



Neurobiological Concomitants of Autism as Informers of Clinical Practice: a Status Review

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Abstract

Objectives Although a great deal of research is conducted into the neurobiological correlates of autism, there has been no recent overview of the findings from this research in terms of how they translate to clinical practice. To provide an overview of recent literature in the fields of head size, brain volume, brain region, connectivity between brain regions, and synaptic function, as they apply to autism, with a view to informing clinical practice.

Methods Major empirical and review papers on these topics from the last 30 years were identified via a search of PubMed, Google Scholar, and PsychInfo, using the descriptors ‘autism’, ‘head size’, ‘brain volume’, ‘brain region’, ‘connectivity between brain regions’, and ‘synaptic function’. To distil the key findings relevant to clinical practice, both authors conducted blind reviews, producing a set of ‘key’ papers for this purpose.

Results Each field produced a number of major findings, which were then described and discussed, and translated into a table of ‘Findings’, ‘Diagnostic suggestions’ (for the clinician’s protocols), and ‘Clinical actions’ (suggestions for interactions with carers of autistic children and adults).

Conclusions The stability of the research within each field varies, with some clear findings and others that are yet to be consistently verified. Despite this, some specific clinical implications for diagnosis and treatment (particularly clinician-carer interactions) are described.

Keywords Autism · Neurobiology · Research · Clinica

Autism spectrum disorder (henceforth ‘autism’) is a complex neurodevelopmental disorder that has a median global prevalence of 100/10,000 persons and a male-to-female ratio of 4.2 (Zeidan et al., 2022), although that ratio has been challenged as an under-estimation due to females with autism ‘camouflaging’ their symptomatology (Tubío-Fungueirino et al., 2021). Characterised by persistent deficits in social communication and social interaction, plus restricted, repetitive patterns of behaviour (APA, 2022), autism has been described as a neurological disorder with behavioural manifestations, and, as such, it is relevant to understand the neurobiological factors that may contribute to, and describe, autism. Although a great deal of attention has been given to

the genetic contributors to autism (Iyshwarya et al., 2022; Thapar & Rutter, 2021), there is still some disagreement as to whether reliable genetic factors have been identified (Myers et al., 2020). Alternatively, it is of value and interest to review the current state of research regarding neurobiological factors that contribute to autism, apart from genetic variables.

Autism-specific studies that are most often designed to identify neurobiological differences between autistic and non-autistic research participants tend to cluster around the broad topics of head size, brain volume, brain regions, connectivity between brain regions, and synaptic functions. Because a number of systematic reviews and meta-analyses (mentioned below) have been conducted on these topics individually, clinical practice would be informed if an overview was taken of these findings across topics rather than performing another systematic review of each topic separately. Such an overview could provide the basis for a distillation of the findings from the research literature in terms of their implications for clinical practice. Additionally,

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suggestions could be made for future research that would, in turn, eventually lead to refinement of current research findings and further information relevant to clinical practice.

Therefore, rather than exhaustively re-examining the history of research findings on each of these topics separately, recent research findings will be reviewed for the purpose of collating relatively well-established findings about these neurobiological concomitants of autism, with the aim of informing diagnosis and assessment of autism in clinical settings, and treatment planning that emerges from those procedures. When relevant, reference will be made to any methodological limitations that might adversely impact the veracity of researchers' conclusions, and suggestions will be made for future research.

Because this was not a systematic review as defined by PRISMA, this ms was not identified as such in the title, and the full list of steps set out in PRISMA were not deemed to be relevant because the purpose of this ms was not to review all the individual findings from the literature but rather to provide an overview of those findings as they pertained to clinical practice. Instead, to follow the relevant recommendations from PRISMA, those requirements for the Introduction (PRISMA items 3, 4) and Methods (PRISMA items 5–8) were followed, viz, the rationale for the review, and its objectives in providing a set of key findings, implications for clinical practice, and suggestions for interactions with carers of autistic children were reported (see paras 1 and 2 under Aim and Method). Inclusion criteria were that all major empirical and review papers on these topics from the last 30 years were identified from PubMed, Psycinfo, and Google Scholar using the search descriptors 'autism' with 'head size', or 'brain volume', or 'brain region', or 'connectivity between brain regions', or 'synaptic function'. The search was conducted in the period March–May 2023. Papers were included if both of the two reviewers (the authors of this ms) independently judged the paper to make a contribution rated at least 7/10 on a 10-point scale where 10 = vital to the field and informative to clinicians. From this process, each of the reviewers blindly produced a list of key papers for this review, which was reduced to 75 publications that were agreed by both authors as meeting the aims of reporting key findings and also holding implications for clinical

practice. Using these papers, PRISMA items 23a to 23d (Discussion) were followed to provide a general interpretation of the results in the context of other evidence, describe limitations of the evidence reviewed and the process used to review the literature, and the implications of the research findings within each section, in terms of implications for clinicians, and issues for future research.

Collating Research Findings

Head Size and Brain Volume

Investigations into differences in brain size have involved researchers using various metrics such as 'head circumference', 'whole brain volume', and 'brain structure volume'. In general, these studies adopt a process of taking repeated measures, usually at specific age points during the period from infancy to early-mid childhood, and are aimed at identifying and monitoring brain size variations in autistic children compared to their typically developing peers. Metrics used in this research have included physical measurement of the head perimeter to determine cranial size (i.e. head circumference studies), magnetic resonance imaging (MRI) techniques that permit direct measures of brain volume (e.g. structural and functional MRI studies), which are described in Table 1, and post-mortem studies in which the brain is weighed to determine its mass in comparison to age-based norm groups.

