



## NATIONAL MENTAL HEALTH RESEARCH STRATEGY

### BACKGROUND PAPER: Neurodevelopmental disorders (Session 6B)

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#### Introduction

This background paper adopts the DSM-5 definition of neurodevelopmental disorders, which is quoted below:

*The neurodevelopmental disorders are a group of conditions with onset in the developmental period. The disorders typically manifest early in development, often before the child enters grade school, and are characterized by developmental deficits that produce impairments of personal, social, academic, or occupational functioning. The range of developmental deficits varies from very specific limitations of learning or control of executive functions to global impairments of social skills or intelligence.<sup>1</sup>*

The current categories of neurodevelopmental disorders listed in the DSM-5 include autism spectrum disorders (autism), attention deficit/hyperactivity disorders (ADHD), intellectual disorders (ID), language disorders, specific learning disorders, and motor disorders.

#### Background

The prevalence of selected groups of neurodevelopmental disorders are presented in Table 1. There is a high degree of comorbidity between these conditions, and an estimate of the combined prevalence across all neurodevelopmental disorders is not currently known.

*Table 1. Estimated population prevalence of a selection of neurodevelopmental disorders.*

<b>Condition</b>	<b>Population prevalence</b>	<b>Country</b>	<b>Year published</b>	<b>Reference</b>
Language disorders	7.5%	UK	2016	Norbury et al. <sup>2</sup>
ADHD	4.2%	Australia	2019	Deloitte Access Economics <sup>3</sup>
Motor disorders	4%	UK	2009	Lingam et al. <sup>4</sup>
Autism	2.4%	Australia	2017	May et al. <sup>5</sup>
ID	1.7%	Australia	2016	Bourke et al. <sup>6</sup>

Neurodevelopmental disorders are diverse in their aetiology and phenotype, and so it is not possible to generalise specific research outcomes across all conditions. However, broadly speaking, there are several pillars of 'established' knowledge across these conditions:

- 1. Aetiology:** There is a significant heterogeneity in the aetiology of neurodevelopmental disorders, both between and within diagnostic categories. Taking autism as an example, twin studies indicate that both genetic and environmental factors contribute to the aetiology of the condition.<sup>7</sup> However, there is no single genetic cause that is common to all individuals with autism.<sup>8</sup> Genetic variants differ in terms of their nature and frequency of occurrence in the general population. Inherited genetic variants, which are passed from a parent to an offspring, can occur at all frequencies, from rare to frequent. *De novo* variants, which are not inherited from parents and are newly occurring in the offspring, are mostly very rare. A number of large-scale studies have found that the genetic variants that contribute to autism can span all frequencies and can be both inherited and *de novo*.<sup>9</sup> Environmental factors, such as a variety of pregnancy exposures, have also been associated with a small, increased likelihood of autism diagnosis.<sup>10</sup> The genetic and environmental risk factors lead to differences in neurotypical developmental trajectory, perhaps commencing during prenatal development. However, again, there is considerable variability in findings from neuroimaging studies, and no one brain difference has been observed in all individuals with autism.<sup>11</sup> A similar degree of aetiological diversity has been observed for other neurodevelopmental disorders, particularly ADHD,<sup>12</sup> language disorders<sup>13</sup> and intellectual disability.<sup>14</sup>
- 2. Diagnosis:** Because of the aetiologic variability, diagnoses of neurodevelopmental disorders are based on the behavioural observation of individuals, particularly within social, emotional, communication, and motor domains. Individual diagnostic categories are not considered 'one disorder' in the sense that there is a common cause shared by all individuals with that diagnostic label. Instead, each diagnostic category is best thought of as an 'umbrella term', which describes a range of different children, all with relatively similar behaviours, which may or may not be caused by the same biological factors.<sup>15</sup>
- 3. Phenotypic heterogeneity and comorbidity:** While individuals within a given diagnostic group all show a relatively similar cluster of symptoms (i.e., the diagnostic behaviours), there is a wide range in the severity of these behaviours between individuals. There is also significant comorbidity of neurodevelopmental conditions, which creates further phenotypic heterogeneity within diagnostic categories. For example, it is estimated that up to 59% total comorbidity rate between autism and ADHD.<sup>16</sup>
- 4. Interventions and treatments:** Behavioural therapies are the most common method of clinical intervention for children with neurodevelopmental disorders. While there are a large range of behavioural interventions available, each program typically aims to support the acquisition of developmental skills that are compromised and creating functional impairment in these individuals. There is now good evidence that early and sustained behavioural intervention can mitigate long-term disability and improve functional outcomes.<sup>17,18,19</sup> The development of pharmacological interventions have had mixed success with neurodevelopmental disorders. For example, there is good evidence for the efficacy of stimulant and non-stimulant medications for reducing the core inattentive and hyperactivity symptoms of ADHD.<sup>20</sup> However, there are currently no pharmacological interventions that have adequate evidence for improving the core symptoms of autism<sup>21</sup> and ID. Pharmacological interventions for these conditions target non-core symptoms such as sleep disturbances,<sup>22</sup> anxiety<sup>23</sup> and severe irritability,<sup>24,25</sup> with mixed efficacy.

