Current Developmental Disorders Reports (2019) 6:9–18
https://doi.org/10.1007/s40474-019-0156-7

COMORBIDITIES (D DEWEY, SECTION EDITOR)

The Brain Basis of Comorbidity in Neurodevelopmental Disorders

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Published online: 29 January 2019

Abstract

Purpose of Review Research examining brain development in neurodevelopmental disorders has largely comprised small-scale studies on individual disorders. Findings have confirmed neurodevelopmental disruption and deviation; however, comorbidity between disorders continues to challenge our understanding of brain-behaviour associations. This review discusses early brain development and the etiological factors that may give rise to atypical developmental trajectories, along with neuroimaging insights into neurodevelopmental disorders.

Recent Findings Evidence related to the behavioural, neurological, genetic and environmental factors impacting on brain development is examined. Large neuroimaging databases are currently being used to identify early alterations in brain development and areas of divergence and convergence between disorders are reviewed.

Summary Investigative approaches based on diagnostic groups continue to challenge our ability to elucidate regions of the brain linked to behavioural phenotypes, especially those known to be shared across disorders.

Keywords Neurodevelopmental disorders · Comorbidity · Autism spectrum disorder · Attention deficit hyperactivity disorder · Developmental coordination disorder · Neuroimaging

Introduction

Neurodevelopmental disorders arise from disturbances to processes of brain development during the prenatal period and/or in early childhood and include disorders such as autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), intellectual disability (ID), cerebral palsy (CP) and developmental coordination disorder (DCD). Much research has focused on mapping the etiological, neural and behavioural profiles of these disorders individually, and this work has made considerable impact in advancing prevention, diagnosis and intervention efforts. However, current understanding of neurodevelopmental disorders is potentially limited by two key features observed across diagnoses. First, whilst neurodevelopmental disorders may often be diagnosed based on a primary behavioural phenotype, they share a high degree of clinical comorbidity, suggesting common aetiologies across different disorders [1]. Second, there is often marked heterogeneity in the neurodevelopmental profiles of individuals within a diagnostic category [2]. As a result, investigating the aetiology for a specific neurodevelopmental disorder may not be particularly effective in uncovering critical neural areas and networks involved. The current review examines what is known about the brain basis of comorbidity across neurodevelopmental disorders and discusses the utility of aligning neuroimaging research with clinical phenotypes rather than with diagnostic labels alone. In doing so, we review

This article is part of the Topical Collection on *Comorbidities*

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evidence of transdiagnostic risk factors and mechanisms (i.e. those that are implicated across diagnostic groups).

Early Brain Development

Human brain development is a complex and protracted process, commencing in the early embryonic period and extending through postnatal development to the third and fourth decades of life [3, 4••]. This complex biological pathway arises from an intricate interplay of genetic, environmental, and developmental processes [5•]. In typical development, when the brain reaches maturity, it encompasses billions of neurons [6, 7] and trillions of connections [5•] that support the processing of basic sensory information through to complex functions such as cognition, language and social behaviour [5•, 8].

Brain development begins within the first 3 weeks post-conception with differentiation of neural progenitor cells [9]. Within 8 weeks post-conception, the neural tube forms and neuron production, migration (to target regions of the cortex) and differentiation commences. During the fetal period, neurons develop axons, dendrites and then synapses to integrate within neural networks. This is followed by myelination of axons, supporting increased neuronal conduction and capacity for communication. Hence, the foundations for functional connectivity within the brain are established within the prenatal period [10, 11]. At birth, the gross anatomy of the human central nervous system reflects its final adult form but there are still major developmental processes that occur within early childhood and for a further three decades [3, 12]. More specifically, neuron production (referred to as 'neurogenesis') and axonal growth continues into the postnatal period [12], with grey matter volume doubling in the first year of life and continuing to increase well into the second year [13••]. The formation of synapses (referred to as 'synaptogenesis') peaks in the late fetal and early postnatal period, and myelination increases up to adulthood [14–16]. Whilst genetic and environmental factors (e.g. nutrition, stress, drugs, environmental pollutants) exert interacting effects throughout the prenatal and postnatal period, it is during the postnatal period that experiential influences also become important for guiding and shaping developing neural circuits within the brain. For example, in the early postnatal period, neural connectivity is significantly increased compared to adulthood, due to an overproduction of synapses [17]. Excess synapses are subsequently pruned via processes that are influenced by experiential input, facilitating neural organisation, specialisation and efficiency through a dynamic process of fine-tuning neural connections through experience [9]. To this end, human brain development through the postnatal period is equally as sensitive and dependent on inputs from the environment to support a typical maturational trajectory.