The occurrence of a pathological pattern of brain overgrowth, evident early in the postnatal developmental period in autistic children, has been reported for some time (Courchesne et al., 2001, 2003), and findings gained from head circumference measurement have consistently led to the conclusion that cranial size is larger in autistic children compared to typically developing controls (Aylward et al., 2002; Redcay & Courchesne, 2005). Sacco et al. (2015), in their meta-analysis of 27 studies (participant age range between 2 and 13.6 years), estimated that 15.7% of autistic children exhibited significant head circumference enlargement compared to their same-age peers. Researchers generally agree that the estimated range of brain overgrowth in

Table 1 Methodologies for measuring cranial size in autism: head circumference, brain volume

Head circumference (i.e. cranial size used as a proxy for brain size) is calculated by measuring the distance around the child's head with a non-elastic tape measure held above the eyebrows and ears. The result for a specific child is compared with the expected measure based on age and sex (i.e. from a referenced normative group). Measurements on head size are plotted on developmental charts that contain expected age- and sex-related values to allow for the monitoring of changes in head size that might indicate atypical development (Harris, 2015).

Brain volume (i.e. actual brain size) measures obtained via MRI create detailed in vivo images of the brain that allow assessment of total brain volume as well as region-specific variations in volume (Steen et al., 2007). MRI outputs have been used in studies of autism to illuminate issues of total brain size, atypicalities in specific brain structures, connectivity between brain regions, and associations between structural variations and core autism symptoms.

autism ranges from 15 to 20%, occurs within the first 2 years of life, and progresses according to a distinctive pattern of acceleration/deceleration in growth (Shen & Piven, 2022). More specifically, compared to normative data, autistic infants are born with small-to-normal head size but then experience accelerated head size growth in the first year of life, followed by a subsequent deceleration in head size growth occurring at 12 to 24 months (Hazlett et al., 2017). Although there is consensus on the presence of early brain overgrowth, the age and rate at which deceleration of brain overgrowth occurs, leading to ‘normalisation’ in brain size, continues to be debated, and it has been hypothesised that deceleration in brain overgrowth not only begins close to 12 months of age, but is likely to be minimal prior to the age at which diagnosis usually occurs (i.e. about 2 years) (e.g. Courchesne et al., 2007; Redcay & Courchesne, 2005). This hypothesis has received reasonably consistent support from studies designed to systematically search, critically appraise, and synthesize the existing research on brain growth trajectories in autism (e.g. Faja & Dawson, 2017; Shen & Piven, 2022).

One of the methodological limitations of the use of head circumference in brain overgrowth studies is the possibility of bias. For example, Raznahan et al. (2013), in their review of longitudinal head circumference data gathered between birth and 18 months in male infants, discovered that the method of measurement used to measure brain size affected whether early brain overgrowth was reported to be present. Specifically, studies that compared brain size to standardized norms (e.g. those obtained from the Centers for Disease Control and Prevention, USA) were significantly more likely to report brain enlargement in autism, but comparisons conducted against locally recruited control participants suggested that variation in brain overgrowth was subtler than originally proposed. Small sample sizes and low representation of females within existing data sets continue to impact the robustness of findings on this issue (Hazlett et al., 2017; Steen et al., 2007).

There is also interest in the association between the time at which head circumference accelerates and the first appearance of autism symptoms. It has been shown that the presence and severity of ASD symptoms closely follow the escalation in head circumference (Faja & Dawson, 2017). The number of autistic symptoms observed appears to be correlated with earlier onset of acceleration in head circumference, and findings suggest that children who experience greater increases in head circumference within the first 12 months of life are highly likely to develop a greater breadth of autism-related impairments (Vaccarino & Smith, 2009). Furthermore, the severity of symptoms of social interaction and language/communication deficits is associated with the persistence of brain overgrowth later in childhood (Sacco et al., 2015). Findings such as these are of

clinical importance because it is the number and intensity of autism symptoms that form the basis for determining severity levels of ASD (APA, 2022) and for deciding on necessary supports during the diagnostic process.

Although initial studies of brain overgrowth relied on head circumference measures as their metric, since the early 2000s, the most frequently used measurement processes involve MRI procedures that permit precise and detailed assessment of overall and region-specific brain volumetric status. MRI-driven studies in which total brain volume and other aspects of brain structure (e.g. cortical thickness) are assessed in relation to age-matched comparison groups (e.g. typically developing or developmentally delayed participants) have generally confirmed findings from previous head circumference studies that young autistic children (age range = 2 to 4 years) possess larger total cerebral volumes when compared to typically developing and IQ-matched developmentally delayed groups (Courchesne et al., 2001; Hazlett et al., 2011).

However, there is also some disagreement between the results from head circumference and MRI studies. For example, Yankowitz et al. (2020), in their examination of high-resolution anatomical MRI images from 456 participants (age range = 6 to 25 years; autism $n = 240$ and neurotypical $n = 216$), reported that the autistic participants had larger total brain volumes across all age groups and, based on this finding, argued that brain enlargement did not normalise during childhood but rather remained evident into young adulthood. Furthermore, it appears that larger brain volume trends persist well into adulthood in the case of males (Denier et al., 2022).

