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Resting-state functional MRI and PET imaging as non-invasive tools to study (ab)normal neurodevelopment in humans and rodents

Abbreviated title: **Rs-fMRI and PET to study human and rodent neurodevelopment**

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Abstract

Neurodevelopmental disorders (NDDs) are a group of complex neurological and psychiatric disorders. Functional and molecular imaging techniques, such as resting-state functional magnetic resonance imaging (rs-fMRI) and positron emission tomography (PET), can be used to measure network activity non-invasively and longitudinally during maturation in both humans and rodent models. Here, we review the current knowledge on rs-fMRI and PET biomarkers in the study of normal and abnormal neurodevelopment, including intellectual disability (ID) (with/without epilepsy), autism spectrum disorder (ASD), and attention deficit hyperactivity disorder (ADHD), in humans and rodent models from birth until adulthood, and evaluate the cross-species translational value of the imaging biomarkers. To date, only a few isolated studies have used rs-fMRI or PET to study (abnormal) neurodevelopment in rodents during infancy, the critical period of neurodevelopment. Further work to explore the feasibility of performing functional imaging studies in infant rodent models is essential, as rs-fMRI and PET imaging in transgenic rodent models of NDDs are powerful techniques for studying disease pathogenesis, developing non-invasive preclinical imaging biomarkers of neurodevelopmental dysfunction, and evaluating treatment-response in disease-specific models.

Keywords: neurodevelopment, neurodevelopmental disorders, resting-state functional magnetic resonance imaging, positron emission tomography, rodent models

Introduction

Neurodevelopmental disorders (NDDs) are, according to the DSM-5 (APA, 2013), a broad group of complex neurological and psychiatric disorders, including intellectual disability (ID), autism spectrum disorder (ASD), and attention deficit hyperactivity disorder (ADHD) (Thapar, 2017). Globally, the prevalence numbers of NDDs are highly variable and sparse for individuals living in low- and middle-income countries (Francés, 2022). In general, the prevalence of ID, ASD, and ADHD, ranges from 0.6 to 1.4%, 0.7 to 3% and 5 to 11% respectively (Francés, 2022; Yang, 2022). Since people with NDDs often suffer from multiple comorbidities, like behavioural disturbances, epilepsy, and cognitive impairments, they represent a major public health problem (Thapar, 2017).

NDDs result from disturbances in the development of the central nervous system caused by environmental (e.g., trauma, infection, metabolic disorders) or genetic factors (Ismail, 2019). These disturbances are thought to occur at early stages of brain development, when the brain is still highly plastic and modifiable (Mohammadi-Nejad, 2018). We hypothesise that the abnormalities will continue to evolve as the immature brain develops into a mature brain. Therefore, it is crucial to study brain development in the immature brain and to follow brain development into adulthood in a non-invasive way. While in humans this process takes more than 18 years, rodent models have the advantage of reaching a mature adult brain in only three months (Flurkey, 2007). This makes rodent models ideal for studying disease mechanisms and assessing treatment response.

Imaging has been proposed as a powerful tool for the study of neurodevelopment. Structural imaging has been used in people with NDDs (Del Casale, 2022; Firouzabadi, 2022). However, structural imaging generally does not reveal abnormalities in brain volumetric parameters, and

when abnormalities are found, they often do not correlate with neurodevelopmental outcomes (Green, 2019). Functional and molecular imaging techniques, on the other hand, could provide a bridge between functional and molecular neurodevelopmental abnormalities and outcome.

Resting-state functional magnetic resonance imaging (rs-fMRI) can be used to follow the development of functional networks without the need for active participation of the subject during scanning (Fröhlich, 2016). This makes rs-fMRI the perfect imaging technique to study intrinsic brain function in infants and animal models. Rs-fMRI detects blood oxygenation level-dependent (BOLD) signals from volume elements (voxels) of the whole brain at rest, currently with a temporal resolution of 0.5 to 2 seconds within a 5-to-10 minutes scan period. Spontaneous low-frequency fluctuations (LFFs) in these BOLD signals are an indirect marker of changes in neuronal activity (Biswal, 1995). The correlations between the spontaneous LFFs of different voxels can thereby identify their functional connectivity (FC) (Biswal, 1995; Fröhlich, 2016). In the absence of external stimuli, FC networks are referred to as resting-state networks (RSNs) (Fröhlich, 2016).

Positron emission tomography (PET) is a molecular imaging technique that uses different radiotracers to detect biochemical and physiological changes, based on the quantification of the local tracer concentration (Kumar, 2008). Changes in oxygen consumption, glucose consumption, cerebral blood flow (CBF), receptor densities, neurotransmitter levels, and cerebral protein synthesis can all be detected by PET, and these changes are thought to correlate with structural and functional maturation of different brain regions (Kumar, 2008).

Both rs-fMRI and PET imaging are translational techniques that can be applied to both human and (transgenic) small-animal models in a (pre-)clinical setting. In this review, we provide an overview of the current knowledge on neurodevelopment derived from rs-fMRI and PET data in

104 healthy human and rodent models. We also give examples of how these two techniques have
105 been used to study abnormal neurodevelopment in both models in specific NDDs (ID with or
106 without epilepsy including genetic syndromes, ASD, and ADHD) and address the limitations of
107 current studies.

108 **1 Extrapolating timing of brain development from rodent models to humans**

109 Rodent models are often used as proxies for human biological processes. When using rodent
110 models in neurodevelopmental research, the ability to extrapolate the timing of brain
111 development from rodents to humans is critical (Clancy, 2007b). Compared to humans, rodents
112 have a shorter lifespan and, therefore neurodevelopment takes place in a shorter period of time.
113 After an average gestation period of 19 days in mice and 22 days in rats, rodents are born with
114 less mature brains than full-term infants (Clancy, 2001). Consequently, the critical period for
115 synaptogenesis in human foetuses starts already in-utero, whereas in rodents it occurs completely
116 ex-utero during the first three postnatal weeks (Semple, 2013). It has been suggested that
117 approximately around postnatal day (P) 7 to P13, the rat brain reaches a stage of development
118 equivalent to that of a full-term human newborn in terms of white matter development and
119 axonal outgrowth (Boksa, 2010; Semple, 2013) (Fig.1). In rodents, neurogenesis is complete by
120 around P15, whereas in humans it can continue until 2.5 years of age (Semple, 2013).
121 Myelination peaks at around P20 in rodents and between 2 and 5 years of age in humans, and
122 continues into adulthood (Nishiyama, 2021; Semple, 2013). In addition, a rodent brain reaches
123 90-95% of its adult weight between P21 and P28. A similar plateau is reached in humans at 2-3
124 years of age (Semple, 2013). Although it is an oversimplification to translate developmental
125 milestones by age between species using a linear scale, the first and second halves of rodent
126 gestation and the first postnatal week roughly correspond to the first, second, and third trimesters

of human pregnancy, respectively (Clancy, 2007a). Overall, the period from foetal age to 3 years of age is known to be the most important for brain development in humans, with rapid synaptogenesis, dendritic growth, myelination, and development of white matter fibre tracts, whereas in rodents this period encompasses the first three postnatal weeks.

2 Functional connectivity networks using resting-state functional MRI provide insight into normal brain development

2.1 Rs-fMRI in normally developing humans

Rs-fMRI studies in children before the age of three have significantly increased our knowledge of the maturation of FC during this important period of brain development (Gao, 2017; Mohammadi-Nejad, 2018). Therefore, we focus mainly on the FC changes detected by rs-fMRI during this period and relate these changes to neurodevelopmental milestones (Fig.2).

From 20 weeks of gestation until birth

The earliest rs-fMRI studies were performed *in utero* on healthy human foetuses between 20 and 26 weeks of gestation. They showed the presence of immature RSNs and interhemispheric (long-range) FC (Jakab, 2014; Schöpf, 2012; Thomason, 2013; van den Heuvel, 2018). This is followed by a period of expansion, leading to an increase in the proportion and strength of inter- and intra- (e.g., between frontal and temporal lobes) hemispheric FC, and in short-range connections (e.g., within frontal and parietal lobes) (Jakab, 2014; Thomason, 2013). Interestingly, foetuses with a mean gestational age of 33 weeks that have higher FC between the motor network and regions supporting motor function, will develop motor skills more rapidly in infancy. Moreover, in the same foetuses, reduced FC between the motor network and anterior cingulate, insula, and lateral cerebellar regions was also associated with advanced motor skills at

4 months of age (Thomason, 2018). Both findings support the idea that an earlier FC formation, as well as more active and earlier specialisation are associated with faster neurodevelopment.

The neonatal period

At term birth, some primary cortical networks, such as the somatosensory, motor, and auditory networks, are functionally synchronised and resemble adult-like topologies soon after birth (Alcauter, 2014; Doria, 2010; Fransson, 2007; Lin, 2008; Smyser, 2010; Toulmin, 2015). Higher-order networks, on the other hand, are only primitively present at birth (Table 1) (Alcauter, 2014; Doria, 2010; Gao, 2013). These primitive higher-order networks already have an important prognostic value, as early connections between these networks in preterm born infants are predictive of cognitive outcome at term equivalent age (Della Rosa, 2021). For example, higher FC strength between the medial prefrontal cortex (part of the default-mode network (DMN)) and the executive control network in newborns is associated with higher cognitive scores at 6 months of age (Della Rosa, 2021). Few thalamocortical connections, e.g., between the thalamus and the primary sensorimotor cortex and between the thalamus and the salience network, are also established in newborns (Alcauter, 2014; Toulmin, 2015). The latter may be important for the neonate, as the salience network guides selective attention, and the thalamus serves as a relay station for critical evaluation of different events (Gao, 2017). Finally, the amygdala shows FC with other brain regions, and the specific profile of these neonatal connections has been shown to be predictive of emerging anxiety and cognitive development at 6 months of age (Graham, 2016). In summary, the neonatal brain exhibits a balance between long-range connections and a high degree of local connectivity, termed “small-world” topology (Graham, 2021).