**5. Endurance across the lifecourse:** While these conditions are most often diagnosed in childhood, they almost always persist into adolescence and adulthood.

A recent paper provided an analysis of autism research funding in Australia during the years 2013-2017 (see Figure 1),<sup>26</sup> summarised according to the categories defined by the Interagency Autism Coordinating Committee (IACC) in the US. The largest category of funding was for biological research (27% of total), followed by treatments and interventions (20%) and infrastructure and surveillance (e.g., biobank development, 20%). The smallest category of funding was for screening and diagnosis. While no data on research funding allocation in Australia for other neurodevelopmental disorders could be identified, there is no reason to believe that this would be substantially different to that observed for autism.

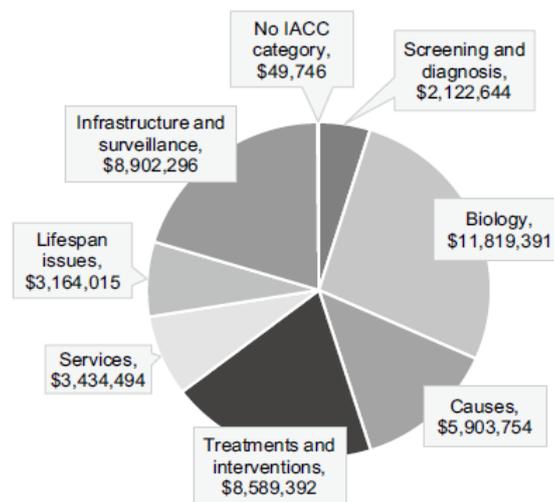


Figure 1. Distribution of autism research funding for the period 2013-2017<sup>26</sup>

### Gaps and uncertainties

Recent reviews have highlighted a number of key gaps in our understanding of neurodevelopmental disorders.<sup>27,28,29</sup> Some of these are described below, maintaining a focus on those gaps that provide a clear impediment to improving clinical care and long-term outcomes. Possible research questions that may help in filling these knowledge gaps are also provided.

#### **Optimising the early clinical pathway**

The operation and decision making of Health and Disability systems have not kept pace with scientific understanding. Currently, clinical service provision for neurodevelopmental disorders often commences at the point that a diagnosis is received (typically between 3 and 6 years of age), despite the clinical knowledge to identify symptomatology and functional impairments earlier in life. Recent diagnostic guidelines have highlighted that the dependence on the provision of a diagnostic label as the catalyst for clinical interventions is a flawed approach,<sup>30</sup> which not only ignores scientific evidence regarding the clinical heterogeneity incorporated within diagnostic labels, but also creates significant bottlenecks in service provision at the point of diagnosis. The recommended clinical approach is to provide intervention supports as soon as a clinical need is identified, irrespective of the presence or absence of a diagnostic label.<sup>19,30</sup>

- How does Australia develop an early childhood surveillance system that is both accurate in identifying neurodevelopmental disorders, and does not overwhelm downstream clinical services?
- How does Australia transition from diagnostic-driven clinical systems to a transdiagnostic system that provides service based on an individual's needs rather than the presence or absence of a diagnostic label?
- Can we develop and validate assessment tools that map directly to basic cognitive and biological processes, and therefore may be more clinically informative than diagnostic labels for determining effective treatment targets?