There are also data suggesting that subtypes of autism may exhibit different patterns of brain overgrowth. For example, it has been reported that young children with ‘regressive autism’ (i.e. children who appear to be acquiring the expected developmental milestones between 12 to 36 months of life, but who then demonstrate a severe loss of speech and social skills) (Bradley et al., 2016) show greater total cerebral volume than those with early infantile autism (children who show evidence of atypical development between 18 months to 3 years) (Nordahl et al., 2011). Perhaps expectedly, regressive autism is associated with greater levels of intellectual impairment and functional incapacity, leading to poorer prognostic outcomes due to loss of skills in verbal communication and socialisation that are likely not to recover with time (Thompson et al., 2019).

It has been suggested that global trends on skill recovery in children with regressive autism are likely to be partially confounded by methodological considerations, such as the definitions used to classify regression and the particular methods for measuring persistent delays in communication/social skill development. For instance, in a longitudinal study of 129 autistic preschool children, Prescott and Ellis

Weismer (2022) measured receptive and expressive language outcomes in regressive and non-regressive children at four time points (average age at first measure = 44 months; average age at last measure = 66 months). Using this process, those researchers reported that the expressive-receptive language discrepancies and lower receptive language capabilities found at 44 months were not evident at 66 months, thus challenging data from cross-sectional studies focused on measuring child functioning only at one point in time.

The major limitation in research on brain volume that impedes transference of these findings to clinical settings is the argument that, although neuroimaging studies have assisted in understanding in vivo brain variations that are relevant to autism, their findings pertain to group trends that do not necessarily account for individual cases observed in clinical settings. That is, although Ecker (2017) argued that, by increasing awareness of autism-specific neurological trends relating to atypicalities in brain maturation in early childhood and variation in neuroanatomical regions of the brain, MRI investigations have helped to establish a unique pattern of neurodevelopmental factors that are characteristic of autism, this pattern does not readily translate to clinical case-by-case findings that show substantial variation in neuroanatomical phenotype.

Neuroanatomical Differences in Autism

Structural Differences

When discussing the major neuroanatomical variations most frequently reported for autistic participants, and the associations of those variations to core autism impairments and skill atypicalities, it is necessary to bear in mind that robust findings on any scientific issue must (at least) represent the features/experiences of the group under investigation and also differentiate that group from other similar clusters of individuals. Relevantly, structural neuroimaging studies suggest some evidence of group differences between autistic and non-autistic participants, but there are also large within-group variations for autistic people (Amaral et al., 2008; Ecker, 2017), attesting to the complexity and variability of the autism phenotype. In addition, the brain atypicalities observed in autism are not always unique to this condition

and are evident in other developmental disorders. Furthermore, because autism frequently co-exists with conditions such as ADHD and anxiety, it is difficult to adequately explain the relative influence of autism on brain variation. In general, findings on structural atypicalities in the brain are reported in regard to several larger neurocognitive systems that are believed to link with the defining behaviours of autism (Laidi et al., 2022). However, most research on this issue refers to alterations in brain structures and/or regions, and (for consistency) this discussion will maintain that convention.

Structural neuroimaging studies most often report that particular brain regions (i.e. frontotemporal and frontoparietal areas, amygdala, hippocampal complex, cerebellum, basal ganglia, and anterior and posterior cingulate) are altered in autistic groups and that these morphological differences contribute to the onset of autism symptomatology. Table 2 lists the brain regions that are consistently implicated in core autism features (Amaral et al., 2008; Lee et al., 2022).

To better understand the state of the field in regard to neuroanatomical differences in autism, it is salutary to briefly adopt a historical perspective. For example, in a small preliminary post-mortem study (7 autistic boys and 6 typically developed male children aged 2 to 16 years), Courchesne et al. (2011) reported that the autistic boys had 67% more neurons than the control children, and that neuron count-by-weight plots revealed that overgrowth was concentrated in the prefrontal cortex of the autistic boys. This finding led the researchers to hypothesize that accelerated brain growth occurred during the prenatal period because cortical neurons are believed not to continue developing in the postnatal period. Hazlett et al. (2011) adopted a longitudinal MRI approach to examining early growth trajectories in brain volume and cortical thickness in autistic children versus age-matched controls. MRI scans occurred at two time points (at age 2 years for 59 autistic children and 38 controls; at age 5 years for 38 autistic children and 21 controls). Findings revealed a disproportionate enlargement in temporal lobe white matter, plus increased cortical surface area in the autistic group. In contrast, the rate at which brain growth occurred across ‘multiple brain regions and tissue

Table 2 Major brain regions associated with autism symptoms¹

Social impairment	Communication deficits	Repetitive and restricted behaviours
Orbitofrontal cortex	Inferior frontal gyrus	Orbitofrontal cortex
Anterior cingulate cortex	Superior temporal sulcus	Anterior cingulate nucleus
Fusiform gyrus	Supplementary motor area	Basal ganglia
Superior temporal sulcus	Basal ganglia	Thalamus
Amygdala mirror neurons	Substantia nigra	
Inferior frontal gyrus	Thalamus	
Posterior parietal cortex	Pontine nuclei cerebellum	

¹Based on Amaral et al. (2008) and Lee (2022)

compartments' and cortical thickness remained relatively equivalent in both groups (Hazlett et al., 2011). In general terms, atypical brain growth has been identified in both grey and white matter (Durkut et al., 2022), with data obtained from post-mortem and imaging studies revealing that this is possibly due to greater surface area in the cortex, greater density of neurons, and abnormalities in the arrangement/packing of neuronal material in the brain.