The protracted developmental trajectory (albeit, marked by periods of rapid change particularly within the earliest years of life; [18, 19]) and plasticity of the human brain early in development is thought to allow the organism to maximally adapt and respond to the surrounding environment. However, a prolonged, sensitive period of development also means that the human brain is vulnerable to the effects of potential adverse genetic, environmental and developmental events for a longer period than other organs [9]. Moreover, these events (genetic and/or environmental and their interaction) can exert differential impacts on the brain [20, 21] as a function of their timing, due to different regions of the brain maturing at different rates. The brain is built in a hierarchical manner, whereby more basic systems (such as those involved in sensory motor processing) are established first, with higher-level systems and circuits later integrated to support increasingly complex functions (such as language, cognition, social behaviour, executive functions) [22–24]. This hierarchical development results in a highly interdependent system, both in terms of development and function. For example, structures and circuits that emerge at a particular point in development are necessary precursors for subsequent complex systems to emerge [5•]. In addition, this interdependency means that more complex circuits and functions incorporate and depend on the quality of input provided from more basic pathways [25•, 26]. To this end, perturbations occurring at one stage of development (especially very early in development), could exert pervasive and cascading effects on later-developing systems and/or more complex brain circuits and functions [23, 25•, 27].

Etiological Factors Impacting on Brain Development

The precise molecular mechanisms that give rise to neurodevelopmental disorders and their heterogeneous phenotypes remain relatively unknown. However, a wide array of heritable, genetic, epigenetic, developmental, and environmental factors (and their complex interactions) have been implicated. Critically, many of these etiological factors (i) have their origins in the prenatal period and (ii) exert effects on very early brain development. Indeed, common across the neurodevelopmental disorders are widespread atypicalities in brain structure, function and connectivity from very early in development, often well before overt behavioural signs of the disorder have manifested. For example, alterations in neuronal migration, synapse formation and myelination (all within the prenatal period) have been implicated in ASD and ADHD based on post-mortem tissue samples and genetic studies [28–32]. Despite occurring early in development, these perturbations can exert lasting behavioural, cognitive and developmental difficulties throughout the lifespan, likely a

consequence of the brain's hierarchical, interdependent nature that can lead to cascading effects on subsequent development [23, 25•].

Whilst it is well-established that the various neurodevelopmental disorders have been associated with early alterations in brain development (at least at the group level), the diagnosis of a high proportion of these disorders currently remains behaviourally defined despite the efforts of clinicians to identify a specific aetiology such as a chromosomal or other genetic disorder. There are few biological markers (neural or otherwise) for behaviourally defined neurodevelopmental disorders with sufficient sensitivity or specificity at the level of the individual for clinical application. Despite distinctions amongst neurodevelopmental disorders in terms of core diagnostic symptoms, there is substantial co-occurrence and overlap in behavioural signs and amongst diagnostic categories. For example, amongst individuals with ASD, it is estimated that approximately 30–70% also have an ID [33–35], 30–65% meet criteria for ADHD [36, 37] and more than half (50–80%) also show signs of DCD [38, 39]. Similarly, approximately 13–20% of children with ADHD also meet criteria for ASD [40], whilst amongst children with DCD, 50% also meet criteria for ADHD [41, 42] and ~ 30% meet criteria for ASD [43]. In individuals with CP, approximately 50% are reported to have ID [44], 19% ADHD [45] and 9% ASD [46]. This high comorbidity poses challenges for diagnosis, prognosis, and intervention targets. Increased research in this area into the future, and an improved understanding of the biological bases of comorbidity, will shed light on aetiological mechanisms of atypical development, as well as improving and delineating clearer intervention targets across diagnostic categories.