The first two years of life

Primary networks undergo little refinement and increase in volume and strength during the first two years of life (Gao, 2015). Higher-order networks and thalamocortical FC, on the other hand, undergo major changes with expansion of long-range FC, followed by further strengthening and refinement (Alcauter, 2014; Gao, 2013). This refinement leads to a significant reduction in short-range FC and the creation of long-range shortcuts (Gao, 2011). It is also known as functional specialisation and enables global and efficient information transfer (Gao, 2011). For example, the DMN is well synchronised by 1 year of age, and that has an adult-like topology by 2 years of age (Gao, 2009). Like the DMN, the salience network develops relatively early, reflecting the rapid emergence of self-awareness in the first year of life (Alcauter, 2015). This is thought to lay the foundation for the development of other higher-order networks (Alcauter, 2015). The executive control network, on the other hand, is still in an immature state at 1 year of age (Gao, 2015).

From the age of 1 year, networks begin to interact, and these network interactions are thought to be essential for normal neurodevelopment. For example, the DMN is anticorrelated with the dorsal attention network (DAN) - part of the Task Positive Network (TPN) -, and this anticorrelation is further strengthened during maturation (Gao, 2013). Thalamus-salience connections also develop, and the strength of this FC can significantly predict working memory performance and intelligence quotient (IQ) (Alcauter, 2014). Next, FC transitions to asymmetry in language regions (inferior frontal gyrus and superior temporal gyrus). The rate of this transition in infants has been shown to predict language outcomes at 4 years of age (Emerson, 2016).

Overall, rs-fMRI studies show that the first two years of life are critical for brain development, as it is during this period that the higher-order networks develop, and that strengthening, functional specialisation and interaction of the formed RSNs takes place.

From three years of age to adulthood

By three years of age, the basic functional networks are in place, after which neurodevelopment is mainly characterised by reorganisation, 'fine-tuning', plasticity, and remodelling of the established networks (Gilmore, 2018). Small-world topology does not change significantly from childhood to adulthood in terms of path length (λ) and clustering coefficient (γ) (Fair, 2009; Supekar, 2009). Nevertheless, the architecture of RSN connectivity is changing. They become more lateralised and form additional connections with other networks (Fair, 2007; Kelly, 2009). Functional specialisation, characterised by a decrease in short-range FC and an increase in long-range FC, continues into adulthood (Fair, 2009; Fair, 2007; Kelly, 2009). This leads not only to an increase in overall FC strength, but also to an increase in global and local network efficiency (Fan, 2021).

In particular higher-order networks undergo a prolonged period of developmental maturation into adulthood (C. L. Li, 2019). For example, despite the relatively early formation of the DMN, regions within the DMN, particularly between the medial prefrontal cortex and the posterior cingulate cortex, are only sparsely functionally connected during the first decade (Fair, 2008; Kelly, 2009; Supekar, 2010). These FCs develop into a cohesive, interconnected network by adulthood (Fair, 2008; Kelly, 2009; Supekar, 2010). Overall FC increases from childhood to adulthood following a non-linear asymptotic growth curve shape, the so-called functional maturation curve. This can be used to make accurate predictions about an individual's brain maturity (Dosenbach, 2010).

In summary, primary cortical networks generally develop before higher-order networks, but the critical neurodevelopmental period for each network differs between different networks (Gao, 2017). The formation of the basic RSNs occurs from the third trimester of pregnancy until three years of age. During this period, RSNs and network interactions have been shown to predict neurodevelopmental outcomes at later ages. Thereafter, RSNs strengthen and become functionally specialised, enabling efficient information processing.

2.2 Rs-fMRI in normally developing rodents

In the mid-2000s, several research groups have successfully performed rs-fMRI in rodents (Lu, 2006; Lu, 2007; Pawela, 2008; Williams, 2006; Zhao, 2008). They demonstrated the presence of brain networks in adult rats, including the primary somatosensory network, and the visual network, suggesting that BOLD fluctuations are conserved across species (Lu, 2007; Pawela, 2008; Zhao, 2008). Subsequent studies confirmed the presence of FC in (young) adult mice (Mechling, 2014; Stafford, 2014). They showed that several FC networks, including the somatosensory network, the visual network, and the DMN, as well as the 'small-world topology', could be identified in mice, and that these networks were highly translatable to human networks (Table 1) (Mechling, 2014; Stafford, 2014).

Zoratto *et al.* (2018) performed rs-fMRI in anaesthetised Wistar rats during the juvenile period at P21-25, P28-32, and P35-39. They showed an increase in FC between the three time periods, particularly between the hippocampus and striatum (Zoratto, 2018). Another study characterised the developmental changes in FC from juvenile (P30) to adult (P70-90) age in awake rats (Ma, 2018). A region-of-interest based FC analysis showed similar results to humans; first, the overall adult FC pattern was already present at juvenile age, but, to some extent, FC was still changing, especially between P30 and P49. Second, the maturation time of different RSNs differed

between regions. Third, the authors demonstrated a decrease in interhemispheric FC between homotopic counterparts during neurodevelopment. This phenomenon indicates functional specialisation. Functional specialisation was further supported by a decrease in short-range FC, and an increase in long-range FC during development from juvenile to adult age (Ma, 2018). In conclusion, neurodevelopment continues at a slow pace during the juvenile period, with findings similar to those described in humans (Fair, 2009; Fair, 2007; Kelly, 2009). As the overall whole-brain FC pattern is largely established by juvenile age, imaging at earlier stages of development would provide more critical information regarding neurodevelopment.

3 Molecular imaging with PET provides insight into normal brain development

3.1 PET studies in normally developing humans

PET studies of neurodevelopment in the healthy paediatric population are rare due to the need for ionising radiation. The high number of dividing neural progenitor cells makes the developing brain vulnerable to stressors, including ionising radiation (Verreet, 2015). Indeed, exposure to high doses of ionising radiation *in utero* has been shown to cause neurodevelopmental abnormalities in humans and rodents (Pasqual, 2020; Verreet, 2015). The embryonic period has been identified as the most vulnerable period in both species (Pasqual, 2020; Verreet, 2015). However, evidence for adverse effects of low doses (<100mGy) on global cognitive function or specific cognitive subdomains in humans is limited or inconsistent (Pasqual, 2020).

Glucose metabolism

Brain maturation is thought to be associated with regional changes in cerebral metabolism (Kinnala, 1996). 2-Deoxy-2[^{18}F]-fluoro-D-glucose ([^{18}F]-FDG) PET allows the visualisation and quantification of cerebral glucose metabolism (H. T. Chugani, 1986). Studies using [^{18}F]-FDG PET in normal neurodevelopment have only been performed in children with other disorders that

are not thought to interfere with normal development, such as a history of suspected hypoxic-ischemic brain injury (Kinnala, 1996), extracranial malignancy (London, 2014, 2015), epilepsy (H. T. Chugani, 1986; H. T. Chugani, 1987; Pilli, 2019; Trotta, 2016; Van Bogaert, 1998), or deafness (Kang, 2004). Earlier studies quantified the local cerebral metabolic rate of glucose (H. T. Chugani, 1986; H. T. Chugani, 1987; Kinnala, 1996), whereas more recent studies calculated standard uptake values (SUV) of [^{18}F]-FDG (Barber, 2018; London, 2014) or used statistical parametric methods (Kang, 2004; London, 2015; Trotta, 2016; Van Bogaert, 1998).

During the neonatal period, glucose metabolism is higher in subcortical than in cortical structures, and then gradually increases to reach adult levels by 2 years of age (H. T. Chugani, 1986; H. T. Chugani, 1987; Kinnala, 1996). Chugani *et al.* (1987) also included older individuals (5 days to 15 years). They showed that glucose metabolism continues to increase, exceeding adult values by more than twofold at 3 years of age. The rate of glucose metabolism then remains stable until about 9 years of age, after which it declines and returns to adult levels by the end of the second decade (Fig. 3) (H. T. Chugani, 1987). In contrast, more recent studies have calculated SUVs, and have shown a progressive increase in [^{18}F]-FDG uptake in different brain regions into adulthood (Barber, 2018; London, 2014). The SUV is the dimensionless ratio of the image-derived radioactivity concentration to a normalisation factor, typically the injected dose of radioactivity divided by body weight (S.-C. Huang, 2000). It is a semiquantitative measure of brain metabolism that is subject to many variables (e.g.: body composition and dose to scan time) (Barber, 2018). The calculation of the glucose metabolic rate takes into account other factors such as the arterial plasma glucose concentration (S.-C. Huang, 2000). Therefore, the calculation of the glucose metabolic rate is theoretically more accurate. It is intuitively also highly likely that the metabolic rate is high in the first decade and then declines, as this may

reflect rapid brain maturation and growth followed by more efficient signalling due to myelination and synaptic pruning.

Some studies used statistical parametric mapping to calculate the regional glucose metabolism adjusted for global activity (Kang, 2004; Trotta, 2016; Van Bogaert, 1998). Kang *et al.* (2004) included deaf children aged 1 to 15 years. The authors showed a linear increase in adjusted glucose metabolism with age in the frontal lobes (Kang, 2004). The other two studies included participants aged 6 to 38 years (Van Bogaert, 1998) and 6 to 50 years (Trotta, 2016). They showed that adjusted metabolic glucose metabolism followed a non-linear inverted U-shaped pattern in the thalamus, anterior cingulate cortex, and dorsolateral prefrontal cortex, with the highest increase mainly before the age of 30. This was followed by a linear increase in the hippocampus and regions of the cerebellum (Trotta, 2016; Van Bogaert, 1998). In conclusion, while the absolute glucose metabolism values are highest in the first years of life and then tend to decrease, the adjusted glucose metabolism values continue to increase in most brain regions, especially up to the age of 30. The latter shows that brain maturation continues well into adulthood.

One study has shown that cortical glucose metabolism also becomes increasingly asymmetric during adolescence (Pilli, 2019). However, other studies have shown little or no asymmetry between contralateral brain regions (Barber, 2018; London, 2014). Asymmetric [^{18}F]-FDG uptake may also be sex-specific, as the rate of increase and absolute values of FDG uptake differ between females and males (Kang, 2004).