Although the specific aspects of brain anatomy and function that have been associated with autism have remained reasonably consistent since these early studies, the sophistication of neuroimaging technologies and data-analysis protocols have progressed significantly, plus a dedication to resolving the methodological limitations that have led to inconclusive findings in some previous research. In particular, possible confounds such as small sample size, and within-sample heterogeneity that can occur from additional participant features such as age, sex, handedness, autism severity, and co-existing conditions (Floris et al., 2021a, 2021b), have been addressed in the more recent literature.

Brain Asymmetry

One major focus of this research has been the question of how structural and functional brain asymmetry differs in autistic children compared to typically developing children, and how that difference influences daily functioning. The typically developing brain will exhibit reasonably high symmetry, but with structural variations existing between the two hemispheres (Kuo & Massoud, 2022). The left and right sides of the brain differ in the type of information they process (such as sensory stimuli) and the particular behaviours they regulate. This right-left brain variation is referred to as hemispheric specialisation or brain lateralisation and, by permitting each hemisphere to fulfil its own particular functions, is believed to increase neural space without also increasing brain size (Rogers, 2021). fMRI studies have identified inter-hemispheric differences in overall functioning, with the left hemisphere showing evidence of greater intra-hemispheric' (i.e. within itself) activity and the right hemisphere recruiting stronger intra-hemispheric (i.e. left and right hemisphere) inputs during processing (Gotts et al., 2013) in non-autistic participants.

However, meta-analytic data suggest that autistic participants are likely to exhibit altered lateralisation, with a reduction of the typical leftward asymmetries in the language and motor regions of the brain, although effect sizes for these comparisons are generally small (Fu et al., 2020). For example, in a large-scale study (i.e. 1774 autistic participants and 1809 neurotypical control participants recruited from 54 independent data sets), Postema et al. (2019) used a harmonised protocol for image analysis to examine structural brain asymmetry in autism and reported a general trend towards decreased asymmetry in autistic participants compared to

controls, with most effects remaining unaffected by participant age, sex, IQ, symptom severity, and medication. Additionally, significant correlations were observed between autism diagnosis and variations in cortical thickness asymmetry, primarily in the medial frontal, orbitofrontal, and cingulate and inferior temporal brain regions, thought to be related to restricted, repetitive, and stereotyped behaviours in autistic participants.

Floris et al., (2021a, 2021b) argued that heterogeneity in autism samples was responsible for the statistical results being restricted to only small effect sizes, as was reported in the Postema et al. (2019) and other related studies. In an attempt to overcome this limitation, Floris et al., (2021a, 2021b) used normative modelling rather than autism versus control group comparisons to examine brain asymmetry. This modelling technique, which is similar to statistical approaches that refer to percentile rank scores to position individuals on a bell curve representing a diverse range of presentations, applies centiles of variation in a population to analyse individual differences in brain lateralisation with the aim of identifying neural stratification markers capable of creating phenotypic subtypes. The final participant sample (autism group = 259 males and 93 females; neurotypical group = 155 males and 79 females) represented both sexes and a wide age range (i.e. 6 to 30 years). Floris et al., (2021a, 2021b) mapped highly individualised trends in right- and leftward lateralisation in the language, motor, and visuospatial regions that correlated with autism symptom severity. In specific terms, most of the variance in extreme rightward pattern was accounted for by language delay, while core symptom severity explained most variance in extreme leftward pattern alterations. However, all effect sizes were small.

Further on the issue of brain asymmetry, in a relatively small (i.e. 34 autistic and 26 developmentally delayed toddlers) longitudinal study, Fu et al. (2020) used structural MRI and diffusion tensor imaging to measure grey matter asymmetries in all cortical parcellation units and white matter lateralization across the white matter skeleton at two time points (2–3 years of age (as a baseline) and at 4–5 years (review)). Results indicated that the autistic group demonstrated white matter fractional anisotropy at baseline and review, both groups showed evidence of rightward asymmetry in a notable proportion of cortical parcellation units (precentral gyrus, posterior cingulate gyrus, amygdala), and the autistic children exhibited significant changes in this asymmetry between baseline and review. Grey matter lateralisation correlated with social and communication impairment at baseline, and white matter asymmetry was significantly associated with social impairment and restricted/repetitive behaviour at review. Importantly, the autistic and developmentally delayed children were more similar than different on most measures.

In another study that applied multi-modal imaging techniques to assess inter-individual differences in integrated grey- and white-matter morphology (i.e. structure, shape, and size) in 185 autistic versus 159 non-autistic participants representing a wide age (6 to 30 years) and IQ range, Mei et al. (2022) identified one multi-modal pattern that was unique to the autistic group. That pattern related to variation in grey matter volume specifically in precentral and postcentral areas, paired with white matter alterations in the superior longitudinal fasciculus. In relation to core autism features, the variations in white matter were significantly associated with restricted and repetitive behaviour in autistic participants.

