REVIEWS

A Bibliometric Review of Executive Function as Cognitive Endophenotypes in Parents of Children with Neurodevelopmental Disorders

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ABSTRACT

Purpose: *The main aim of this study was to review whether first-degree relatives (parents) and their children with neurodevelopmental disorders (NDD) are cognitive endophenotypes in executive functioning.*

Method: *A survey design was employed from May 2018 to January 2019, using an online and offline database of national and international ISSN Journals and ISBN books.*

Results: *A bibliometric analysis was conducted on 19 of the 63 reviewed studies. A PRISMA Flow diagram and Harvest Plot have been used to depict the results of the analysis*

Conclusion and Implications: *Delineation of executive functions (EF) as cognitive endophenotypes of NDD is, first of all, useful in exploring the genetic basis of these disorders; secondly, for identifying which cognitive traits may be important to it; and thirdly, to initiate and promote better educational practices and cognitive remediation. With a disclaimer that this analysis is only as inclusive as possible in the field of endophenotypes in NDD, limitations in the various studies have been identified, along with future suggestions for research.*

Key words: *genetic, Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD), working memory, inhibition, cognitive flexibility*

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INTRODUCTION

The genetics of cognition and brain-behaviour relationships in healthy and pathological states are a major aspect of research and treatment in this century (Kremen et al, 2016). In psychiatry and psychology, one method of understanding the gene action on behaviour is to have a clearly defined disease entity such as a diagnosis, for example with DSM 5 (Glahn et al, 2014). Another method is to use endophenotypes, which are heritable "markers" associated with disease genes and measurable in both affected and unaffected individuals (Glahn et al, 2014).

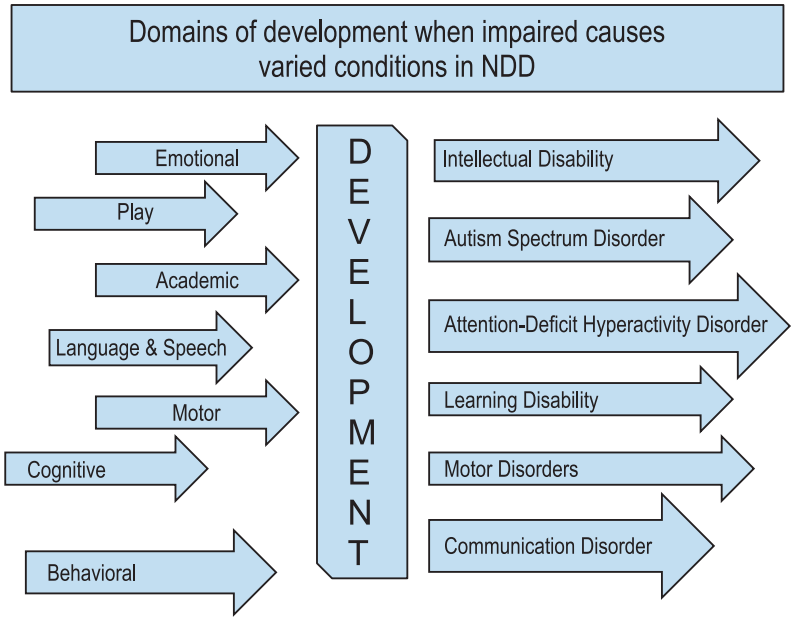
The term "neurodevelopment" is defined as the dynamic inter-relationship between genetic, brain, cognitive, emotional and behavioural processes across one's developmental life span (Boivin et al, 2015). Any significant and persistent disruption to this dynamic relationship through such factors as environment or/ and genetic, can lead to NDD and disability (Boivin et al, 2015). Though NDD are of importance, it has not been considered as a significant public health problem of children in a developing country like India (Rathi & Francis, 2009).