Findings from twin and family studies, demonstrating high heritability rates amongst neurodevelopmental disorders (e.g. ASD ~ 80–90% [47], ADHD ~ 60–90% [48]) and DCD ~ 70% [42, 43]), support the contention that there may be shared etiological and pathophysiological mechanisms across these disorders. For example, it has been demonstrated that when one monozygotic twin was diagnosed with ASD, the probability of co-occurrence in the other twin was approximately 15% for ADHD and 12% for DCD [43]; these rates are contrasted with prevalence estimates in the general population of ~ 3–7% [49–51] and 2–5% [52, 53], respectively. In line with these findings, recent large-scale studies have found inflated rates of various neurodevelopmental disorders amongst siblings and family members of probands with an ASD diagnosis, including ADHD [54], ID and DCD [55]. These high heritability rates imply a strong role for shared genetic influences as one common aetiological factor amongst many of these disorders.

Whilst the identification of specific shared genes, gene networks and genetic variants implicated across neurodevelopmental disorders is still an emerging and complex field of research, there has been considerable progress already made in advancing our understanding of the neural and pathophysiological mechanisms involved in the development of neurodevelopmental disorders. For example, SHANK3, TSC1/2 and RBFOX1 have all been implicated in ASD, ADHD, and ID [56]. All of these genes are implicated in brain development and function. For instance, the SHANK3 gene plays an integral role in the formation and maturation of dendritic spines, along with supporting connections between neurons [57], TSC1/2 complex is critically involved in cell growth and axon guidance [58], and RBFOX1 encodes a splicing regulatory factor expressed in neurons and muscle [59].

In addition to these specific genes, copy number variations have also been identified across neurodevelopmental disorders, suggesting a highly complex genetic architecture in the aetiology of these disorders. For example, deletions and duplications at the 16p11.2 locus have been frequently implicated across several psychiatric and developmental disorders, including DCD, ASD, ID and language disorders [60]. Recently, this work has been extended to explore potential neural signatures associated with these variants in order to shed light on their role in brain function, and potentially, inform neural pathways underlying the development of neurodevelopmental disorders. For example, it has been demonstrated that individuals with a deletion or duplication of the 16p11.2 region show alterations in brain structure and function compared to individuals without a deletion or duplication on this locus [61–64]. Moreover, this work has demonstrated that the specific effects of a 16p11.2 variant on brain structure and function are dependent on whether the individual carries a deletion versus duplication. For example, alterations in the visual evoked potential (which represents an electroencephalographic [EEG] readout of the early-maturing visual pathway in the brain) have been identified in children with 16p11.2 deletions and duplications comparted to typically developing children [62]. However, where the deletion carriers displayed increased amplitude in their EEG response, duplication carriers showed a decreased amplitude [62]. Similar opposing effects have been identified in structural imaging studies where individuals with a deletion show increased brain volumes (evident across cortical and subcortical structures) compared to control individuals whilst duplication carriers show decreased brain volume [64]. In lieu of the widespread effects of the variant across brain structures and in early maturing functional pathways (such as the visual pathway), it has been suggested that 16p11.2 is implicated in very early brain development [64]. Together, this emerging field of research is highlighting the role of potential shared genes and genetic variants in the aetiology of neurodevelopmental disorders and their purported downstream effects on early brain development and functioning.