Studies designed to explore the neurological underpinnings of the social communication and social interaction impairments in autism have assessed autism-related alteration in the limbic system (amygdala, hippocampus, basal ganglia, cingulate gyrus). The initial findings, suggesting early enlargement of the amygdala that resolved with age (Greimel et al., 2013), have been extended to include more limbic system units. More recently, Banker and colleagues (2021) commented that structural variations in the hippocampus are likely to have a greater influence on social impairment than was initially thought, leading them to call for further investigation of this brain region. Lee et al. (2022) examined an amygdala-connected network (defined as the regions with monosynaptic connections to the amygdala) to assess how regions linked to the amygdala might contribute to its volumetric variations. Those researchers examined volumes of 32 amygdala-linked regions in structural MRI scans taken at four time points (mean ages: 39, 52, 64, 137 months) in autistic and non-autistic children. Their findings suggested that the amygdala-linked network of autistic children showed greater diagnostic variation that increased over time, with most atypicality evident for children who exhibited larger social impairments at first measurement. Interestingly, this effect was only observed for regions with monosynaptic connections to the amygdala. Qualitative sex differences occurred in relation to the regions in which variations were most evident, with the left fusiform and superior temporal gyri being most affected in females and the bilateral subgenual anterior cingulate cortices showing greater variation in males (Lee et al., 2022). To further clarify the volumetric variations that are possibly associated with overgrowth within the limbic system, Li et al. (2022) conducted an MRI study involving 251 infants (aged 6 to 24 months) in which they took a volumetric analysis specifically of the amygdala and hippocampal subfields. These researchers reported that participants who subsequently received a diagnosis of autism also exhibited greater left and right volumes in the amygdala/hippocampal regions.

Brain Connectivity in Autism

Although some early studies reported that the brain connectivity patterns of autistic participants differed from those of typically developing peers by exhibiting distinctive patterns of weaker connectivity between distant regions (i.e. long-range under-connectivity) paired with stronger connectivity within close brain regions (i.e. local over-connectivity) (Belmonte et al., 2004), more recent data do not offer unanimous support for this dichotomy. For example, in a systematic review of studies that employed MEG and EEG methods to assess functional and effective connectivity in autistic samples, O'Reilly et al. (2017) reported relatively strong support for long-range under-connectivity but cautioned that the patterns involving local connectivity required further clarification.

To examine the hypothesis that atypical developmental trajectories in adolescence could result in unique functional connectivity patterns, Lawrence et al. (2019) used MRI and resting-state fMRI to assess functional connectivity in the default mode network (DMN), salience network, (SN) and central executive network (CEN) during early-, mid-, and late-adolescence in 16 autistic and 22 non-autistic participants. Results indicated that functional connectivity between CEN and DMN showed significantly altered developmental trajectories in the autistic group and led to the suggestion that age should be considered in investigations of brain connectivity. To that end, recent attention has been focused on early infancy to establish whether disruptions in functional connectivity patterns in early life might be predictive of later autism onset. Dickinson et al. (2021) collected spontaneous EEG data in 65 infants (with and without familial risk for autism) at 3 months of age and applied vector regression analyses to predict the likelihood of children exhibiting autism symptoms at 18 months of age. Results indicated that the pattern of lower frontal connectivity plus elevated temporoparietal connectivity at 3 months predicted a greater presence of autism symptoms at 18 months.

In an attempt to overcome the limitation of a small sample size, Ilioska et al. (2022) examined resting-state fMRI to determine differences in functional connectivity and correlations between functional connectivity and severity of autism symptoms in 796 autistic participants (141 females) aged between 5 and 58 years and used 1028 typically developed participants (256 females) aged between 5 and 56 years as a control group. Autism was associated with hypo-connectivity that affected sensory and higher-order attentional networks, correlating with the social impairment, restricted/repetitive behaviour, and sensory atypicality features of autism. Hyper-connectivity occurred between the default mode network and the remaining brain and also between cortical and subcortical systems, correlating with social impairment and sensory processing. The lack of significant

interactions between diagnosis and age/sex indicated that the connectivity patterns found in this study were likely to be stable across the lifespan. Relatedly, a significant positive correlation between anxiety and sensory features and a significant inverse correlation between sensory features and directional frontoparietal connectivity, specifically in relation to avoiding sensory stimuli (Sarmukadam et al., 2023), suggest that connectivity may be influenced by the autistic feature of sensory sensitivity, plus the relatively high levels of anxiety that often accompany that sensitivity in autistic youth (Bitsika et al., 2016).

There is some evidence that autism may manifest differently in males and females (Mandy et al., 2012) and that that manifestation may be a product of underlying neuroanatomical differences, particularly in terms of grey and white matter (Lai et al., 2013). However, there is a paucity of research findings reported on sex differences in functional brain connectivity (Tavares et al., 2022), which was addressed by those authors. They examined resting-state fMRI data obtained from 83 autistic participants (40 females, 43 males) and 85 typically developing controls (43 females, 42 males). Autistic participants exhibited increased connectivity in the executive control network in comparison to the control group, and autistic males showed greater disruption in the cerebellum networks, with females displaying altered connectivity in visual, language, and basal ganglia networks.