India has the world's largest birth cohort of about 26 million (Arora et al, 2018; Gavi, 2018). With better infant survival rates (Gavi, 2018) of the neonates born pre-term and with lower gestational age, the risk of NDD in countries such as India has increased (Zaka et al, 2018). The prevalence rates of NDD in Indian children in the age-group of 2-6 years were found to be between 2.9% and 18.7%, depending on the sites examined, according to the Inclen trust study (Arora et al, 2018). Children in the age-group of 6-9 years had prevalence rates of about 6.5% to 18.5% for any one of the aforementioned NDD, with 1/5th of these children having a co-morbidity of one or more NDD (Arora et al, 2018).

NDD are conditions that are difficult to conceptualise (Thapar et al, 2017). NDD arise due to impairments in the developing brain and/or central nervous system (Bakare et al, 2016). They originate during the developmental stages of the antenatal, post-natal, infancy and early childhood periods and are characterised by a delay or disturbance in the acquisition of skills under various domains such as motor, sensory, speech and language, social and cognition, presented in heterogeneous conditions such as Attention-Deficit-Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), Vision Impairment (VI), Epilepsy (Epi), Neuromotor Impairments such as Cerebral Palsy (NMI-CP), Hearing Impairment (HI), Speech and Language Disorders and Intellectual Disability (ID) (Jeste, 2015). Figure 1 presents a diagrammatic representation of the domains

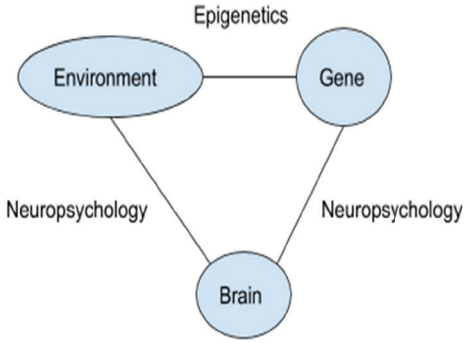
of development and the conditions of NDD. Many studies have established the genetic basis for a few of the NDD such as ADHD, ASD, and LD (e.g., Doyle et al, 2005a; Rommelse et al, 2008; Jester et al, 2009; Moll et al, 2014; Losh et al, 2017).

Figure 1: Diagrammatic Representation of Domains of Development and Conditions of NDD



Boivin et al (2015) suggest that genetic studies on NDD have been due to three mutually interactive domains, as given in Figure 2.

Figure 2: Interactive Domain of 3 Mutual Areas of Research (Boivin et al, 2015)



Taken from Boivin et al (2015)

Figure 2 suggests that epigenetics is the area of research between the environment and gene socio-evolutionary processes while neuropsychology is the strategic area of research between environment and brain as well as brain and gene processes (Boivin et al, 2015). One domain by which neuropsychology can contribute towards deciphering genes and brain and vice versa, is through the concept of endophenotypes (Glahn et al, 2014).

Endophenotypes are popular in psychiatry and psychology ever since their introduction by Gottesman and Shields in 1972 (Gottesman & Shields, 1976) and then later by Gottesman and Goulds (2003), due to their apparent proximity to genotypes (Insel & Cuthbert, 2009). If any symptoms of the disorder or traits of the disorder run in families by expressing themselves as subclinical, genetically meaningful traits, then they are believed to constitute endophenotypes (Losh et al, 2017). According to these researchers, heritability and stability (state independence) represent pivotal components of any useful endophenotype from the six criteria provided (Gould & Gottesman, 2006). These endophenotypes can be cognitive, neuroanatomical, biochemical, endocrinological or neurophysiological in nature (Cruz et al, 2013). The criteria for a neurocognitive function are provided by Rommelse et al (2008) as follows:

1. Heritability of neurocognitive dysfunction in which at least the same genes influence both the endophenotype and phenotype.
2. As the first-degree relatives are more likely to carry some of the susceptible genes of the disorder, neurocognitive dysfunction is to be seen in non-affected first-degree relatives of the proband.
3. Such neurocognitive dysfunction is observed in the disorder.

Hence, this states that for any neuropsychological deficits to be useful as endophenotypes, it is imperative to include both the affected and non-affected individuals in the study (Rommelse et al, 2008).