Whilst there is a strong genetic (and heritable) component to many neurodevelopmental disorders, the genetic background appears to interact with various environmental factors (that are shared across disorders) to increase risk. As such, in addition to shared genetic aetiological influences contributing to the manifestation of neurodevelopmental disorders, there are also other interacting factors. For example, complications in pregnancy and childbirth, such as hypoxia, fetal growth restriction and prematurity have all been linked to atypical brain development and increased rates of ASD, ADHD, DCD, ID and CP [65–70]. There are also a wide range of other factors, such as socioeconomic status (SES) [71–73], prenatal stress [74], prenatal alcohol exposure [75, 76], and elevated prenatal testosterone [77] associated with alterations in early brain development and subsequent neurodevelopmental outcomes. Some of these factors are associated with specific neurodevelopmental disorders (for example, prenatal alcohol exposure is causative of fetal alcohol spectrum disorder [FASD]), whilst others appear to confer general neurodevelopmental vulnerability; for both types of risk factor (specific and general), impacts on brain and behaviour are nuanced and dynamic. For example, one study found that low SES was associated with low white matter fractional anisotropy in 3–21 year olds; additionally, there was an interaction between SES and white matter microstructure such that cognitive flexibility was preserved in individuals with high SES and low white matter fractional anisotropy, but not for those with low SES [78]. In cases of teratogen exposure, findings from animal studies demonstrate that impacts on structural and functional pathology are similarly influenced by interactions between genes and pre- and postnatal environments [79], as well as the timing, dose, pattern and duration of exposure. To this end, the aetiology of most neurodevelopmental disorders is currently best understood as a complex interplay of genetic, environmental and developmental factors that interact to disrupt early development and impact upon early brain development.

The Neural Overlap and Divide: What Have We Learnt From Neuroimaging?

Neuroimaging and neurophysiological techniques (e.g. magnetic resonance imaging, electroencephalography, functional near infrared spectroscopy, magnetoencephalography) offer enormous opportunity to examine deviations in brain anatomy, function and connectivity associated with atypical brain development. Whilst advances in technology have provided invaluable insight into the neurobiology of neurodevelopmental disorders, the issue of comorbidity continues to challenge researchers working in this field. Disorder-focussed imaging studies have, in many ways, complicated our understanding of potential neuroimaging-based markers associated with domains of cognition and behaviour. The evaluation of detailed clinical profiles of individuals recruited for studies is often not considered, running the risk that neurological markers identified may not be associated with the primary diagnostic symptoms of the condition studied. In recent years, heterogeneity and overlapping phenotypes have received increasing attention (e.g. [80, 81, 82••, 83–85]), with co-occurrence considered the rule rather than the exception [86]. There has been a worldwide shift in research interest towards disentangling dimensions of cognition and behaviour, utilising mechanistic transdiagnostic approaches (processes reflecting a causal, functional mechanism for co-occurrence, [87]) to interrogate brain-behaviour relationships and enhance our understanding of specific neurological regions and networks that may be associated with specific clinical profiles unique or common to different neurodevelopmental disorders. There is also increased recognition of the changing nature of the brain and whilst there is still much debate surrounding these changes in typically developing individuals (see [88]), there is enhanced focus on longitudinal changes occurring in neurodevelopmental disorders, which are likely to result in changes to patterns of behaviour at different stages of the lifespan.

Whilst a variety of techniques have been used to study the human brain in vivo, over the past two decades, EEG and magnetic resonance imaging (MRI) have emerged as favoured approaches. EEG is a measure of postsynaptic brain activity with high temporal resolution that is more tolerant to motion artefact, making it a particularly useful technique for application in young children and clinical populations. MRI has various scanning sequences, which can be used to produce detailed three-dimensional anatomical images, characterise and visualise white matter tracts (diffusion MRI), brain activation patterns at rest (resting-state MRI) and during the performance of tasks (functional MRI), along with connectivity between regions and networks. Compared to EEG, MRI has high spatial resolution but is less tolerant to motion artefact, which can make scanning young children and clinical cohorts challenging and can restrict the tasks that can be performed. Scanning sequences and analytical techniques available through these modalities have advanced remarkably over time, enabling researchers to continually push the boundaries to gain greater insight into the widespread alterations in brain morphology and function.

