A Pelphrey (Eds.): *Handbook of Autism and Pervasive Developmental Disorders*. 4th Edition. New Jersey, USA: John Wiley and Sons Inc. DOI: 10.1002/9781118911389.hautc17, pp. 411-423.

S.A.G.E. 2004. Statistical Analysis for Genetic Epidemiology Release 5.0. From <http://darwin.cwru.edu/sage/pages/referencing.php> (Retrieved on 10 March 2020).

Schmitt LM, Bojanek E, White SP, Ragozzino ME, Cook EH, Sweeney JA, Mosconi MW 2019. Familiality of behavioral flexibility and response inhibition deficits in autism spectrum disorder (ASD). *Mol Autism*, 10: 47. DOI: 10.1186/s13229-019-0296-y.

Solanki RK, Kumar A, Satija Y, Gupta S, Singh P 2016. An Indian experience of neurocognitive endophenotypic markers in unaffected first-degree relatives of schizophrenia patients. *Indian J Psychiatry*, 58: 20-26. DOI:10.4103%2F0019-5545.174356.

Stoodley CJ 2016. The cerebellum and neurodevelopmental disorders. *Cereb*, 15: 34-37. DOI:10.1007/s12311-015-0715-3.

Thapar A 2020. ADHD: Progressing from genetic discoveries to biological insights. *Am J Psychiatry*, 177: 802-804. DOI: 10.1176/appi.ajp.2020.20070961.

Thapar A, Cooper M, Rutter M 2017. Neurodevelopmental disorders. *Lancet Psychiatry*, 4: 339-346. DOI:10.1016/S2215-0366(16)30376-5.

Thapar A, Rutter M 2015. Neurodevelopmental disorders. In: Anita Thapar, Daniel Pine, James F Leckman, Stephen Scott, Margaret J Snowling, Eric A Taylor (Eds.): *Rutter's Child and Adolescent Psychiatry.* 6th Edition. West Sussex, UK: John Wiley and Sons Ltd, pp. 31-40.

Thissen AJ, Rommelse NN, Hoekstra PJ, Hartman C, Heslenfeld D, Luman M et al. 2014. Attention deficit hyperactivity disorder (ADHD) and executive functioning in affected and unaffected adolescents and their parents: challenging the endophenotype construct. *Psychol Med*, 44: 881-892. DOI: 10.1017/S0033291713001153.

Urbaniak GC, Plous S 2007. Research Randomizer (Version 3.0). Computer Software. From<http://www.randomizer.org/> (Retrieved on 22 March 2019).

Van Eylen L, Boets B, Cosemans N, Peeters H, Steyaert J, Wagemans J et al. 2017. Executive functioning and local-global visual processing: candidate endophenotypes for autism spectrum disorder? *J Child Psychol Psychiatry*, 58(3): 258-269. DOI: 10.1111/jcpp.12637.

Venkatesan S 2002. Reappraisal of Bombay-Karnatak version of Binet Simon Intelligence Scales (1964). Indian J Clin Psychol, 29: 72-78. From < https://s3.amazonaws.com/academia.edu.documents/32852038/37-BKT-VALIDATION.pdf?> (Retrieved on 14 September 2019).

Venkatesan S 2004. *Children with Developmental Disabilities: A Training Guide for Parents, Teachers, and Caregivers*. SAGE.

Venkatesan S 2009a. *Ethical Guidelines for Biobehavioral Research*. Mysore: All India Institute of Speech and Hearing.

Venkatesan S 2009b. *Readapted Version for 2016: NIMH Socio-economic Status Scale*. Secunderabad: National Institute Mentally Handicapped Currently 'National Institute For Empowerment of Persons with Intellectual and Developmental Disabilities'.

Wong D, Maybery M, Bishop DV, Maley A, Hallmayer J 2006. Profiles of executive function in parents and siblings of individuals with autism spectrum disorders. *Genes Brain Behav*, 5: 561-576. DOI: 10.1111/j.1601-183X.2005.00199.x.

Paper received for publication in May, 2020
Paper accepted for publication in September, 2020