One of the functional domains for which there is considerable evidence of meeting the endophenotypic criteria in first-degree relatives having deficits, is that of EF (Rommelse et al, 2011). Also, as one of the factors affecting EF in parents, genetic studies have reported as much as 40-80% influence in EF skills in young children (Leve et al, 2013).

Just like any other neuropsychological constructs, EF is also wide- ranging and multidimensional. Many functions such as prioritising and sequencing of

behaviour, inhibiting familiar or stereotyped behaviours, maintaining a mental set or an idea of what task or information is needed at any moment, ignoring tasks that are irrelevant or distracting, switching between various relevant information, categorising, multi-tasking different situations or information are included in the term of EF (Banich, 2009).

Many views are prevalent on the cognitive components of EF and in the manner in which the frontal lobe is linked to various executive functions. Nevertheless, there is general agreement on three core components of EF which were given by Miyake et al (2000) and later agreed upon by many other researchers (e.g., Lehto et al, 2003). They are:

a. Inhibitory control or inhibitions of dominant or prepotent responses,

b. Shifting between mental sets or tasks also called cognitive flexibility,

c. Updating and monitoring of working memory representations.

From these basic components, other higher order cognitive functions of creativity, reasoning and decision-making adaptive behaviours emerge (Collins & Koechlin, 2012).

Executive Function, therefore, is an overall term referring to varied neuropsychological processes such as inhibition, working memory, cognitive flexibility/set shifting, fluency, planning and inhibitory control. EF processes involve a distributed cerebral network (Colette et al, 2006).

Objective

The main objective of this review is to explore such cognitive endophenotypes in first-degree relatives of children with NDD.

METHOD

Study Design

A survey research design was adopted for the purpose of this study. It was conducted from May 2018 – January 2019, using Google and MSN search engines in the following databases: NCBI, Semantic Scholar, Google Scholar, Researchgate and PubMed - where national and international publications in the field of psychology and neuroscience were available. Studies published from

1993 to 2018 were considered for review. The key words used were: Executive functions deficit in parents as endophenotype, Parental executive functions, Executive functions in parents, Autism endophenotype, ADHD endophenotype, Dyslexia endophenotype, Learning

Disability endophenotype, Cerebral palsy endophenotype, Families of Neurodevelopmental disabilities, Cognitive deficits in parents of children with NDD.

Procedure

Data collection procedure was according to the inclusion and exclusion criteria provided in Table 1.

Table 1: Inclusion and Exclusion Criteria

No.	Inclusion Criteria	Exclusion Criteria
1.	Any research article / book published in reputed Indian and/or International Journals	Opinion and Call-for-research papers in the area of Endophenotypes
2.	Original studies published in English Journals only	Studies that investigated only siblings and teachers in EF as Endophenotypes of children with NDD
3.	Study objectives with cognitive or EF in parents of children with NDD	Studies that investigated EF in parents of children with mental disorders
4.	Full-text articles with DOI only	Studies that investigated other cognitive functions such as face-recognition, phonetic processing, reading ability, visual processing, reaction time, memory, eye-movement tracking ability, Broader Autism Phenotypes, Cognitive models in ASD without EF, in parents as endophenotypes or biochemical or neuroanatomical endophenotypes in NDD

5.	Studies from 1993 to 2018 on EF as neuropsychological measure	Studies on EF in parents of adolescents and adults with ASD, ID, LD only

On the basis on inclusion and exclusion criteria, the studies reviewed in this article are depicted in the PRISMA Flow Diagram

Figure 3: PRISMA Flow Diagram (Moher et al, 2009)