### ***Tailored interventions***

While there is now good evidence for a range of interventions that can mitigate long-term disability and improve functional outcomes, there remains little understanding about which individuals may benefit most from which pharmacologic and non-pharmacologic interventions. The current ‘trial and error’ approach to intervention decisions creates the potential for patient harm, and wastage of finite financial resources.

- Which existing pharmacologic and/or non-pharmacologic interventions are likely to lead to the best outcomes for any given clinical profile?
- What neurodevelopmental impairments, including common comorbidities, are not well served by existing interventions, and can we develop new interventions to meet these needs?
- How can existing and new interventions be scaled so that they are available to any individual that requires them, and at an affordable cost?

### ***Biological research***

The past two decades has seen an unprecedented level of biological research into neurodevelopmental conditions. While this research investment has resulted in a large volume of interesting and potentially important science, broadly speaking, the knowledge gained has not translated to better individual outcomes.

- How can existing knowledge of the biological pathways underpinning neurodevelopmental disorders biologic be used to improve individual outcomes?
- Are there additional areas of biological enquiry that are necessary or helpful to advance patient outcomes? Can we use existing infrastructure (e.g., biobanks) to achieve this knowledge, or is new infrastructure required?

### ***Complex presentations***

A significant minority of individuals with neurodevelopmental disorders have substantial difficulties with verbal communication, and are considered ‘minimally verbal’. A further minority of individuals exhibit severe and challenging behaviours, such as irritability, aggression and self-harm. These individuals with more ‘complex’ presentations have historically received limited research attention, despite the substantial impact of their disabilities on their day-to-day functioning (and that of their family), and the disproportionately intensive clinical resources required for their clinical management.

- Can we develop new interventions, or refine existing interventions, that provide better support to individuals with complex presentations (e.g., minimally verbal, or with severe and challenging behaviours) and their families.
- Can we scale these interventions to provide equitable access across the entire population?

### ***Primary and secondary education***

The school years are a bridge between early childhood and adulthood, and are not only critical in supporting intellectual development, but also in fostering social, emotional, communicative and behavioural skills. However, the school environment and mainstream curricula present unique challenges for students with neurodevelopmental disorders, and many schools and educators are not equipped to adequately cater to the needs of these children. As one example of this challenge, school exclusion is more common in children with neurodevelopmental disorders than in the general population.<sup>31,32</sup>

- What barriers currently exist in school settings that limit the education opportunities of students with neurodevelopmental disorders?
- What adjustments could be made to the school environment (including in teacher education and preparedness) that would improve the educational opportunities for students with neurodevelopmental disorders?
- How can these adjustments be feasibly implemented within school settings?

### ***Tertiary education and employment***

The vast majority of research into neurodevelopmental disorders has focussed on the childhood period, and historically there has been comparatively little research into post-school life. A greater understanding of how to foster positive transitions to post-school life – particularly the transition to further education and employment – is critical to improving the adult outcomes of individuals with neurodevelopmental disorders.

- How can adolescents with neurodevelopmental disorders be best supported before, during and after the transition to post-school life?
- How can tertiary education providers best support the further education of students with neurodevelopmental disorders?
- How can employers be supported to become better prepared to offer employment to individuals with neurodevelopmental disorders?

### ***Health and wellbeing***

It is well-established that mental health problems are very commonly experienced by individuals with neurodevelopmental disorders. Recent evidence has also suggested that individuals with neurodevelopmental disorders may have a reduced life expectancy;<sup>33,34</sup> findings that have been linked to the challenges these individuals face in interacting with our existing health systems.

- What preventative measures can be taken to improve the mental and physical health of individuals with neurodevelopmental disorders?
- Can we develop efficacious interventions that target common mental and physical health comorbidities of neurodevelopmental disorders, while also minimising side-effects?
- How can health systems be designed to better cater to the needs of individuals with neurodevelopmental disorders?

## **Challenges**

These gaps in our knowledge of neurodevelopmental disorders are likely driven by several factors, some of which are described below.