Finally, the question of whether autism-related connectivity patterns might have a role in explaining individual differences in autism phenotype was addressed by Buch et al. (2023), who identified four replicable autism subgroups with distinct functional connectivity alterations linked to differences in expression of autism-related genes that influenced molecular transmission relating to synaptic functioning, G-protein coupled receptor signalling, and protein synthesis. This is a field that is in its infancy and may repay further attention.

Synaptic Functioning

At a fundamental level of neuroanatomy, synaptic functioning is linked to connectivity, and there is some evidence to indicate that synaptic functioning could be impaired in autistic people, as evidenced by studies investigating the molecular bases of autism. For example, some different gene variants have been implicated in disruptions to functioning (Südhof & Malenka, 2008). One of these, the SHANK3 gene, has received persistent attention as an ‘autism risk variant’, and although no detailed attention is being paid to genetic factors in this review, SHANK3 can be cited as an example of the effects that genetic factors may have upon synaptic functioning and the ways in which those effects are likely to influence autism risk/symptomatology.

The SHANK3 gene is estimated to be present in 1 to 2% of autism cases and is involved in encoding a protein concentrated in the brain but also present in other areas of the body (Soorya et al., 2013). This SHANK3-encoded protein plays a significant role in postsynaptic density at excitatory glutamatergic synapses and thus affects neuronal function (Vyas et al., 2021). Rare inherited and de novo mutations in the SHANK3 gene have been reported for some time in animal and human studies, with associated impacts including alterations to synaptic maturation and function, disrupted neural communication, ‘abnormal’ brain development, and impaired cognitive and behavioural functioning (e.g. Boccuto et al., 2013; Huang et al., 2023; Uchino & Waga, 2013). As examples of how the SHANK3 mutation may influence ASD features, Guo et al. (2019) found structural and functional alterations in the glutamatergic synapses of the pyramidal neurones in the anterior cingulate cortex in mice with a SHANK3 mutation and noted that this was linked to disrupted social behaviour. Using high-resolution functional and structural MRI techniques in adult male mice, Pagani et al. (2019) demonstrated the mechanism via which SHANK3 mutations related to disrupted functional connectivity and abnormal grey matter morphology in the prefrontal brain areas and argued that these alterations were associated with social-communication impairments in SHANK3 mutation carriers, such as autistic people. Vyas et al.’s (2021) review clarified the differences in synaptic functioning and plasticity likely to occur across early developmental stages in rodent models of SHANK3 for autism and identified alterations in numerous brain regions hypothesized to facilitate mis-wiring in the developing brain that created disturbances in neural output and communication, leading to the onset of autism-related social impairments.

Implications for Clinical Practice

The major source of implications for clinical practice that arise from this literature is the effect that the findings have on diagnostic procedures and treatment planning. Each of the topics reviewed above is examined in Table 3, with a view to implementing the relevant and confirmed findings in diagnostic, clinical, and treatment settings. Particular emphasis is placed upon how the clinician might incorporate the research findings about the neurological aspects of autism into their daily practice when planning diagnostic procedures, plus the ways that research findings reported above can be implemented into intervention planning and consultation with carers. To enhance that process, a table of suggested sequential steps that might be taken in clinical settings is supplied below.

The essential and underlying assumption for this paper and Table 3 is that findings from neurobiological research into

Table 3 Pathways for incorporating neurobiological research findings into clinical practice

	Findings	Diagnostic suggestions	Clinical actions
Head circumference	• Small to normal head size at birth, accelerated head size growth during first year of life, may be followed by deceleration in head circumference at about 12 to 24 months • Links with severity of social interaction and language/communication deficits with brain size growth in later childhood • Confirmed by MRI data re: larger cerebral volumes • May extend into adulthood • 'Regressive' ASD link with greater cerebral volume • Brain atypicalities may not be isolated to ASD • Key areas are frontotemporal, frontoparietal regions, amygdala, hippocampus, cerebellum, basal ganglia, and anterior/posterior cingulate • Grey and white matter inculcated • May have altered brain hemisphere lateralisation, but effect sizes are small • Some evidence of effects on language and core ASD symptoms • Some evidence of specific brain region asymmetry links with particular ASD symptoms • Evidence of long-range underconnectivity but caution needed regarding local over-connectivity • Lower frontal connectivity plus higher temporo-parietal connectivity predicts ASD symptoms at 18 months of age • Connectivity patterns stable over lifetime • Interaction between anxiety and frontoparietal connectivity and sensory features • Males and females may show different connectivity patterns • Initial indications of different functional connectivity patterns across ASD subgroups	• Take note of head size at birth, monitor head size during first 2 years • Use non-invasive measurement methods, but be aware of possible bias in adopting norm-based approaches when interpreting measurement data • Watch for emergence of ASD symptomatology soon after accelerated head size growth • Consider MRI as confirmation measure • Observe for 'regressive' ASD • Be aware of individual differences • Adopt possible multi-disorder approach (i.e. not necessarily ASD) • Undertake assessment of range of disorders	• Alert carers at birth, encourage observation of head size and ASD symptoms during first 2 years of life • Clinician to follow-up signs of small head size and ASD symptoms at 12 months and 2 years • Prepare carers for early intervention • Plan interventions that reflect links with severity in social interaction and communication
Neuroanatomical structural differences			• Alert carers to possible range of disorders associated with brain atypicalities • Discuss possible interventions for different disorders
Brain asymmetry		• Be aware of possible presence of brain lateralisation atypicality, and effects • May be indicated by ASD symptomatology	• Discuss with carers the concept of brain lateralisation and benefits of this in terms of cognitive functioning • Review differences in brain lateralisation in ASD, emphasising individual nature of effects
Brain connectivity		• Consider effects of age and sex on connectivity patterns • Understand relationship between connectivity patterns and ASD symptoms • Include connectivity in diagnosis and assessment protocols, plus setting of treatment goals and protocols, even if unobservable directly • Accept inconsistency of connectivity-ASD symptom relationships across individuals	• Explain concept of connectivity, correlates, and effects to carers • Emphasise to carers the role of connectivity in ASD symptoms as a method of understanding child's behaviour (rather than simply 'disordered') • Instil 'individual' nature of connectivity and ASD symptom patterns in discussions with carers
Synaptic functioning	• Linked with connectivity patterns • May be influenced by genes (SHANK3) • SHANK3 present in 1 to 2% of autistic individuals • Mutations of SHANK3 may be linked with disrupted social behaviour	• Consider hereditary patterns as suggestive of genetic influences on synaptic functioning, and to connectivity	• Inform carers of gene-synaptic function-connectivity links • Provide support for parents re: possible genetic aspects of synaptic functioning ASD