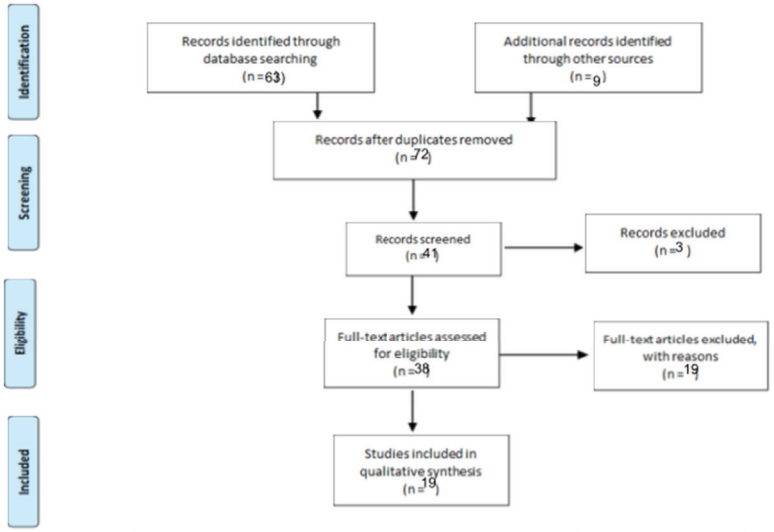


Figure 3: Prisma Flow Diagram depicting the procedure for review

(Moher et al, 2009) given in Figure 3.

RESULTS and DISCUSSION

In keeping with the aim of the paper, 19 studies were identified in the area of EF in parents of children with NDD, and their usefulness as neurocognitive endophenotype construct (Table 2).

Table 2: Studies on EF as endophenotypes in Parents of Children with NDD

Sl. No.	Sample Size of Parents	Type of NDD in children	EF Components Assessed	Results	References
1.	46 parents 33 parents 16 parents	ASD Down Syndrome TD	Verbal and Spatial WM & Language Comprehension	No significant difference between groups	Szatmari et al (1993)
2.	25 parents of children with severe symptoms 25 parents of children with mild symptoms 25 parents	ADHD ADHD TD	Attention, Set-shifting, Verbal WM	No significant difference between groups	Murphy & Barkley (1996)
3	48 parents 60 parents	ASD Down Syndrome	Planning	Significant difference between groups	Piven & Palmer (1997)
4	40 parents 40 parents 40 parents	ASD LD TD	Attention, Cognitive Flexibility, Planning, Spatial WM, Spatial STM	Few differences between parents of ASD and LD groups. Impaired EF in ASD group compared to control group	Hughes, et al (1997)

5	160 parents 36 parents 42 parents	ASD ID - Down Syndrome TD	Intellectual functioning having WM tasks, Reading and Spelling ability	No significant differences	Fombonne, et al (1997)
6	190 parents 79 parents 115 parents	ADHD COS TD	Attention, Set-shifting	No differences between groups	Asarnow et al (2002)
7	11 parents of children & adolescents 17 parents of children & adolescents	ASD TD	Spatial WM using oculomotor delayed response task	Significant difference found	Koczat, et al (2002)
8	165 parents 80 parents 141 parents	ADHD Combined type ADHD Inattentive type TD	Response Inhibition, Set-shifting, Planning and Processing Speed	Impairment in parents of combined ADHD type in set-shifting and processing speed	Nigg et al (2004)
9	106 parents 189 parents 243 parents	ADHD unaffected parents members ADHD parents affected TD	Set- shifting, WM, Attention and Response Inhibition	Impairments in both the parents of ADHD as compared to controls	Doyle et al (2005b)

10	62 parents 30 parents	ASD ID	Set-shifting ability, Planning, Visuo-motor function and attention	No significant effects seen	Bolte & Poustke (2006)
11	145 parents 96 parents	ASD TD	Planning, Set-shifting, Response Inhibition, Verbal and Nonverbal WM	ASD and control parents differed in WM and Set-shifting. No significant difference between planning or inhibition seen.	Wong et al (2006)
12	39 parents of children and adults with ASD 53 parents of children and adults 47 parents	ASD OCD TD	Planning, WM--Verbal Spatial, Attention, Mental Set--shifting	Compared to control parents, both ASD and OCD parents performed worse.	Delorme et al (2007)
13	76 parents 41 parents	ASD TD	Verbal WM	Significant differences between the groups	Gokcen et al (2007)
14	83 parents 32 parents	ASD TD	Planning, Set-shifting, Cognitive control	No significant difference found	Losh et al (2009)