Cerebral blood flow (CBF)

CBF rates can be used as a surrogate measure of local energy demand, as the two are closely related (Kumar, 2008). Few studies have used PET to assess CBF in normal developing children

using either the inhalation method with $C^{15}O_2$ or injection with $H_2{}^{15}O$ (the gold standard) (Altman, 1988; Andersen, 2019; Takahashi, 1999). In the neonatal period, CBF values are low but variable. Andersen *et al.* (2019) measured whole brain CBF in 4 healthy children within the first 3 days of life. CBF rate in these children ranged from 15 to 22.2 ml/100g/min (mean: 17.8 ml/100g/min) (Andersen, 2019). In another study, CBF values ranged from 13 to 55 ml/100g/min (mean: 23.6ml/100g/min) in 5 term born healthy neonates aged 3 to 14 days (Altman, 1988). Takahashi *et al.* (1999) calculated the ratio of CBF to that in adults, and showed that CBF is low at birth, and increases during development until about 8 years of age. More specifically, between 3 and 8 years of age, CBF values peak at 140% to 175% of adult values. After 8 years of age, CBF decreases and reaches adult levels during adolescence (Takahashi, 1999). Interestingly, this pattern follows the same trend as the developmental pattern of glucose metabolism determined by Chugani *et al.* (1986).

By analogy, arterial spin labelling MRI is able to quantify CBF. Unlike $H_2{}^{15}O$ PET, this technique can be used non-invasively and without the need for an ionising tracer, as it uses magnetically labelled arterial blood water protons as an endogenous tracer (Ferré, 2013). This technique has also been used to demonstrate an increase in CBF during the first years of life (Kim, 2018; Paniukov, 2020; Z. Wang, 2008).

Overall, PET studies to assess CBF are scarce. The few studies that have been performed have shown highly variable CBF values during the neonatal period and an increase in CBF during the first decade of life. These findings have been confirmed by arterial spin labelling MRI.

Neurotransmitters

PET can also be used to visualise and measure different neurotransmitters using specific radiotracers (Sander, 2017). Gamma-aminobutyric acid (GABA) is a major inhibitory

neurotransmitter, that plays a critical role in brain development and in physiological processes such as memory, attention, and stress reactivity (Andersson, 2019). Changes in $GABA_A$ neurotransmission in response to sensory stimuli are thought to lead to synaptic plasticity (Andersson, 2019; Kumar, 2008). This hypothesis is supported by two [^{11}C]-flumazenil (FMZ) PET studies performed in children with a history of epilepsy, which is not thought to interfere with normal development. They showed that $GABA_A$ receptor density increases rapidly during the first two years of life, eventually exceeding adult levels (D. C. Chugani, 2001; H. T. Chugani, 2013). In the following years, $GABA_A$ receptor density decreases by 25% to 50% to reach adult levels between 14 and 17.5 years in subcortical regions, and between 18 and 22 years in cortical regions (D. C. Chugani, 2001). Interestingly, during the first three postnatal months, $GABA_A$ receptor binding patterns resemble those of neonatal glucose metabolism pattern, with higher tracer binding in subcortical than in cortical regions (H. T. Chugani, 2013).

Glutamate is the major excitatory neurotransmitter that plays a role in brain development and function and binds to several receptors. One of these receptors is the metabotropic glutamate receptor 5 ($mGluR_5$), a receptor involved in neuronal proliferation and differentiation (Jansson, 2014). The tracer [^{18}F]-3-fluoro-5-[(pyridin-3-yl) ethynyl]benzonitrile (FPEB) binds to $mGluR_5$. Two [^{18}F]-FPEB PET studies have found a decreasing availability of $mGluR_5$ from young adult to older age (Leurquin-Sterk, 2016; Mecca, 2021). So far, no [^{18}F]-FPEB PET studies have been performed in a healthy population during early neurodevelopment.

Dopamine is involved in the motivational component of reward-motivated behaviour, motor control, and control of hormone release, and is therefore thought to be a driving factor in adolescent behaviour (Wahlstrom, 2010). The earliest dopamine PET study was conducted in children aged 10 years (Jucaite, 2010). In this study, the authors showed a decrease in brain D1

receptor binding from 10 to 30 years of age, most pronounced in the cerebral cortex (Jucaite, 2010). The decrease in brain dopamine D1 and D2 receptor binding with age from adulthood has also been demonstrated in PET studies using the tracers [^{11}C]-SCH23390, 3-N-[^{11}C]-methylspiperone ([^{11}C]-NMSP), and [^{11}C]-raclopride (Larsen, 2020; Suhara, 1991; Y. Wang, 1998; Wong, 1984). In conclusion, the availability of both mGluR5 and dopamine receptors decreases with advancing age. PET studies performed during the first decade of life would provide critical information on the importance of these receptors during brain maturation.

Serotonin plays an important role in neuronal proliferation, migration, and development (Kumar, 2008). In utero serotonin depletion leads to microcephaly, delayed neurogenesis, and disruption of synaptic connectivity in sensory cortices (Kumar, 2008). Serotonin has indeed been shown to be a driver of neurodevelopment (D. C. Chugani, 1999). Using of alpha[^{11}C]methyl-L-tryptophan (AMT) PET, it has been shown that the capacity for serotonin synthesis of children between the ages of 2 and 5 years of age with normal neurodevelopment is twice that of adults. This is followed by a decline towards adult levels between the ages of 5 and 14 years. In addition, serotonin levels decline to adult levels earlier in girls than in boys, corresponding to an earlier onset of puberty (D. C. Chugani, 1999).

In conclusion, a few isolated PET studies have shown that cerebral glucose metabolism, CBF, $GABA_A$ receptor density and serotonin synthesis are higher during the first decade of life and exceed adult levels, after which they decline. This underlines the importance of the first years of life for brain development. In addition, both glucose metabolism and $GABA_A$ receptor density are higher in subcortical regions than in cortical regions during the neonatal period. Further PET studies using different radiotracers in the healthy population are warranted to provide additional molecular longitudinal *in vivo* information on normal neurodevelopment.

3.2 PET studies in normally developing rodents

To our knowledge, four longitudinal [^{18}F]-FDG PET studies have been performed in rats from adolescence to adulthood (Choi, 2015; D. Jiang, 2018; Donglang Jiang, 2020; Xue, 2022). Consistent with human studies (Barber, 2018; London, 2014), [^{18}F]-FDG SUV increased in the striatum from 2 (juvenile) to 4 (adult) months of age (D. Jiang, 2018). Choi and colleagues (2015) showed that in awake male rats adjusted glucose metabolism increased in the frontal lobes from 5 (juvenile) to 10 (young adult) weeks of age, and then decreased in the left frontal cortex from 10 to 15 weeks of age. Interestingly, this non-linear inverted U-shaped pattern resembles the adjusted glucose metabolism pattern detected in humans from 6 to 50 years of age (Trotta, 2016). However, not all findings in rats were similar to the human situation. While an increase in adjusted glucose metabolism activity in the thalamus and cerebellum was observed in human adolescents (Trotta, 2016; Van Bogaert, 1998), rats showed a decrease in both brain regions between 5 and 10 weeks of age (Choi, 2015).

Three of the four longitudinal studies examined metabolic correlations (connections) between brain regions (Choi, 2015; Donglang Jiang, 2020; Xue, 2022). The first found significantly increased metabolic connectivity between the retrosplenial cortex, medial prefrontal cortex, and motor cortices from 5 to 10/15 weeks of age. Additionally, increased energy efficiency, defined as the ratio of metabolic connectivity strength to normalised FDG uptake of each brain region, was found in the retrosplenial cortex and medial prefrontal cortex with increasing age (Choi, 2015). This increased energy efficiency was also demonstrated by Jiang *et al.* (2020).

A small-world topology was found in 2-month-old (adolescent) rats (Donglang Jiang, 2020). Xue *et al.* (2022) found no change in normalised path length from adolescence (2 months) to adulthood (18 months) in rats (Xue, 2022). Both of these findings are similar to the rs-fMRI

findings in humans (Fair, 2009; Supekar, 2009). In contrast, Jiang *et al.* (2020) found a decrease in normalised path length (λ), and an increase in the small-world index from 2 to 9 months of age in rats, indicating more efficient information transfer between long-distance nodes (Donglang Jiang, 2020). However, they only included six rats.

In summary, most rodent [^{18}F]-FDG PET studies show increased adjusted glucose metabolism, increased metabolic connectivity, and increased energy efficiency from juvenile to adult age, and these findings are similar to the human situation. However, two studies also found results that were inconsistent with the human situation (Choi, 2015; Donglang Jiang, 2020). Small sample sizes and differences in methodology may explain these discrepancies. Further studies comparing the healthy human and rodent populations are warranted to determine the full translational validity of rodent neurodevelopmental PET studies.

4 Rs-fMRI and PET as tools to study abnormal early brain development

In the next section, we discuss rs-fMRI and PET studies in people with specific NDDs, namely ID (with or without epilepsy), ASD, and ADHD (Tables 1 and 2).

4.1 Intellectual disability with or without epilepsy

4.1.1 Rs-fMRI and PET in humans with intellectual disability with or without epilepsy

ID is defined as deficits in intellectual and adaptive functioning with an onset during the developmental period (APA, 2013). ID can be part of a syndrome, for example Down syndrome and Fragile X syndrome, and all ID syndromes have an increased susceptibility to developing epilepsy (Robertson, 2015). Here we discuss how rs-fMRI and PET have been used to study ID. To our knowledge, no study has used both techniques simultaneously in the same patient population.

