
SHORT COMMUNICATION

Neuropathology of autism

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ABSTRACT

In persons with autism and similar illnesses, post-mortem examinations allow for a direct examination of brain tissue. Several review publications have focused on certain elements of post-mortem abnormalities, but none has compiled the full body of post-mortem research. In this paper, we examine the evidence from post-mortem studies of autism and associated illnesses with autistic characteristics. Despite the fact that the literature is made up of a small number of research with small sample sizes, numerous strikingly consistent conclusions may be found. The layering of the cortex is essentially unaffected, although there are consistent reductions in the number of minicolumns and abnormal myelination. Abberant synaptic, metabolic, and proliferative,

apoptotic, and immunological pathways have all been implicated by transcriptomics. Non-coding RNA, abnormal epigenetic profiles, GABAergic, glutamatergic, and glial dysfunction are all implicated in autism pathophysiology by sufficient repeatable evidence. Overall, the cerebellum and frontal cortex are the most frequently implicated, with significant region-specific changes occasionally revealed. The research on related illnesses including Rett syndrome, Fragile X, and Copy Number Variants (CNVs) that predispose to autism is notably scarce and contradictory. Larger trials are needed that are matched for gender, developmental stage, co-morbidities, and pharmacological treatment.

Key Words: *Autism Spectrum Disorder (ASD); Post-mortem studies; Systematic review*

INTRODUCTION

Autism is a complex neurodevelopmental condition that affects around one out of every 100 children. Describe it as having issues with social cognition and communication, as well as repetitive behaviours and hypersensitivity to environmental stimuli. Individuals have a wide range of comorbidities, including seizures, Attention-Deficit/Hyperactivity Disorder (ADHD), and other cognitive deficits, in addition to these main symptoms. Autism is still primarily a ubiquitous and diverse condition that is diagnosed by examining a person's behaviour and development, with the severity of symptoms varying from patient to patient [1,2]. The term Autistic Spectrum Disorders (ASD) is used in the Diagnostic and Statistical Manual 5 to encompass several clinical conditions that share core symptoms: autism (as above), Asperger syndrome (as above but milder and/or without communication difficulties), Pervasive Developmental Disorders-Not Otherwise Specified (PDD-NOS), where distinctions between all three conditions have been abandoned, as well as Rett syndrome and rare genetic disorders predating autism (as above but predating (e.g., Fragile X syndrome). In the F84 section of the

International Classification of Diseases (ICD) _10, Rett syndrome and other known causes of ASDs are also included (WHO, 1992). All of these syndromes are referred to as autism and related illnesses in this article [3]. Several genetic and environmental factors play a significant influence in the beginning and development of autism, despite the fact that the aetiology is yet unknown. Hundreds of genomic loci and autism risk alleles have been identified, with inherited genetic variation accounting for over 40% of the risk for .Wang et al. (2014) found that genetic perturbations in developmental programmes related to ASD, as evidenced by high co-expression of ASD susceptibility genes, are more likely to occur during two distinct periods of development and affect two different regions: the second trimester frontal-somatomotor neocortex and the perinatal/postnatal cerebellar cortex. Furthermore, many prenatal environmental variables, such as maternal stress response activation and prenatal exposure to chemicals, have been linked to an increased risk of ASD [4]. There are three types of genetic variables that have been linked to ASDs. For starters, single gene mutations are responsible for about 5% of cases, such as Fragile X and Rett Syndrome. Indeed, not

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everyone with Fragile X or Rett Syndrome exhibits autistic symptoms. With Fragile X, the prevalence of autism is roughly 30%–54 percent in males and 16 percent–20 percent in females (Kaufmann et al., 2017), and 61 percent in females with Rett Syndrome. Second, significant genomic Copy Number Variants (CNVs), such as gene segment deletions and duplications, are responsible for about 10% of ASD cases [5]. 16p11.2, 22q11 deletion, 15q11-q13 deletion, 15q13.3 microdeletion, and 15q11-13 duplication are all examples of human chromosomal deletions and duplications (Fernandez et al., 2010; Wu et al., 2014; Hogart et al., 2009; Varghese et al., 2017). Third, polygenic risk factors contribute for at least 20% of ASD risk, owing to the accumulation of common de novo single-nucleotide variations. Recent developments in genetic tools, particularly whole-exome sequencing and induced pluripotent stem cell (iPSC)-derived models, have aided in elucidating aspects of the illnesses' neurobiology. Post-mortem research has also added to our understanding of ASD, despite the restricted availability of human postmortem material and the technical difficulties of investigating the human brain [6]. Autism BrainNet, BrainNet Europe Consortium, and the Australian Brain Bank Network are just a few of the brain banks and biopsy networks that exist in the UK, US, and around the world to facilitate the acquisition of post-mortem brain tissue for ASD research. Disease-related abnormalities at the cellular, synaptic, and molecular levels can be observed by studying brain tissue directly, allowing identification of neuronal populations and their neural networks (Lewis, 2002). As a result, post-mortem studies are a valuable addition to other methods, serving as a link between the clinical manifestation and the underlying molecular and cellular pathology [6,7].