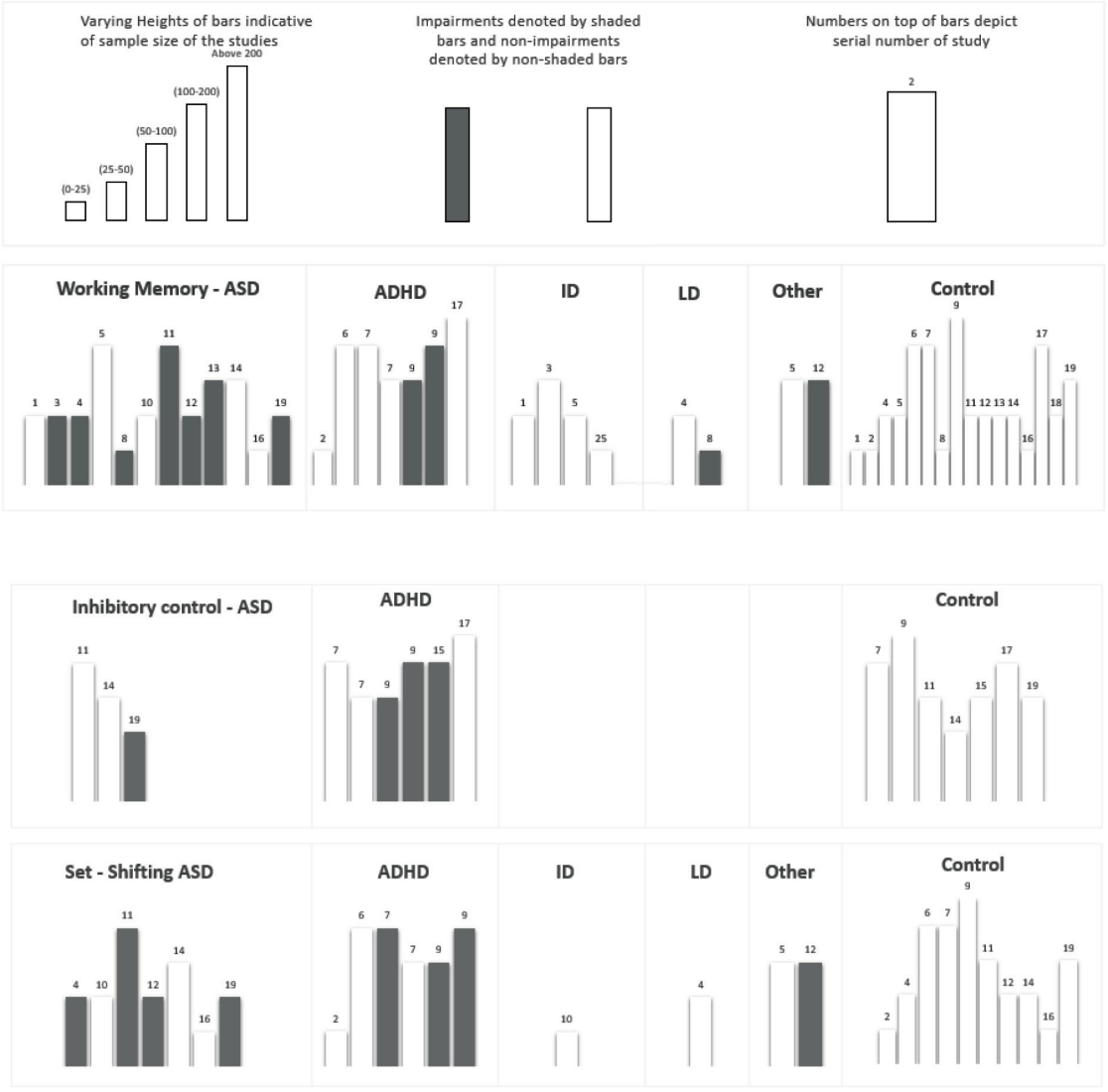
15	104 parents 88 parents	ADHD TD	Inhibitory control	Significant difference between the 2 groups	Goos et al (2009)
16	36 parents 28 parents	ASD TD	Planning and Set-shifting	All performed poor in EF tasks	Nydén et al (2011)
17	238 parents 147 parents	ADHD TD	Inhibition, Verbal WM, Spatial WM	No significant differences found	Thissen et al (2012)
18	40 parents 40 parents	LD TD	Verbal WM	Significant difference found	Bonifacci, et al (2013)
19	37 parents 58 parents	ASD TD	Inhibition, Cognitive Flexibility, WM, Planning	Significant difference in WM, Cognitive flexibility & Response inhibition	Van Eylen et al (2017)