Whilst studies have reported findings that appear to be quite unique between diagnostic conditions, such as accelerated areas of brain growth early in life in children with ASD [89] compared to delays reported in children with ADHD [90], there have also been areas of convergence. Some of the neurological regions implicated across multiple disorders include the precuneus (e.g. [81, 91]), cerebellum (e.g. [92, 93]), white matter areas like the corpus callosum (e.g. [80, 94, 95]), corticospinal tract (e.g.

[7, 96]) and inferior longitudinal fasciculus (e.g. [96–98]), along with the default mode and ventral attention networks (e.g. [99–101]). Whilst most of these studies include single or two disorder comparisons, they demonstrate possible areas of convergence or neurological intersections likely associated with the overlapping symptomology seen across disorders.

Over the past decade, technical advances in methods for data acquisition and automated processing are making multisite large-scale imaging studies increasingly feasible and in recent years, large neuroimaging database repositories have been established. These include open-source databases such as ADHD-200 [102•] and the Autism Brain Imaging Data Exchange (ABIDE I and II, [103•, 104•]). These collaborations, linked through the Preprocessed Connectomes Project (PCP, http://preprocessed-connectomes-project.org/index.html) are, for the first time, allowing large-scale analyses to be conducted to examine the convergent and distinct boundaries of clinical diagnoses.

One such study combining the ADHD-200 and ABIDE databases through the PCP for cross-disorder comparisons is a recent study by Kernbach and colleagues [82••]. The study used resting-state MRI to examine the functional connectivity of the default mode, dorsal attention and salience networks in 1305 participants with ADHD, ASD and typically developing controls. Using a hierarchical Bayesian modelling framework, the study revealed 45 sources of variation in default mode network coupling, which were present to varying extents in both clinical groups, but not distinctly associated with only one group. Three connectivity factors were identified, associated with both clinical disorders, providing evidence of shared dysfunctional connectivity networks. Even though comparisons are limited by the databases available (i.e. only ADHD and ASD datasets currently available), the PCP will inevitably lead to increased collaboration and establishment of new datasets in other clinical groups with high rates of co-occurrence. Studies of this nature, particularly if combined with extensive phenotypic and genetic information (where available), have the potential to produce the greatest clinical insights across the neurodevelopmental continuum.

Large-scale databases are also being established to examine the timing of neurological changes in early development. One such project is the Developing Human Connectome Project (dHCP, [105•]). It is conducting MRI scans of infants in utero and early infancy, which will be combined with cognitive, environmental and genetic data to evaluate brain changes over time. Whilst the project will advance the understanding of typical brain development, it also has substantial potential to identify how early perturbations (e.g. preterm birth) and other risk factors (e.g. genetic variation) may alter brain development early in life. With the aim of imaging over 1500 infants, collecting structural, resting-state functional MRI and diffusion imaging, this database will be particularly valuable in uncovering how particular susceptibilities may give rise to disturbances in brain development and different clinical phenotypes. The database will become publicly available, meaning it can be expanded further, potentially with infants who are imaged longitudinally who carry increased risk for neurodevelopmental disorders or showing early behavioural markers.