Angelman syndrome and Prader-Willi syndrome are both characterised by ID and result from a deletion of a maternal or paternal imprinted region on chromosome 15q11-q13, a region encoding the $GABA_A$ receptor subunit genes *GABRB3*, *GABRA5*, and *GABRG3* (Hogart, 2007). In adults with Prader-Willi syndrome (19.9-29.6 years), a significantly lower [^{11}C]-FMZ binding was observed in the frontal cortex, temporal cortex, cingulate, and insula compared to controls, demonstrating that the deleted GABR genes result in a reduced number of $GABA_A$ receptors (Lucignani, 2004). Indeed, in a 19-year-old patient with Angelman syndrome caused by a pathogenic variant in *UBE3A*, [^{11}C]-FMZ binding was higher in the frontal, parietal, hippocampal, and cerebellar regions than in Angelman syndrome patients (2-6 years) with a maternal 15q11-q13 deletion (Holopainen, 2001).

Fragile X syndrome is a genetic disorder associated with ID (Telias, 2019). Both GABA and glutamate are thought to play a role in the pathogenesis of Fragile X syndrome, as evidenced by several *in vitro* studies (Telias, 2019). Indeed, significant reductions in brain $GABA_A$ and $mGluR_5$ receptors have been demonstrated in adults with Fragile X syndrome using PET imaging (Brašić, 2022; D'Hulst, 2015; Mody, 2021).

Down syndrome, also known as trisomy 21, is caused by a third copy of chromosome 21, and is characterised by ID and dysmorphic features (Gardiner, 2010). Down syndrome has been studied using rs-fMRI, and these studies have generally shown a mixed pattern of both hyper- and hypo-connectivity (Csumitta, 2022; Pujol, 2015; Wilson, 2019). Pujol et al. (2015) studied young adults (18-32 years) with Down syndrome and showed a pattern of increased FC of the ventral brain system (the amygdala/anterior temporal region, and the ventral aspect of both the anterior cingulate and frontal cortices) associated with emotional processes, motivation, and learning, and decreased FC of the dorsal brain system (dorsal prefrontal and anterior cingulate cortices, and

posterior insula) associated with executive functions. Interestingly, both patterns were negatively correlated with communication skills scores, suggesting that the pattern of FC changes as a whole may serve as a biomarker of neurodevelopmental dysfunction (Pujol, 2015). Csumitta et al. (2022) argued that it is difficult to separate neurodevelopmental abnormalities from possible age-related neurodegeneration in adults with Down syndrome, and performed rs-fMRI in children, adolescents, and young adults (7- 23 years) with Down syndrome. They found a widespread increase in FC. In addition to a younger study population, the authors suggest a different data analysis (e.g., no global signal regression) to be a possible reason for the discrepancy with the study by Pujol et al. (2015) (Csumitta, 2022).

Some genetic syndromes, such as Dravet syndrome and Rett syndrome, are characterised by an initial normal neurodevelopment followed by a neurodevelopmental arrest or regression (Haginoya, 2018; Liao, 2019). This maturational arrest has also been observed using [^{18}F]-FDG PET and may reflect a developmental regression of brain networks (Haginoya, 2018; Kumar, 2018; Villemagne, 2002). For example, while the glucose metabolism patterns were still normal in children with Dravet syndrome under the age of 3 years, a profound reduction in glucose uptake was observed in the cortex of older patients (Haginoya, 2018; Kumar, 2018). Next, an infantile glucose pattern, characterised by relatively increased glucose metabolism in the frontal cortex and cerebellum and decreased glucose metabolism in the occipital cortex, was observed in 3- to 8-year-old children with Rett syndrome (Villemagne, 2002). Yoshikawa *et al.* (1991), on the other hand, used $C^{15}O_2$ PET to demonstrate that the ratio of frontal to temporal CBF was lower than the normal age-matched ratio in children with Rett syndrome aged 3 to 18 years (Yoshikawa, 1991). Villemagne *et al.* (2002) propose that mitochondrial dysfunction is the

underlying cause of the uncoupling between brain glucose utilisation and CBF in Rett syndrome (Villemagne, 2002).

In more than 90% of cases, Rett syndrome is caused by pathogenic variants in the X-linked gene *MECP2* (Liao, 2019). This disorder is known to lead to defects in the dopaminergic neurotransmitter system. Indeed, a significant reduction in dopamine 2 receptors in the striatum has been demonstrated in patients with Rett syndrome (15-32 years) using [^{11}C]-NMSP PET (Wong, 2018).

People with ID often have epilepsy, and vice versa (Snoeijen-Schouwenaars, 2021). One subpopulation is developmental and epileptic encephalopathy (DEE), a severe condition in which cognitive function is affected by both the epilepsy and the underlying (mostly genetic) cause (Scheffer, 2020). While many studies have investigated FC changes in the context of epilepsy (Abela, 2014; Moody, 2021), a more limited number of studies have investigated the association between FC and cognitive impairment in this patient population (Paldino, 2017). In a case report of a 5-year-old DEE patient with progressive loss of developmental milestones, suppressed spontaneous BOLD fluctuations and a pervasive lack of normal FC were observed. Remarkably, following corpus callosotomy surgery, recovery of FC was demonstrated in concordance with the development of new skills (Pizoli, 2011). Furthermore, in children with childhood epilepsy with centrotemporal spikes (7-13 years), abnormal FC organisation within the DMN was shown to correlate with cognitive and socio-emotional development (Ofer, 2018). Similarly, in children with focal intractable epilepsy (8-17 years), increased FC within the DMN was associated with higher scores for working memory scores, whereas stronger anticorrelation between the DMN and the salience network was associated with higher IQ scores (Ibrahim, 2014). Finally, some

studies have shown an association between FC patterns and intelligence in children, adolescents, and adults with focal epilepsy (Qin, 2020; Songjiang, 2021; Struck, 2021).

Children with epileptic spasms syndrome also often, but not always, have neurodevelopmental delay (Arai, 2023). In this population, [^{18}F]-FDG PET has been shown to be a powerful predictive tool, when performed at the right time (Itomi, 2002). In a cohort of children with cryptogenic epileptic spasms syndrome, [^{18}F]-FDG PET performed 3 months after initial therapy was more useful for prognostication than [^{18}F]-FDG PET performed at the onset of spasms (Itomi, 2002). Children with cortical hypometabolism on PET 3 months after the start of therapy had a significantly higher rate of developmental delay at a later age (3 to 8 years). In addition, a favourable neurodevelopmental outcome was more likely if PET at the onset of epileptic spasms showed abnormalities that were not present on follow-up PET 3 months later (Itomi, 2002). Another study confirmed these results (Natsume, 2014).

In conclusion, neurotransmitter PET studies have demonstrated their utility in revealing the effects of the underlying genetic defect on neurotransmitters, which may be of interest in the development and evaluation of novel therapeutics. [^{18}F]-FDG PET and rs-fMRI findings correlate strongly with cognitive development. The use of both imaging techniques to assess and especially predict neurodevelopmental outcomes in specific ID syndromes requires further investigation.

4.1.2 Rs-fMRI and PET in rodent models of intellectual disability with or without epilepsy

To the best of our knowledge, no rs-fMRI study has been performed in a rodent model of ID. However, three PET imaging studies have been conducted in juvenile and adult rodent models of ID, namely in Dravet syndrome, Fragile X syndrome, and Rett syndrome (Afshar, 2022; Ricobaraza, 2019; Wong, 2018). Two showed results similar to those in humans (Afshar, 2022;

Wong, 2018). In the first, longitudinal [^{18}F]-FPEB PET imaging was performed in a mouse model of Fragile X syndrome (FMR1 knock-out (KO) mice) at juvenile and adult ages (Afshar, 2022). This study confirmed the reduced availability of mGluR5 throughout the brain. The second study used PET with [^{11}C]-NMSP in humans (15-32 years) and [^{11}C]-raclopride in mice with MECP2-related Rett syndrome (7-10 weeks) to assess and compare D2 dopamine receptor binding in both species. This combined human-rodent study demonstrated a significant reduction in striatal D2 dopamine receptors in the striatum in both species, suggesting that the MECP2-deficient mice are an appropriate and highly translational model to study dopaminergic deficits in Rett syndrome (Wong, 2018).

The third study showed results that appear to contradict those found in humans. An overall increase in glucose uptake was observed in a mouse model of Dravet syndrome (1-8 months) (Ricobaraza, 2019), while children older than 3 years with Dravet syndrome have reduced cortical glucose uptake (Haginoya, 2018; Kumar, 2018). The authors suggested that the influence of anti-seizure medication in patients and different normalisation methods could be a possible explanation for these conflicting results (Ricobaraza, 2019). We argue that the mismatch in neurodevelopmental stage between humans and mice may also contribute to the difference in results.

In summary, while there is some promising evidence for the translatability of PET imaging results from rodent models of ID to humans, further studies using rs-fMRI and PET in age- and genotype-matched monogenic rodent models and humans are warranted to support this hypothesis further.

4.2 Autism spectrum disorder (ASD)

4.2.1 Rs-fMRI and PET in humans with ASD

Individuals with ASD have persistent deficits in social communication and interaction combined with restricted, repetitive behaviours that are evident before the age of 3 years (APA, 2013). A large number of studies have used rs-fMRI or PET to investigate changes in individuals with ASD (for rs-fMRI reviews: (Hull, 2016; Picci, 2016; Rane, 2015); for PET reviews: (Kowalewska, 2021; X. Li, 2021; Tan, 2022; Zürcher, 2015)).

Many, but not all, rs-fMRI studies have shown long-range cortico-cortical hypoconnectivity, combined with cortico-subcortical hyperconnectivity (Cerliani, 2015; Delmonte, 2013; Di Martino, 2014; Oldehinkel, 2019). For example, FC is increased between sensorimotor and subcortical or cerebellar networks, while FC is decreased between visual association, somatosensory, and motor networks (Oldehinkel, 2019). These FC alternations are thought to reflect impaired visual-motor and multisensory integration (Oldehinkel, 2019).