[WM = working memory, ASD = Autism Spectrum Disorder, LD = Learning Disability ADHD = Attention Deficit Hyperactivity Disorder, ID = Intellectual Disability, OCD = Obsessive-Compulsive Disorder, COS = Childhood onset Schizophrenia, TD = typically developing]

These studies have been plotted in a Harvest Plot (Figure 4), which is a mainstay of this study. Harvest Plot, which was introduced by Ogilvie et al (2008), is a unique method of plotting a matrix of evidence gathered on a given topic (Crowther et al, 2011). This method presents information in a unique schematic manner, which can encompass any number of similar studies put in a definitive manner and is mostly used in interventional studies (Ogilvie et al, 2008); however, in the present instance, the same has been attempted on a survey design. The rows depict the three aspects of EF. The columns depict the varied conditions of NDD and the control population of normal adults, while rows depict the components of EF. The bars are depicted in varying heights, denoting the sample size of the study. The bars have numbers on them, again indicative of the serial number of

the studies as in Table 2. The shaded and unshaded bars are indicative of results showing significance and non-significance in the differences obtained between the NDD and control groups of the studies, respectively.

Figure 4: Harvest plot depicting evidence for components of EF as Endophenotypes in parents with children with NDD and their respective control groups.



Though this list is neither exhaustive nor all-inclusive in the domain of NDD and endophenotypes, these studies on first-degree relatives of NDD seem to have emerged from the genetic emphasis of ASD and Down syndrome in the late 1980s and 1990s. In ASD, the general cognitive impairments, communication, language and social skills were explored, mostly as a part of Broader Autism Phenotype (e.g., Bolte & Poustke, 2006).

Many neuropsychological aspects have been explored in the first-degree relatives of children with NDD such as intellectual functioning, EF, reading and spelling ability, eye-movement abnormality, local visual processing, Central Coherence Theory, Theory of Mind, reading speed, phonological awareness (Piven & Palmer, 1997; Koczat et al, 2002; Bolte & Poustke, 2006; Nyden, 2011; Bonifacci et al, 2013). After a clear enumeration of criteria on identifying the "endophenotype" in psychiatry and psychology (Gottesman & Gould, 2003), many family studies on ADHD, ASD and Schizophrenia, in particular, were published (Rommelse et al, 2008; Allen et al, 2009; Rommelse et al, 2011). Other areas where this construct was explored are bipolar disorders (Raust et al, 2014), major depression (Merikangas et al, 2017) and anxiety disorders (Müller et al, 2015).

One of the salient features of the reviewed studies has been the type of design used. All of them have a case-control group as the research design (Table 3). The age group of the parents in most of the studies has been in the range of 23 - 50 years, with both mothers and fathers considered, though there seems to be an underestimation of fathers in most of the studies (e.g. Szatmari et al, 1993; Murphy & Barkley, 1996; Asarnow et al, 2002; Nigg et al, 2004; Bolte & Poustke, 2006; Wong et al, 2006). The age group of the proband children varies from 2 -18 years (e.g., Asarnow et al, 2002; Doyle et al, 2005b; Goeken et al, 2009), with some studies considering adults with NDD and their parents (e.g., Piven & Palmer, 1997; Delorme et al, 2007; Thissen et al, 2012). Many studies have considered the siblings as well, along with parents (Wong et al, 2006; Delorme et al, 2007; Goos et al, 2009; Van Eylen et al, 2017).