autism can provide valuable information to guide clinicians in several ways. As seen in column 2 of Table 3, there are some findings that can be accepted for this purpose, with the caveat that this is an active field of research, and therefore, these findings may be augmented but are relatively unlikely to be seriously challenged. Familiarity with the contents of column 2 will provide the clinician with a basic framework of knowledge to incorporate into everyday practice. Column 3 is more specific and suggests some ways in which the knowledge in column 2 might be translated into everyday clinical settings and actions. These suggestions are also vulnerable to change as knowledge advances but are designed to provide a more detailed and informed background perspective for the clinician that might (for example) extend beyond the results of standardised tests and their results. While these test results are valuable in *classifying* the autistic individual, they do not necessarily provide any *understanding* of why the person has scored in a particular way on the scale used. Incorporation of the current findings presented in column 3 into clinical thinking and reflection allows the clinician to be better informed in a basic sense but also more able to translate the column 2 findings into specific clinician actions. Column 4 extends that process to the kinds of carer-based interactions that are essential to good clinical practice by suggesting some ways in which the findings from the literature (column 2) may be made amenable to carers by helping them to understand the behaviour of their autistic child. This is an important step that takes the clinician-carer relationship beyond simple reporting of test/diagnosis results and instead involves the carer as a more informed partner in the processes of understanding why autistic behaviour occurs. As well as helping in the process of reflecting on how that behaviour might be either challenged via effective therapeutic endeavours, or simply understood and accepted as a visible manifestation of neurobiological phenomena that make the autistic person who they are, enlisting the carer in viewing the autistic person's behaviour and perspective as outcomes of organic (i.e. neurobiological) factors rather than simply being 'unusual'. This can elevate the issues confronting carers of autistic persons to a more manageable level than is common when there is no attempt to promote a real understanding of the reasons for autistic behaviour. Understanding the organic reasons for autistic behaviour can also inform functional analytic approaches that seek to explain the results that the behaviour is aimed at producing.

Conceptual and Methodological Issues for Future Research

The conceptual and methodological aspects of measurement of neurobiological parameters can influence the robustness of findings and, thereby, the applicability of

those findings to clinical contexts where the focus is on implementing diagnoses, functional assessments, therapies, and interventions in line with best-practice guidelines. In their review of three major conceptual and methodological challenges to the generalisability of findings from neuroimaging studies, Mazzone and Curatolo (2010) identified the need to (i) use research tasks that specifically target the neural processes of interest, (ii) reduce the inconsistency in research findings by focussing on homogeneous symptoms, severity, and comorbidity, and (iii) control for the effects of differences in autistic participants' ages by adopting longitudinal research methodologies.

In terms of research tasks, Elliott et al. (2020) have highlighted the difficulties in creating effective experimental tasks in studies of autistic participants in their meta-analysis of commonly used task-based fMRI measures, concluding that task-based fMRI measures do not possess sufficient stability to be used in studies designed to discover brain biomarkers or individual differences in autism. This lack of stability has often led to discrepant findings, not only because experimental tasks differ greatly from one study to the next, but also because they do not accurately represent (for example) typical social settings where autistic people experience difficulty understanding and responding to social cues (Lockhart et al., 2023). Although a great deal of research into neurobiological correlates of autism is done via MRI, Wang et al., (2013, p.2) noted that 'EEG can be used across a wider range of age groups and developmental abilities... has a higher relative tolerance for movement, has higher temporal resolution, is more clinically available, and can be used to collect repeated measurements because...it is non-invasive'. Thus, it may be that greater use of EEG could provide a more informative and stable source of data for studies of the neurobiology of autism.