FC abnormalities have also been reported within various primary and higher-order networks. In general, increased FC has been found within the motor, visual, DMN, and salience networks (Uddin, 2013; Washington, 2014). These findings have been associated with more severe autistic traits (Oldehinkel, 2019; Uddin, 2013; Washington, 2014). Uddin et al. (2013) showed that the FC pattern of the salience network was the most important discriminator of the presence/absence of ASD, and that this pattern could also predict restricted and repetitive behaviour scores (Uddin, 2013).

[^{18}F]-FDG PET studies in individuals with ASD show conflicting results. Glucose metabolism patterns of global increase (Rumsey, 1985), local decrease in temporal lobes (H. T. Chugani, 2007; Dilber, 2013), anterior cingulate cortex (Haznedar, 1997) or striatum and thalamus

(Haznedar, 2006), and mixed patterns (Anil Kumar, 2017; Chivate, 2016; Mitelman, 2018) have all been demonstrated in children or adults with ASD. Next, multiple studies have shown a lower CBF in the temporal lobes of children with ASD compared to controls (Boddaert, 2002; Duchesnay, 2011; Zilbovicius, 2000). Duchesnay *et al.* (2011) found that the pattern of right superior temporal sulcus hypoperfusion combined with left postcentral area hyperperfusion predicted of ASD with 88% accuracy. In addition, CBF in the superior temporal sulcus is negatively correlated with more severe autistic traits (Gendry Meresse, 2005).

Few PET studies have investigated possible neurotransmitter disturbances in ASD, looking at $GABA_A$, mGluR5, serotonin, and dopamine. Some studies have found no significant differences in $GABA_A$ (α5) (Fung, 2021; Horder, 2018), 5-HT2 serotonin (Girgis, 2011), and D1 or D2/3 dopamine receptor availability (Kubota, 2020; Schalbroeck, 2021a; Schalbroeck, 2021b) between individuals with ASD and controls. Others have shown decreased $GABA_A$ α5 receptor binding (Mendez, 2013), increased mGluR5 expression (Brašić, 2021; Fatemi, 2018), decreased serotonin synthesis (Chandana, 2005; D. C. Chugani, 1997) and 5-HT2 receptor binding (Beversdorf, 2012; Nakamura, 2010), increased striatal presynaptic dopamine synthesis (Nieminen-von Wendt, 2004), and increased dopamine transporter binding (Nakamura, 2010) in adults with ASD. These findings have been correlated with more severe autistic traits (Fatemi, 2018; Kubota, 2020; Nakamura, 2010). Interestingly, Murayama *et al.* (2022) performed both [^{11}C]-FLB457 PET and rs-fMRI in individuals with ASD. They found reduced extrastriatal D2/D3 receptor availability in ASD compared with controls, and the reduction was most pronounced in the thalamus. These lower levels correlated with a lower FC between the thalamus and superior temporal sulcus, and between the cerebellum and medial occipital cortex (Murayama, 2022).

579 Fragile X syndrome is a NDD characterised by ID, but it is also the leading genetic cause of
580 ASD. More than a third of the people with Fragile X syndrome also have ASD (Telias, 2019).
581 Remarkably, the reduced $GABA_A$ and mGluR5 receptor binding detected in adults with Fragile
582 X could not be replicated in more heterogeneous cohorts of adults with ASD (Brašić, 2022;
583 Brašić, 2021; D'Hulst, 2015; Horder, 2018; Mody, 2021). This finding suggests that the
584 neurotransmitter dysfunctional is a gene-specific finding, rather than being a general pattern seen
585 in all people with ASD.

586 In conclusion, the results of the rs-fMRI and PET studies in ASD are often inconsistent and
587 inconclusive. Differences in the age of participants is one factor that could influence the results,
588 as functional and molecular brain patterns change during development. First, FC abnormalities
589 have been shown to already emerge before the onset of clinical symptoms, as early as 6 months
590 of age, and may predict the diagnosis of ASD (Emerson, 2017). Second, some abnormalities
591 emerge or progress after the onset of ASD symptoms (Washington, 2014). Finally, both PET and
592 rs-fMRI studies have shown delayed maturation patterns in young children with ASD, which
593 eventually develop into a normal pattern at a later age (D. C. Chugani, 1999; Nebel, 2014;
594 Zilbovicius, 1995). We argue that other possible factors contributing to the inconsistencies
595 include the often small number of participants, the clinical heterogeneity of ASD, and
596 differences in study design and study population.

597 **4.2.2 Rs-fMRI and PET in rodent models of ASD**

598 Rodent studies typically model specific monogenic forms of ASD **(Hulbert, 2016)**. This
599 circumvents the problem of clinical and aetiological heterogeneity that is present in many of the
600 human cohort studies. Indeed, a comparison of 16 different transgenic mouse models of ASD
601 showed that all individual models were characterised by distinct, spatially distributed FC

602 changes, and that there was no abnormal FC pattern that was common to all aetiologies (Zerbi,
603 2021). This finding argues against the existence of a specific resting-state FC-based biomarker
604 for ASD (Zerbi, 2021). For example, longitudinal rs-fMRI assessment was performed at juvenile
605 (≈P34), young-adult (≈P58), and adult (≈P112) ages in two different transgenic mouse models of
606 ASD. They showed reduced FC between sensory-processing areas from juvenile to adult age in
607 the *fmr1* KO mice compared to controls, whereas reduced FC in the DMN, salience network, and
608 hippocampal areas became apparent only between adolescence and adulthood in the contactin-
609 associated protein 2 KO (*Cntnap2* KO) mice. Interestingly, the timing of the abnormal FC
610 coincides with the expression profile of both genes (Zerbi, 2018). In adult *Cntnap2* KO mice,
611 hypoconnectivity between DMN nodes was shown to be associated with reduced social
612 behaviour (Liska, 2018). Administration of oxytocin to *Cntnap2* KO mice normalized FC
613 patterns and rescued social deficits, illustrating the potential use of rs-fMRI-based biomarkers to
614 assess treatment effects in the context of neurodevelopmental dysfunction (Choe, 2022).

615 Adult Shank3B KO mice are a widely used model of ASD. The mouse model showed reduced
616 prefrontal FC, and this reduction was associated with impaired social communication (Pagani,
617 2019). Second, increased subcortical $mGluR_5$ receptor availability was observed in this mouse
618 model (Cai, 2019). Both findings were similar to those seen in studies of humans with ASD,
619 although here the increased $mGluR_5$ receptor availability was found in cortical brain regions
620 (Brašić, 2021; Fatemi, 2018). To the best of our knowledge, neither imaging study has ever been
621 performed in the specific subset of individuals with pathogenic variants in the *SHANK3* gene,
622 precluding a direct comparison with the human situation.

623 In another study, the availability of $GABA_A$ and $GABA_A$ α5 subunits was measured by
624 autoradiography using the tracers [^{11}C]-FMZ and [^{11}C]-Ro15-4513 in three different adult ASD

mouse models (*Cntnap2* KO, *Shank3B* KO, 16p11.2 deletion) (Horder, 2018). $GABA_A$ and $GABA_A$ α5 subunit availability did not differ from wild-type controls in any of the mouse models, similar to what has been shown with PET imaging in heterogeneous cohorts of adults with ASD using the same tracers (Horder, 2018).

Few studies have demonstrated the translational value of rodent rs-fMRI studies to the human ASD situation. Reduced prefrontal FC and reduced long-range FC synchronisation between prefrontal and associative cortical areas were found in both children with 16p11.2 deletion and in adult 16p11.2$^{+/-}$ mice (Bertero, 2018). One study compared FC findings in awake children with neurofibromatosis type 1 due to a heterozygous pathogenic variant in the *NF1* gene with awake, head-fixed *Nf1*$^{+/-}$ adult mice (Shofty, 2019). Although not performed at the same developmental stage, reduced FC in the cingulate cortex, and increased cortico-striatal FC were observed in both models (Shofty, 2019).

In summary, various transgenic mouse models of ASD have confirmed the presence of aberrant patterns of molecular and functional brain development. These patterns are conserved across species, although hypoconnectivity appears to be more prominent in mouse models, whereas within-network hyperconnectivity patterns are more commonly described in humans. Importantly, abnormalities in ASD detected by rs-fMRI and PET are aetiology dependent, highlighting the importance of using homogeneous study populations in both rodent and human imaging studies.

4.3 Attention deficit hyperactivity disorder (ADHD)

4.3.1 Rs-fMRI and PET in humans with ADHD

ADHD is an NDD characterised by hyperactivity-impulsivity and/or inattention (APA, 2013). In rs-fMRI studies, a delay in the maturation of higher-order networks such as the DMN is a

consistent finding (Castellanos, 2008; Fair, 2010; Qiu, 2011; Uddin, 2008). This delay in maturation is supported by several studies showing hypoconnectivity within the DMN, and a reduced anticorrelation between the DMN and the executive control network/DAN in children, adolescents, and adults with ADHD (Castellanos, 2008; Fair, 2010; Hoekzema, 2014; Marcos-Vidal, 2018; Qiu, 2011; Sun, 2012; Uddin, 2008). The reduced anticorrelation has been suggested to explain inattention, as activation of the DMN would interfere with sustained attention (Posner, 2014).

Hypoconnectivity has also been described in other higher-order networks of people with ADHD. Wang et al. (2018) investigated the effects of the single-nucleotide polymorphism (SNP) rs3746544 of the synaptosomal-associated protein 25 (SNAP25) gene, which confers a high risk for ADHD, on brain FC and on working memory capacity. They found hypoconnectivity in the anterior cingulate cortex (salience network) and in the right dorsolateral prefrontal cortex (executive control network) in children carrying the rs3746544 T allele in a homozygous state (C. Wang, 2018). These findings correlated with poor working memory performance (C. Wang, 2018). In addition to reduced prefrontal FC, reduced glucose metabolism in the prefrontal cortex has been shown in individuals with ADHD (Ernst, 1994; Zametkin, 1990). These findings, together with the fact that the prefrontal cortex encompasses both the DMN and the executive control network, suggest that the prefrontal cortex plays an important role in the pathogenesis of ADHD.