Several narrative review articles describing various elements of ASD neuropathology have been published. GABAergic deficits, mitochondrial dysfunction, microglial impairments, and neuroanatomical changes, as well as the implications of epigenetic and transcriptome investigations, have been the focus of these studies (Varghese et al., 2017; Fatemi and Folsom, 2015; Frick et al., 2013; Bauman and Kemper, 2005; Ansel et al., 2017; Smith et al., 2019a; Wei et al., 2014). However, no comprehensive systematic review has been published to date that describes and synthesises the nature of the numerous findings in post-mortem investigations, including the genetic, epigenetic, and transcriptome patterns found in ASD brains. In this work, we examine the evidence from postmortem ASD investigations in detail. We also include post-mortem findings in illnesses that typically occur with autism, such as Fragile X Syndrome (FXS), Rett Syndrome (RTT), 15q11-13 duplication, and DiGeorge syndrome, which is unusual but essential [8].

The majority of research merely stated that the individuals had an autism or ASD diagnosis. In the majority of the studies, the diagnosis was made using the gold standard diagnostic tools for ASD, the Autism Diagnostic Interview (ADI) or Autism Diagnostic Interview-Revised (ADI-R), and sometimes using diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV) (Bell, 1994) or ICD-10 criteria. Other ASD screeners, such as the Autism Diagnostic Observation Schedules (ADOS) and the Childhood Autism Rating Scale (CARS), as well as medical records and family interviews, have been utilised in a number of studies to assess individuals. Only one study had an ASD case diagnosed with RTT, and seven studies had cases diagnosed with both ASD and 15qdup. Megalencephaly (increased brain weight >2.5 Standard Deviation (SD) above the mean) was shown to be a common

characteristic of autism/ASD in an early neuropathological investigation. Four of the six brains examined were abnormally big and hefty.

Except for one study that includes the clinical history of all three patients and states that one patient was also diagnosed with ASD and molecular/chromosomal analysis confirmed the presence of a full mutation allele, none of the post-mortem studies below mention how FXS was diagnosed or whether or not these cases also had an ASD diagnosis [9].

Hinton et al. (1991) found long, thin, immature spines in two FXS participants aged 15 and 41. However, no significant alterations in neuronal counts were found in neocortical layers II–VI of the cingulate and temporal association areas when compared to controls. Irwin et al. (2001) studied the dendritic spines on layer V pyramidal cells in the temporal and visual cortices in three male FXS cases, finding longer dendritic spines in both cortical regions with immature morphology and higher spine density on distal segments of apical and basilar dendrites in three year. Greco et al. published a follow-up study.

The hippocampus showed abnormalities such as focal thickening of the hippocampal CA1 and inconsistencies in the morphology of the dentate gyrus. Purkinje cell counts in the cerebellar vermis were reduced in all lobules as well as the lateral cortex of the posterior lobe of the cerebellum. There were also scattered foliar white matter axonal and astrocytic abnormalities, as well as modest but excessive internal granular cell layer undulations. Both the anterior and posterior lobes of the vermis showed panfoliar atrophy as compared to five age-matched controls, with the posterior lobule (VI to VII) showing preferential atrophy. Abnormal dendritic spine lengths and shape have been documented in FXS on a constant basis, which could indicate a lack of normal dendritic spine maturation and/or pruning during development that persists into adulthood. Transcriptomic analysis has linked astrocyte and microglia markers, as well as other immune system function and inflammatory response genes, to a variety of diseases. In ASD samples, increased miR-155p5 gene expression, a proinflammatory miRNA implicated in a variety of inflammatory disorders, has been frequently found. Microglial activation may also be a neuroimmune system response to synaptic or neuronal abnormalities, which could contribute to ASD pathogenesis. Animal and cellular models will be used to help researchers better understand potential neuroinflammation processes in ASD.

CONCLUSION

In summary, the current paper provides a psychological and neuroscientific description of working memory, including theoretical models of working memory, as well as neural patterns and brain regions involved in working memory in healthy and diseased brains. Working memory is thought to be the foundation for many other cognitive functions in humans, and knowing working memory mechanisms would be the first step toward understanding other parts of human cognition like perceptual or emotional processing. Following that, it would be reasonable to investigate the relationships between working memory and other cognitive systems.

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