Homogeneity of symptomatology, severity, and comorbidity may be enhanced by careful application of participant inclusion criteria. Despite increasing use of 'gold standard' clinical testing protocols (e.g. ADOS-2, SRS-2) to ensure that participants are classified accurately in relation to diagnosis, cognitive functioning, and severity level, congruency between participants on these variables is often not achieved despite large sample sizes, due to the heterogeneity of individual symptom profiles within the general classifications given by these standardised instruments. One possible strategy would be to extend the analysis of data from these standardised assessments and apply statistical clustering methods to identify subgroups of autistic participants within large samples (Bitsika et al., 2008; Nordahl et al., 2022).

Longitudinal studies are capable of monitoring brain alterations over time and across clearly defined developmental stages to account for the influence of life

stage-specific trajectories. Caruana et al. (2015) defined longitudinal studies as those which implement continuous or repeated measures over a pre-determined timespan in order to monitor aspects of individuals' performance or functioning over prolonged periods. This type of study is particularly valuable when investigating the associations between person-specific factors (e.g. rare *de novo* genes, aberrant connectivity) and conditions (e.g. autism core features). Recent longitudinal neuroimaging studies (e.g. Dickinson et al., 2021; Fu et al., 2020; Lawrence et al., 2019), which often implement two or three measurement points, suggest that the use of longitudinal approaches is in its infancy in this field. It is acknowledged that longitudinal research is complex, cumbersome, and costly, but also worthy of aspiring to in order to gain meaningful insight into the neurological functioning of autistic people—especially when personalised treatment is the goal.

Three further methodological issues occur reasonably frequently in research into the autism brain. First, whilst there is a strong tradition in neuroscience of using rodent models to explore neurological phenomena and pharmacological effects, rodent-focused findings cannot always be generalised to humans. Second, the functional assessment literature that is based upon understanding the reasons why a person might engage in particular patterns of behaviour often highlights the view that atypical social (and even repetitive) responses not only result from impairment but also environmental adversity and the individual's response to that adversity. If this is the case, then more in-depth insights into brain atypicalities and processes might be derived by including data collection on participants' life circumstances (e.g. stress, intervention effects) and unique experiences. Third, data-collection protocols, involving autistic children/adolescents and autistic adults with cognitive impairment, are often biased towards asking others about the experiences of the autistic person (e.g. carer-reported behavioural scales such as the SRS-2). This procedure not only minimises opportunities for the autistic person to describe their own reactions/interpretations but (at times) might also lead to invalid data that do not necessarily reflect the person's actual experiences. There is ample evidence that parents of autistic children/adolescents tend towards over- or under-reporting their children's responses, especially in relation to anxiety and mood (Bitsika & Sharpley, 2020; Bitsika et al., 2021; Sharpley et al., 2016). This appears to arise, in part, from difficulties in interpreting the autistic children's internal states on the basis of behaviour that might appear odd or unpredictable, although the parent's own anxious/depressed state may also contribute to their misinterpretation of their child's anxiety state. Therefore, incorporating autistic participants as reporters of their own experiences could be a relevant adjunct to the clinical testing protocols that are typically used for classification purposes in neuroimaging brain studies.

Some limitations to the review protocol also require acknowledgement. As stated in the opening sections of this paper, the PRISMA protocol was applied in those items that were judged to be relevant to this kind of review, which departs from a systematic review or meta-analysis in the fundamental aspect of not seeking to exhaustively review each individual piece of research, but rather to provide an overview of other reviews and reports that emphasises clinical implications. Therefore, although the relevant items from PRISMA were adopted for this review, the findings and their implications identified are limited by the period of search (the last 30 years) and the time the search was conducted (May to June 2023). It is highly likely that future research findings within the fields focussed upon in this review will challenge some of the conclusions and recommendations made here. The use of two independent searchers and raters of the literature added reliability to the process used to obtain relevant research findings, but that process could be strengthened by the use of a larger number of personnel. PubMed, PsycInfo, and Google Scholar provide a focussed and encompassing database, but there is always the possibility that some other relevant papers might appear elsewhere or be unpublished. Similarly, although the fields of research reviewed here (head size, brain volume, brain region, connectivity between brain regions, and synaptic function) represent the major identified neurobiological research foci for autism, genetic aspects were not reviewed in detail because of the relative lack of agreement across studies in their contribution to autism. That may change with time and further research and would be a valuable field to return to in future reviews.

Autism is commonly referred to as a neurodevelopmental disorder (APA, 2022), but there is ample evidence that some of the symptoms of ASD such as attention to detail, tolerance of repetitive tasks, and special/circumscribed interests may be advantageous in some workplace settings (Austin & Pisano, 2017; Bury et al., 2020). When considering autism in children, some comments have been made that the symptom of restricted interests may be alternately viewed as either obsessive (Baron-Cohen & Wheelwright, 1999) or ritualistic (Baker, 2000), implying impairment or dysfunction. However, these behaviours may be reconceptualized as strong or absorbing interests and be managed successfully in classrooms (Wood, 2021), resulting in a productive advantage in learning settings.

While this kind of reconceptualising of autistic traits is admirable, understanding *why* the particular behaviour occurs from a neurobiological perspective (rather than 'autism is just a series of impairments') and extending that into functional analytic models of behaviour can offer a logical and evidence-based link between neurophysiology and behaviour, which may be utilised by clinicians as triggers for

their actions, and also provide a bridge between the clinician and the carer so that the autistic person's behaviour is understood, accepted, and modified if needed, but without psychosocial stigma.

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