Changes in FC in other networks have shown more contradictory results. For example, FC in the cortico-striatal network has been shown to be both increased (Costa Dias, 2013; Sanefuji, 2017; Tian, 2008) and decreased (Cao, 2009; Hong, 2015; Mills, 2012; Posner, 2013) in people with ADHD. These inconsistent findings may be due to the subtype of ADHD included in the study.

For example, Sanefuji *et al.* (2017) found hyperconnectivity within the cortico-striatal network only in individuals with the hyperactive/impulsive subtype. Furthermore, the nigro-striatal network is a dopaminergic circuit (del Campo, 2013). The presence or absence of prior exposure to methylphenidate (a norepinephrine–dopamine reuptake inhibitor) may therefore also influence imaging results. Indeed, treatment with methylphenidate has an impact on imaging findings, as it has been shown to decrease striatal dopamine receptor binding (del Campo, 2013; Rosa-Neto, 2005; Volkow, 2007b), decrease subcortical dopamine synthesis (Ludolph, 2008), and increase regional CBF in the cerebellar vermis (Schweitzer, 2003) in people with ADHD. It is therefore important to consider the treatment status of patients when interpreting the results of rs-fMRI and PET studies.

Because dopamine plays a critical role in the motivational component of reward-motivated behaviour and in the control of mood and movement, dopamine dysfunction has been implicated in the pathogenesis of ADHD (Volkow, 2011). However, to date, there is no consensus on the dopamine metabolic pattern in ADHD. The tracers [^{18}F]-DOPA/[^{18}F]-FDOPA/L-[^{11}C]-DOPA, [^{11}C]-PE2I/[^{11}C]-cocaine/[^{11}C]-altropane, and [^{11}C]-raclopride can be used to measure the integrity of the presynaptic dopamine system, dopamine transport (DAT), and dopamine D2/D3 receptor binding, respectively. Several studies suggest reduced presynaptic dopamine function, particularly in subcortical regions (Forssberg, 2006; Ludolph, 2008), midbrain (Ludolph, 2008) and prefrontal cortex (Ernst, 1998), irrespective of treatment status. However, an older study failed to find presynaptic dopamine differences in the subcortex or prefrontal cortex, and found a non-significant increase in midbrain dopamine synthesis in adolescent ADHD patients, even when treated with a psychostimulant (Ernst, 1999). In addition, different studies have found inconsistent results regarding the availability of D2/D3 receptors in people with ADHD

compared with controls. One study reported a decrease in D2/D3 receptor availability (Volkow, 2007b), whereas other studies showed no differences (del Campo, 2013; Jucaite, 2005) or even an increase (Rosa-Neto, 2005). Finally, different studies have shown conflicting results regarding DAT expression. In adults with ADHD, one study found higher DAT in the right caudate nucleus (Spencer, 2007) and another found lower DAT in the left caudate nucleus and nucleus accumbens (Volkow, 2007a) compared to healthy controls. These differences have been explained by differences in the 5'DAT (*SLC6A3*) haplotype (Drgon, 2006), the degree of methylation of the *DAT1* promoter (Wiers, 2018), and medication status (Fusar-Poli, 2012).

Not only treatment status or ADHD subtype, but also sex seems to influence imaging results. For example, glucose metabolism has been shown to be lower in females with ADHD, whereas [^{18}F]-DOPA uptake has been shown to be lower in males with ADHD (Ernst, 1994; Ernst, 1998; Zametkin, 1993).

In summary, similar to ASD, ADHD is a very heterogeneous disorder, and variable imaging results may be due to differences in study design, treatment status, and clinical heterogeneity. However, several studies point toward common disease mechanisms, including delayed maturation of higher-order networks, prefrontal hypoconnectivity, and prefrontal glucose hypometabolism.

4.3.2 Rs-fMRI and PET studies in rodent models of ADHD

ADHD is a complex but highly heritable NDD, influenced by multiple genetic, social, and environmental factors (Al-Mubarak, 2020). ADHD is thought to be a polygenic rather than a monogenic disorder, so transgenic rodent models of ADHD are limited. To date, three mouse models of ADHD have been used in rs-fMRI and/or PET studies (Brown, 2011; Ha, 2020; S. M. Huang, 2016; Poirier, 2017; Zoratto, 2017).

Zoratto *et al.* (2017) applied rs-fMRI to the Naples-High-Excitability (NHE) rat model, a model with phenotypic features similar to the inattentive ADHD subtype. This rat model showed reduced FC between the prefrontal cortex, dorsal striatum, and hippocampus at adult age (Zoratto, 2017). In contrast, the 6-week-old Spontaneously Hypertensive (SHR) rat model, a model with phenotypic features similar to the hyperactive/impulsive ADHD subtype, showed stronger cortico-striato-thalamo-cortical connections compared to controls (S. M. Huang, 2016). Poirier *et al*. (2016) also found evidence for a stronger cortico-stratal network in awake 6-week-old SHR rats. Using individual component analysis (ICA), they showed a component consisting of the medial striatum and ventromedial prefrontal cortex in the SHR rats, a component that was not found in the control strains (Poirier, 2017). The inconsistent findings between the two rat models (NHE vs SHR) are similar to what has been demonstrated in humans and may be due to the different subtypes of ADHD (Sanefuji, 2017).

Next, and in contrast to what has been described in humans with ADHD (Castellanos, 2008; Fair, 2010; Qiu, 2011; Uddin, 2008), the SHR rat model showed hyperconnectivity within the DMN (S. M. Huang, 2016).

Ha *et al.* (2020) used the same SHR rat model to investigate the metabolic connections using [^{18}F]-FDG PET at 4 and 6 weeks of age. The authors showed delayed maturation of limbic and (sub-)cortical connections together with reduced right fronto-striatal connections at 6 weeks of age. The latter is inconsistent with the study by Huang *et al.* (2016), which may be due to a different imaging technique (awake [^{18}F]-FDG PET vs rs-fMRI under anaesthesia) or selection of animals (only phenotypically positive rats were selected in the study by Ha *et al.* (2020)).

Another rodent model of ADHD is the neurofibromatosis type 1 (NF1) mouse model, which has been shown to have attentional deficits. Using [^{11}C]-raclopride PET imaging, this mouse model

showed higher striatal dopamine D2 receptor binding at adult age compared to wild-type controls (Brown, 2011). Upon initiation of methylphenidate, striatal [^{11}C]-raclopride binding was restored to wild-type levels (Brown, 2011). Although there are still discrepancies between studies regarding D2 receptor availability in people with ADHD, all studies have shown that methylphenidate reduces the D2 receptor binding (del Campo, 2013; Rosa-Neto, 2005; Volkow, 2007b).

In conclusion, rodent models of ADHD have demonstrated their usefulness in investigating the pathomechanisms of ADHD. Very careful phenotyping is however required as findings need to be correlated with the correct subtype of ADHD in humans.

Future challenges and opportunities

Rodent models as standardised models for heterogeneous human study populations

Rs-fMRI and PET studies have been shown to be useful for non-invasively and longitudinally studying neurodevelopment, predicting neurodevelopmental outcomes, and evaluating the effects of therapy in both human and rodent models. To date, there is a paucity of functional and molecular imaging studies performed in humans before the age of 2 years, the critical period of neurodevelopment. This may be due to ethical considerations such as the need for sedation, and, in the case of PET imaging, the use of radioactive tracers. In addition, small sample sizes, heterogeneous study populations (e.g., variability in age, treatment, phenotype, and aetiology), and differences in imaging protocols and data analysis techniques have led to variable and sometimes conflicting results.

Transgenic rodent models could be used to circumvent these difficulties. They have comparable stages of brain development to humans, and they have a high translational potential when applied

762 to the corresponding human monogenic disorder, rather than to the general NDD population.
763 Careful aetiological stratification of study populations is therefore warranted. In this way, rodent
764 models offer an opportunity to study disease mechanisms and therapeutic response to (novel)
765 treatments in a more standardised manner, and to select the most relevant imaging modalities
766 that could later be applied in humans. Since PET and rs-fMRI may provide complementary
767 information about neurodevelopment or neurodevelopmental abnormalities, studies using both
768 techniques simultaneously would be beneficial. To cover the critical period of
769 neurodevelopment, this would imply that the imaging techniques should be applied to rodents of
770 less than three weeks old. To our knowledge, only three rs-fMRI and PET studies have been
771 performed in rodents during this period, possibly due to technical and practical considerations
772 (Guadagno, 2018; López-Picón, 2019; Radonjic, 2013). These studies have shown that the
773 developing brain is vulnerable to harmful environmental factors during the perinatal period and
774 that the subsequent neurodevelopmental abnormalities can be detected at an early age using rs-
775 fMRI and PET (Guadagno, 2018; Radonjic, 2013).

776 Challenges of small-animal rs-fMRI during the first three postnatal weeks: difficulties related to
777 small size and influences on BOLD signals.

778 There are several challenges to performing rs-fMRI in infant rodents. Firstly, the small rodent
779 must be able to be fixed in the MRI scanner, but the standard equipment available is typically
780 designed for adult rodents. One solution is to use a mouse bed for rat pups, or to adapt the mouse
781 bed for mouse pups so that the mouse is stabilised in the scanner.

782 Secondly, there is uncertainty about the effects of the anaesthesia on infant rodents, which may
783 differ from those in older animals. It is well known that the depth of anaesthesia and the
784 pharmacological effects of different anaesthetics influence BOLD signals, and hence FC patterns

(Grandjean, 2014). While the combination of vasodilating low-dose isoflurane and i.v. medetomidine is currently the standard approach, Guadagno et al. (2018) chose to use <2% isoflurane in P18 rat pups and adjusted the dose based on oxygenation and respiratory rate (+/- 42 breaths/min for P18 rats). This anaesthesia protocol would result in suppressed FC, but the authors argued that it was sufficient to perform a seed-based analysis (Guadagno, 2018). To avoid the confounding factor of anaesthesia, methods to perform rs-fMRI in awake (young) adult rodents have been explored (Becerra, 2011). However, pre-school children would also need to be sedated to perform rs-fMRI, and the translational potential of imaging results from infant rodents to infants may be higher if the depth of anaesthesia is similar.