Table 3: EF Studies and Nature of Study

Sl. No.	Study	Design of the Study	Aim of the Study
1.	Szatmari et al, 1993	Case-Control	To compare the siblings & parents of ASD probands with those of Down's Syndrome

2.	Murphy & Barkley, 1996	Case-Control	To examine if biological parents of ADHD children show impairment in EF tests as compared to biological parents of TD children
3.	Piven & Palmer, 1997	Case-Control	To examine rates of more broadly defined ASD phenotype in a sample of multiplex ASD families and comparison subjects
4.	Hughes, et al., 1997	Case-Control	To examine if impairments in EF are apparent in parents of children with ASD and, if so, whether they are associated with abnormalities in everyday interactional skills
5.	Fombonne, et al., 1997	Case-Control	To examine if the first unaffected relatives of ASD exhibit higher ID & impairments and show cognitive profile of BAP
6.	Asarnow et al, 2002	Case-Control	To examine the performance of first-degree relatives of COS and ADHD in neurocognitive assessments
7.	Koczat, et al.,	Case-Control	To evaluate whether the delayed oculomotor response task abnormalities demonstrated by ASD probands also exist in parents of ASD children
8.	Nigg et al, 2004	Case-Control	To evaluate the endophenotype neuropsychological hypothesis in ADHD-affected and unaffected relatives of children with ADHD
9.	Doyle et al, 2005b	Case-Control	To examine the neuropsychological deficits in relatives of girls with ADHD with unaffected and control group relatives

10.	Bolte & Poustke, 2006	Case-Control	To investigate the tendency for local processing style and executive dysfunction in parents of subjects with ASD as compared with EOS and ID
11.	Wong et al, 2006	Case-Control	To examine the potential endophenotypes for ASD by specifying the EF profile characterising BAP
12.	Delorme et al, 2007	Case-Control	To see if different components of EF in first-degree unaffected relatives of ASD & OCD are endophenotypes
13.	Gokcen et al, 2007	Case-Control	To examine if Verbal WM and different aspects of Social Cognition are endophenotypes of ASD
14.	Losh et al, 2009	Case-Control	To gain insight into neuropsychological features that index genetic liability to ASD
15.	Goos et al, 2009	Case-Control	To compare the inhibitory control in children with ADHD, their siblings and their parents
16.	Nyden, et al., 2011	Case-Control	To examine the endophenotype of ASD in multiple incidence families
17.	Thissen et al, 2012	Case-Control	To investigate the association between ADHD and EF during adolescence
18.	Bonifacci, et al., 2013	Case-Control	To examine if parents of children with LD show endophenotypes for reading disorders and other cognitive, behavioural, environmental characteristics as compared to children who are TD
19.	Van Eylen et al, 2017	Case-Control	To evaluate the endophenotypic criteria for EF and local global visual processing in ASD and TD relatives

[ASD = Autism Spectrum Disorder, TD = Typical Development, ID = Intellectual Disability, EOS = Early Onset Schizophrenia, ADHD = Attention Deficit Hyperactivity Disorder, EF =Executive Functions, BAP = Broader Autism Phenotype, COS = Childhood Onset Schizophrenia]

Most of the studies have stratified the sample on the basis of age, sex, IQ, socioeconomic status (SES) of the first-degree relatives (e.g., Murphy & Barkley, 1996; Fombonne et al, 1997; Hughes et al, 1997). All the assessments for EF have been chosen on the basis of the specific cognitive functioning they tap (e.g., Murphy & Barkley, 1997; Piven & Palmer, 1997; Wong et al, 2006) though limitations on account of not using a wide range of cognitive measures to tap EF have been reported (e.g., Szatmari et al, 1993; Doyle et al, 2005b; Losh et al, 2009). The use of more ecologically valid tasks for the assessment of EF is observed (Wong et al, 2006; Thissen et al, 2012).