### ***Inadequate funding***

Given the relatively high prevalence and lifelong burden of neurodevelopmental disorders, the funding allocated to the study of these conditions appears disproportionately low. While it is difficult to identify concrete figures in this regard, one recent analysis found that \$19,319,780 was allocated by the NHMRC to autism research projects.<sup>26</sup> This represents a very small fraction of the estimated >\$3b allocated in NHMRC research funding over this period. While no data on research funding allocation could be easily located for

other neurodevelopmental disorders, there is no reason to think the funding pool would be significantly higher than that allocated to autism.<sup>35</sup>

### ***Focus of research***

While there has been some variety in the research areas funded, the largest pool of NHMRC research funds have been allocated to biological investigations.<sup>26</sup> Although this funding has led to many interesting and potentially important scientific advances, there is no tangible evidence that it has led to better individual outcomes. A focus on this latter goal is important to fill the research gaps previously outlined. In this regard, there needs to be explicit action taken, including targeted grant calls that focus on research that will directly lead to improving individual outcomes, as well as longer grant funding periods, which will facilitate larger and potentially more impactful projects.

### ***Overly onerous ethical approval requirements***

All research involving human participants must respect and protect those involved. In Australia, this process is typically governed by NHMRC-endorsed Human Research Ethics Committees (HREC). Over the recent years, there has been increasing concern about the increasing paperwork and logistical barriers provided by HRECs to the commencement of research projects, particularly for research that poses little risk to participants.<sup>36,37,38,39</sup> These excessive requirements, combined with limited research budgets and fixed project timelines, means that potentially impactful research projects may not be conducted, despite the limited risks they pose.

### ***National networks***

Many of the translational research goals, such as clinical trials of new and existing interventions, necessitate the recruitment of large numbers of participants across a variety of health, education and disability systems. This requires large-scale, nationwide projects that have multiple sites across Australia. Funding to establish and maintain these research networks, as well as Government commitments to reduce systemic barriers between states, is essential to meeting this aim.

### ***Participatory research***

Community involvement in research is key to improving the potential potency of research questions and the impact of research outcomes.<sup>40</sup> The involvement of the community in the research process is not just reliant on researcher training, but also on the availability of research funding (including, expansions in project timelines) to conduct this important work. At the present time, this funding is not routinely available.

## **Opportunities**

There have been recent changes in the clinical and research governance of neurodevelopmental disorders that provide key opportunities to improve research outcomes in this area.

### ***National Disability Insurance Scheme (NDIS)***

The NDIS is a major reform of the Australian disability sector that provides individuals with individualised funding for reasonable and necessary supports based on their level of functioning. Individuals with neurodevelopmental disorders represent well over half of all participants within the NDIS,<sup>41</sup> including individuals with autism (30% of the total participants in the NDIS), intellectual disability (24%), developmental delay (5%), and global developmental delay (1%). The NDIS provides for the first time a nationally consistent

system of care, and presents unprecedented opportunities for large-scale, Australia-wide research projects that have a focus on improving the outcomes of these individuals.

### ***Development of national research networks***

The past decade has seen the development of new research networks across Australia that focus on the improvement of clinical outcomes in individuals with neurodevelopment disorders. The [Autism Cooperative Research Centre](#) (Autism CRC) was funded in 2013 under the Commonwealth Government's Cooperative Research Centre scheme, and has both increased the funding available for autism research, and played a major role in shifting the national corpus of autism research towards a translational focus.<sup>26</sup> A new national network – [Neurodevelopment Australia](#) – was formed in 2019 with the aim of stimulating and facilitating nation-wide research into the broader range of neurodevelopmental disorders. The establishment of these networks provide a major opportunity to conduct the large, nation-wide research projects that often drive major improvements in clinical management and patient outcomes.

### **Conclusion**

Significant advances have been made in our understanding and clinical care of individuals with neurodevelopmental disorders. A consistent line through all areas of discovery is the tremendous heterogeneity that exists both between and within diagnostic categories. The research challenge that now awaits is how we develop and refine clinical techniques and systems that acknowledge and accept this heterogeneity, and respond in a manner that improves patient outcomes across the life course.

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