Finally, haemodynamic responses may differ at different ages, which would result in different BOLD signals affecting the FC quantification (Colonnese, 2008; Kozberg, 2013). Colonnese et al. (2008) investigated differences in BOLD responses after forepaw stimulation in rats of different ages (P10-12, P13-P15, P20-30, and adult) (Colonnese, 2008). The earliest BOLD response was observed in P13 rats. Subsequently, the BOLD signal amplitude increased and the time to peak decreased with age. The authors stated that the BOLD changes were caused by growth and acceleration of the haemodynamic response, mainly due to the developmental up-regulation of carbonic anhydrase activity, and by the maturation of FC patterns from P13 to adulthood. In addition, both the presence of adult-like vascular density from P10-P17, and the gap-junction coupling of astrocytes (critical for neurovascular coupling) around P11 may contribute to the appearance of the BOLD response around P13. Despite the differences in the BOLD response, the authors demonstrated the effectiveness of fMRI in defining patterns of FC in developing rodents from P13 onwards (Colonnese, 2008). When performing rs-fMRI in

807 infants and young children, the same factors that may influence the haemodynamic response
808 should be considered.

809 Challenges of small-animal PET imaging during the first three postnatal weeks: the effects, mode
810 of administration, and uptake of the radiotracer.

811 There are also some technical and practical considerations when using PET imaging in the first
812 three postnatal weeks. First, the procedure involves exposure to ionising radiation
813 (approximately 25mSv per regular PET/CT scan). Low-dose radiation exposure (<100mSv) has
814 been shown to induce (epi-)genetic changes as well as abnormal neurogenesis in the brain, but
815 the extent to which this is harmful depends on many variables such as genetic background, age,
816 sex, dose, and the type of exposure (Shi, 2009). Prenatal exposure and chronic exposure have
817 been shown to be the most harmful (Tang, 2017). Few studies have investigated the effects of
818 low-dose radiation exposure in mice within the first three postnatal weeks (Buratovic, 2016;
819 Buratovic, 2014; Eriksson, 2016). They showed that a single dose of gamma radiation of
820 350mGy or more at P10 leads to altered behaviour at 2 and 4 months of age (Buratovic, 2014;
821 Eriksson, 2016). The period before P10 has been shown to be the most vulnerable, because
822 disrupted spontaneous behaviour at 2 months of age was only seen when a single dose of
823 500mGy was given at P3 or P10, but not at P19 (Eriksson, 2016). Next, repeated low-dose
824 exposures of 200mGy over 3 consecutive days (P10, P11, and P12) were shown to cause
825 disrupted behaviour at 2 months of age (Buratovic, 2016).

826 Second, the radioactive tracer used in PET imaging must be administered intravenously through
827 a tail vein catheter. The small tail size of infant rodents, especially mice, can make it difficult to
828 perform PET imaging within the first few weeks of life. Third, since the rodents need to be
829 scanned at a pre-weaning age, it is preferable to allow the rodents to recover in their mother's

cage after the procedure. This could potentially result in radioactive contamination of the mother due to urine loss from the scanned pup. In addition, rejection by the mother after the pups return to the cage has been described (Hickman, 2011).

Finally, anaesthetics are used to ensure immobilisation and to avoid motion artefacts during the scanning procedure. However, they could potentially affect PET results when studying neurodevelopment between different age groups. Anaesthetics are known to affect the cerebral vasculature, heart rate and body temperature, and these effects may alter radiotracer uptake (Miranda, 2019). Some studies have shown differential effects of isoflurane, the most commonly used anaesthetic, on physiological parameters in rodents from infancy to adulthood (Loepke, 2006; Stokes, 2021). However, it is currently unknown whether these age-dependent differential effects of anaesthetics also affect radiotracer uptake. If so, this would make it difficult to compare different stages of neurodevelopment. Second, inhaled anaesthetics, such as isoflurane and sevoflurane, could also induce cognitive impairment in rodents, but only when exposed for several hours per day (Shen, 2013). To circumvent the anaesthetic challenges, efforts are being made to perform awake PET in freely moving rodents (Miranda, 2019). However, sedation would also be required in pre-school children.

SV2A PET: a novel and promising tool to study neurodevelopment.

In recent years, several PET radiotracers have been developed to visualise synaptic vesicle glycoprotein 2A (SV2A) *in vivo* (Carson, 2022). A number of radiotracers, including [^{11}C]-UCB-J and [^{18}F]-SynVesT-1, have also been shown to bind with optimal kinetics in mice (Bertoglio, 2020; Bertoglio, 2022b). SV2A is expressed in virtually all synapses and plays an important role in the Ca^{2+}-dependent regulation of presynaptic neurotransmitter release during repetitive stimulation in all vertebrates (Janz, 1999). Therefore, SV2A quantification has been proposed as

a surrogate marker for synaptic density. SV2A PET has been used to detect pathological changes in synaptic density in humans and animal models of neurodegenerative disorders and spinal cord injury (Bertoglio, 2022a; Bertoglio, 2021; Chen, 2021; Delva, 2020). Because synapse formation and subsequent synaptic pruning are essential during neurodevelopment, and because synaptic function underlies cognition, SV2A PET may be a promising tool to study neurodevelopment. Indeed, one study showed that SV2A measurements increase during the third trimester in the foetal brain of pregnant rhesus monkeys (Rossano, 2022). In addition, individual component analysis (ICA) on SV2A PET can be used to identify presynaptic density networks (Akkermans, 2022). These networks are proposed to be neurophysiologically linked to functional RSNs, and may provide providing complementary information in disorders with both functional and molecular alterations (Fang, 2023). To our knowledge, no SV2A PET studies have been performed to study (abnormal) neurodevelopment in humans or rodent models.

Conclusion

Several studies have demonstrated how rs-fMRI and PET studies have contributed to our knowledge of neurodevelopment and neurodevelopmental abnormalities in specific NDDs, mainly in humans but also in specific rodent models. Further work to explore the feasibility of performing functional and molecular imaging studies in small infant animals is essential. Ultimately, if these challenges can be overcome, transgenic rodent models of NDDs are ideal for gaining further insight into disease pathogenesis, developing non-invasive preclinical imaging biomarkers of neurodevelopmental dysfunction, and assessing treatment response.

References

Abela, E., Rummel, C., Hauf, M., Weisstanner, C., Schindler, K., & Wiest, R. (2014). Neuroimaging of epilepsy: lesions, networks, oscillations. *Clin Neuroradiol, 24*(1), 5-15.

Afshar, S., Lule, S., Yuan, G., Qu, X., Pan, C., Whalen, M., Brownell, A. L., & Mody, M. (2022). Longitudinal PET studies of mGluR5 in FXS using an FMR1 knockout mouse model. *Transl Neurosci, 13*(1), 80-92.

Akkermans, J., Zajicek, F., Miranda, A., Adhikari, M. H., & Bertoglio, D. (2022). Identification of pre-synaptic density networks using [(11)C]UCB-J PET imaging and ICA in mice. *Neuroimage, 264*, 119771.

Al-Mubarak, B. R., Omar, A., Baz, B., Al-Abdulaziz, B., Magrashi, A. I., Al-Yemni, E., Jabaan, A., Monies, D., Abouelhoda, M., Abebe, D., Ghaziuddin, M., & Al-Tassan, N. A. (2020). Whole exome sequencing

in ADHD trios from single and multi-incident families implicates new candidate genes and highlights polygenic transmission. *European Journal of Human Genetics, 28*(8), 1098-1110.
Alcauter, S., Lin, W., Keith Smith, J., Gilmore, J. H., & Gao, W. (2015). Consistent anterior-posterior segregation of the insula during the first 2 years of life. *Cereb Cortex, 25*(5), 1176-1187.
Alcauter, S., Lin, W., Smith, J. K., Short, S. J., Goldman, B. D., Reznick, J. S., Gilmore, J. H., & Gao, W. (2014). Development of thalamocortical connectivity during infancy and its cognitive correlations. *J Neurosci, 34*(27), 9067-9075.
Altman, D. I., Powers, W. J., Perlman, J. M., Herscovitch, P., Volpe, S. L., & Volpe, J. J. (1988). Cerebral blood flow requirement for brain viability in newborn infants is lower than in adults. *Ann Neurol, 24*(2), 218-226.
Andersen, J. B., Lindberg, U., Olesen, O. V., Benoit, D., Ladefoged, C. N., Larsson, H. B., Højgaard, L., Greisen, G., & Law, I. (2019). Hybrid PET/MRI imaging in healthy unsedated newborn infants with quantitative rCBF measurements using (15)O-water PET. *J Cereb Blood Flow Metab, 39*(5), 782-793.
Andersson, J. D., Matuskey, D., & Finnema, S. J. (2019). Positron emission tomography imaging of the γ-aminobutyric acid system. *Neurosci Lett, 691*, 35-43.
Anil Kumar, B. N., Malhotra, S., Bhattacharya, A., Grover, S., & Batra, Y. K. (2017). Regional Cerebral Glucose Metabolism and its Association with Phenotype and Cognitive Functioning in Patients with Autism. *Indian J Psychol Med, 39*(3), 262-270.
APA. (2013). Diagnostic and statistical manual of mental disorders (5th ed.).
Arai, Y., Okanishi, T., Kanai, S., Nakamura, Y., Sunada, H., Murakami, H., Yamauchi, K., Noma, H., & Maegaki, Y. (2023). Prediction model for long-term seizure and developmental outcomes among children with infantile epileptic spasms syndrome. *Front Neurol, 14*, 1195252.
Barber, T. W., Veysey, D., Billah, B., & Francis, P. (2018). Normal brain metabolism on FDG PET/MRI during childhood and adolescence. *Nucl Med Commun, 39*(11), 1022-1032.
Becerra, L., Pendse, G., Chang, P. C., Bishop, J., & Borsook, D. (2011). Robust reproducible resting state networks in the awake rodent brain. *PLoS One, 6*(10), e25701.
Bertero, A., Liska, A., Pagani, M., Parolisi, R., Masferrer, M. E., Gritti, M., Pedrazzoli, M., Galbusera, A., Sarica, A., Cerasa, A., Buffelli, M., Tonini, R., Buffo, A., Gross, C., Pasqualetti, M., & Gozzi, A. (2018). Autism-associated 16p11.2 microdeletion impairs prefrontal functional connectivity in mouse and human. *Brain, 141*(7), 2055-2065.
Bertoglio, D., Halloin, N., Lombaerde, S., Jankovski, A., Verhaeghe, J., Nicaise, C., & Staelens, S. (2022a). SV2A PET Imaging Is a Noninvasive Marker for the Detection of Spinal Damage in Experimental Models of Spinal Cord Injury. *J Nucl Med, 63*(8), 1245-1251.
Bertoglio, D., Verhaeghe, J., Miranda, A., Kertesz, I., Cybulska, K., Korat, Š., Wyffels, L., Stroobants, S., Mrzljak, L., Dominguez, C., Liu, L., Skinbjerg, M., Munoz-Sanjuan, I., & Staelens, S. (2020). Validation and noninvasive kinetic modeling of [(11)C]UCB-J PET imaging in mice. *J Cereb Blood Flow Metab, 40*(6), 1351-1362.
Bertoglio, D., Verhaeghe, J., Wyffels, L., Miranda, A., Stroobants, S., Mrzljak, L., Dominguez, C., Skinbjerg, M., Bard, J., Liu, L., Munoz-Sanjuan, I., & Staelens, S. (2021). Synaptic vesicle glycoprotein 2A is affected in the CNS of Huntington's Disease mice and post-mortem human HD brain. *J Nucl Med*.
Bertoglio, D., Zajicek, F., Lombaerde, S., Miranda, A., Stroobants, S., Wang, Y., Dominguez, C., Munoz-Sanjuan, I., Bard, J., Liu, L., Verhaeghe, J., & Staelens, S. (2022b). Validation, kinetic modeling, and test-retest reproducibility of [(18)F]SynVesT-1 for PET imaging of synaptic vesicle glycoprotein 2A in mice. *J Cereb Blood Flow Metab*, 271678x221101648.
Beversdorf, D. Q., Nordgren, R. E., Bonab, A. A., Fischman, A. J., Weise, S. B., Dougherty, D. D., Felopulos, G. J., Zhou, F. C., & Bauman, M. L. (2012). 5-HT2 receptor distribution shown by [18F]