Perhaps to yield more precision, measures from experimental neuroscience could be used, as suggested by Doyle et al (2005b). Studies have been particularly salient on account of the varied research questions probed in the first-degree relatives (parents) of children with NDD and the endophenotypic construct. For example, Doyle et al (2005b) attempted to study the relatives of female probands alone in the area of ADHD. This can be seen as important, as females might require more familial risk factors to express the disorder (Nigg et al, 2004; Doyle et al, 2005b).

Similarly, one of the first studies to report the cognitive, behavioural and emotional profile of the parents of children with LD is by Bonifacci et al (2013). A few studies have investigated probands with childhood-onset schizophrenia and probands with NDD in the context of executive function (e.g., Asarnow et al, 2002; Bolte & Poustke, 2006). Multiple incidence families in ASD and EF have been examined (Piven & Palmer, 1997; Nyden et al, 2011), though sparse in other conditions of NDD.

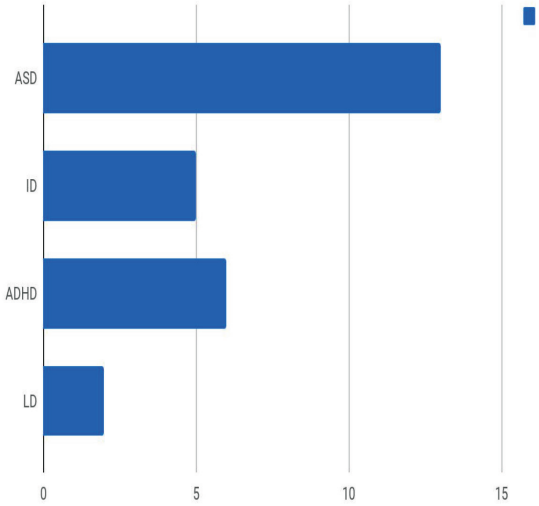
The need for a larger sample size has been stated in most of the studies reviewed. The researchers of many of these aforementioned reviewed studies have not been blind to the diagnosis of the probands during assessment of their relatives. This is another difficulty in such family studies, as it could introduce bias or other confounding factors (Piven & Palmer, 1997). Again, when participants have been recruited through a tertiary source of referral, as in some studies, the representativeness of the sample is a matter of concern (Fombonne et al, 1997).

In the analysis of the results obtained, there is a clear and significant difference in the parental groups of NDD as compared to their control groups, in 14 out of the 19 studies highlighted.

Moreover, the number of conditions in each of the NDD is also demarcated in this set of studies, as given in the bar chart in Figure 5. This shows that the first-

degree relatives in most of the studies are considered to be endophenotypes in comparison to their control group.

Figure 5: Number of Studies on Conditions of NDD



[ASD - Autism Spectrum Disorder; ADHD - Attention Deficit Hyperactivity Disorder; LD - Learning Disability; ID - Intellectual Disability]

Studies in neurocognitive endophenotypes are extensive in the area of ASD and ADHD and highly limited on other disorders of neurodevelopment. Furthermore, such studies are highly restricted in the Indian population. As per this review, there are also no reports on NDD within a single study, although there are various studies targeting ADHD, ASD, and LD separately.

CONCLUSION

Studies on endophenotypes from the field of neuropsychology have contributed to the field of epigenetics. It is important to identify such "markers" as cognitive endophenotypes of NDD, not only for theoretical reasons but also to provide further impetus to genetic investigations from fields such as neuropsychology. The current trend of neuropsychological traits seeking correlation with biochemical / neuroanatomical / physiological measures in NDD can also be observed (Baroni & Castellanos, 2015), which further highlights the immense scope of genetic studies in the present era.

Moreover, such studies might also guide the development of interventional and educational programmes (Moll et al, 2014).

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