Longitudinal brain imaging studies in infants with increased risk or presenting with early behavioural markers are currently limited, with the exception of CP. A recent study by Hazlett et al. [106•] examined brain development in 106 infants at high risk for ASD, with imaging completed at 6, 12 and 24 months of age. Whilst previous studies have demonstrated increased brain growth in the early years (see [107]), the longitudinal study by Hazlett et al. [106•] discovered a period of hyperexpansion in the cortical surface between 6 and 12 months of age, followed by a period of brain volume overgrowth between 12 and 24 months of age in 15 of the high-risk infants who were diagnosed with ASD at 24 months. Brain volume overgrowth between 12 and 24 months was directly linked to emergence and severity of social deficits. A deep-learning algorithm using surface area data taken between 6 and 12 months was also able to successfully predict the later diagnosis of ASD in 81% of children. These findings are consistent with Emerson et al. [108•] who were also able to use MRI imaging taken at 6 months to later predict an ASD diagnosis at 24 months with 96% accuracy. Similarly, using EEG, a number of studies have now demonstrated alterations in brain function within the first year of life that are associated with a later diagnosis of ASD, such as atypical responses to facial stimuli [10, 109] and atypical hemispheric specialisation patterns [110]. A recent, prospective study using EEG demonstrated high rates of sensitivity and specificity as early as 3 months of age in detecting those infants that went on to meet diagnostic criteria for ASD [111]. Whilst studied in an isolated diagnosis, studies like this showcase the potential of neuroimaging to potentially predict later diagnosis. There is the real possibility of taking this research one step further using neuroimaging to predict an individual's later clinical phenotype (rather than just diagnosis), opening the door to very early intervention targeting predicted cognitive and behavioural difficulties before the onset of overt symptoms. This could dramatically change intervention pathways for neurodevelopmental disorders, with the focus shifting to early intervention during the prodromal period when the brain is still in the early phases of establishing critical brain networks.

In summary, studies examining the brain basis of comorbidity using neuroimaging modalities are scarce. There certainly has been an increase in studies examining the overlap that exists between disorders, but these studies are often limited by small sample sizes and recruitment based on confirmation of a diagnosis alone and without characterisation of behavioural phenotypes known to vary within diagnoses.

With the current move into the era of big data, neuroimaging has considerable potential to expand our understanding of deviations in brain development, how they are linked to specific profiles and how this may change across the lifespan. It is important for these datasets to include detailed behavioural and cognitive data wherever possible, so that researchers can look beyond a label.

Conclusions

The current review highlights the need for neurodevelopmental research to go beyond traditional diagnostic manual-based diagnoses and focus on the brain basis for specific clinical phenotypes [2]. The high co-occurrence rates amongst neurodevelopmental disorders and cross-disorder heritability do not support the specificity of the diagnostic systems and guidelines that have been developed. Indeed, until recently, diagnostic guidelines (e.g. according to the DSM-IV) made it difficult for dual diagnosis of many neurodevelopmental disorders (e.g. ASD and ADHD), despite their common clinical co-occurrence. Instead, this co-occurrence necessitates a dimensional, transdiagnostic approach (where the focus is on shared attributes or risk factors across disorders) to enhance our understanding and design interventions across neurodevelopmental disorders. Transdiagnostic, dimensional approaches that transcend existing diagnostic boundaries informed by an understanding of typical and atypical neurodevelopment can be used to differentiate the components of a complex clinical presentation, predict developmental trajectories and guide individualised intervention approaches. The Research Domain Criteria (RDoC) framework put forward by the National Institute of Mental Health is an example of a dimensional approach to identifying psychiatric disorders that integrates genomics, neuroscience and behavioural science, rather than relying solely on descriptive phenomenology [112••]. Extending the RDoC approach, researchers have considered how insights into sensitive periods of brain development, neurodevelopmental trajectories and developmental cascades can contribute to an understanding of the emergence of neurodevelopmental impairment across development and guide early identification and intervention approaches [113]. Together with large neuroimaging datasets available through open science initiatives (e.g. Public Data Database: https://sites.google.com/site/publicdatadatabase/) and complementary data analytic approaches, a transdiagnostic, dimensional approach could inform future revisions of our diagnostic systems, drive identification of novel treatment targets and support the application of precision medicine approaches in the treatment of neurodevelopmental disorders [114].

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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