setoperone PET in high-functioning autistic adults. *J Neuropsychiatry Clin Neurosci, 24*(2), 191-197.
Biswal, B., Yetkin, F. Z., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med, 34*(4), 537-541.
Boddaert, N., Chabane, N., Barthélemy, C., Bourgeois, M., Poline, J. B., Brunelle, F., Samson, Y., & Zilbovicius, M. (2002). [Bitemporal lobe dysfonction in infantile autism: positron emission tomography study]. *J Radiol, 83*(12 Pt 1), 1829-1833.
Boksa, P. (2010). Effects of prenatal infection on brain development and behavior: a review of findings from animal models. *Brain Behav Immun, 24*(6), 881-897.
Brašić, J. R., Goodman, J. A., Nandi, A., Russell, D. S., Jennings, D., Barret, O., Martin, S. D., Slifer, K., Sedlak, T., Mathur, A. K., Seibyl, J. P., Berry-Kravis, E. M., Wong, D. F., & Budimirovic, D. B. (2022). Fragile X Mental Retardation Protein and Cerebral Expression of Metabotropic Glutamate Receptor Subtype 5 in Men with Fragile X Syndrome: A Pilot Study. *Brain Sci, 12*(3).
Brašić, J. R., Nandi, A., Russell, D. S., Jennings, D., Barret, O., Martin, S. D., Slifer, K., Sedlak, T., Seibyl, J. P., Wong, D. F., & Budimirovic, D. B. (2021). Cerebral Expression of Metabotropic Glutamate Receptor Subtype 5 in Idiopathic Autism Spectrum Disorder and Fragile X Syndrome: A Pilot Study. *Int J Mol Sci, 22*(6).
Brown, J. A., Xu, J., Diggs-Andrews, K. A., Wozniak, D. F., Mach, R. H., & Gutmann, D. H. (2011). PET imaging for attention deficit preclinical drug testing in neurofibromatosis-1 mice. *Exp Neurol, 232*(2), 333-338.
Buratovic, S., Stenerlöw, B., Fredriksson, A., Sundell-Bergman, S., & Eriksson, P. (2016). Developmental effects of fractionated low-dose exposure to gamma radiation on behaviour and susceptibility of the cholinergic system in mice. *Int J Radiat Biol, 92*(7), 371-379.
Buratovic, S., Stenerlöw, B., Fredriksson, A., Sundell-Bergman, S., Viberg, H., & Eriksson, P. (2014). Neonatal exposure to a moderate dose of ionizing radiation causes behavioural defects and altered levels of tau protein in mice. *Neurotoxicology, 45*, 48-55.
Cai, G., Wang, M., Wang, S., Liu, Y., Zhao, Y., Zhu, Y., Zhao, S., Zhang, M., Guo, B., Yao, H., Wang, W., Wang, J., & Wu, S. (2019). Brain mGluR5 in Shank3B(-/-) Mice Studied With in vivo [(18)F]FPEB PET Imaging and ex vivo Immunoblotting. *Front Psychiatry, 10*, 38.
Cao, X., Cao, Q., Long, X., Sun, L., Sui, M., Zhu, C., Zuo, X., Zang, Y., & Wang, Y. (2009). Abnormal resting-state functional connectivity patterns of the putamen in medication-naïve children with attention deficit hyperactivity disorder. *Brain Res, 1303*, 195-206.
Carson, R. E., Naganawa, M., Toyonaga, T., Koohsari, S., Yang, Y., Chen, M. K., Matuskey, D., & Finnema, S. J. (2022). Imaging of Synaptic Density in Neurodegenerative Disorders. *J Nucl Med, 63*(Suppl 1), 60s-67s.
Castellanos, F. X., Margulies, D. S., Kelly, C., Uddin, L. Q., Ghaffari, M., Kirsch, A., Shaw, D., Shehzad, Z., Di Martino, A., Biswal, B., Sonuga-Barke, E. J., Rotrosen, J., Adler, L. A., & Milham, M. P. (2008). Cingulate-precuneus interactions: a new locus of dysfunction in adult attention-deficit/hyperactivity disorder. *Biol Psychiatry, 63*(3), 332-337.
Cerliani, L., Mennes, M., Thomas, R. M., Di Martino, A., Thioux, M., & Keysers, C. (2015). Increased Functional Connectivity Between Subcortical and Cortical Resting-State Networks in Autism Spectrum Disorder. *JAMA Psychiatry, 72*(8), 767-777.
Chandana, S. R., Behen, M. E., Juhász, C., Muzik, O., Rothermel, R. D., Mangner, T. J., Chakraborty, P. K., Chugani, H. T., & Chugani, D. C. (2005). Significance of abnormalities in developmental trajectory and asymmetry of cortical serotonin synthesis in autism. *Int J Dev Neurosci, 23*(2-3), 171-182.
Chen, M. K., Mecca, A. P., Naganawa, M., Gallezot, J. D., Toyonaga, T., Mondal, J., Finnema, S. J., Lin, S. F., O'Dell, R. S., McDonald, J. W., Michalak, H. R., Vander Wyk, B., Nabulsi, N. B., Huang, Y., Arnsten, A. F., van Dyck, C. H., & Carson, R. E. (2021). Comparison of [(11)C]UCB-J and

[(18)F]FDG PET in Alzheimer's disease: A tracer kinetic modeling study. *J Cereb Blood Flow Metab*, 271678x211004312.

Chivate, R., Thakrar, P., Narang, J., Kumar, S., Verma, M., & Patkar, D. P. (2016). PET/CT in autism, A Diagnostic tool? *International Journal of Health Sciences and Research, 6*, 99-106.

Choe, K. Y., Bethlehem, R. A. I., Safrin, M., Dong, H., Salman, E., Li, Y., Grinevich, V., Golshani, P., DeNardo, L. A., Peñagarikano, O., Harris, N. G., & Geschwind, D. H. (2022). Oxytocin normalizes altered circuit connectivity for social rescue of the Cntnap2 knockout mouse. *Neuron, 110*(5), 795-808.e796.

Choi, H., Choi, Y., Kim, K. W., Kang, H., Hwang, D. W., Kim, E. E., Chung, J. K., & Lee, D. S. (2015). Maturation of metabolic connectivity of the adolescent rat brain. *Elife, 4*.

Chugani, D. C., Muzik, O., Behen, M., Rothermel, R., Janisse, J. J., Lee, J., & Chugani, H. T. (1999). Developmental changes in brain serotonin synthesis capacity in autistic and nonautistic children. *Ann Neurol, 45*(3), 287-295.

Chugani, D. C., Muzik, O., Juhász, C., Janisse, J. J., Ager, J., & Chugani, H. T. (2001). Postnatal maturation of human GABAA receptors measured with positron emission tomography. *Ann Neurol, 49*(5), 618-626.

Chugani, D. C., Muzik, O., Rothermel, R., Behen, M., Chakraborty, P., Mangner, T., da Silva, E. A., & Chugani, H. T. (1997). Altered serotonin synthesis in the dentatothalamocortical pathway in autistic boys. *Ann Neurol, 42*(4), 666-669.

Chugani, H. T., Juhász, C., Behen, M. E., Ondersma, R., & Muzik, O. (2007). Autism with facial port-wine stain: a new syndrome? *Pediatr Neurol, 37*(3), 192-199.

Chugani, H. T., Kumar, A., & Muzik, O. (2013). GABA(A) receptor imaging with positron emission tomography in the human newborn: a unique binding pattern. *Pediatr Neurol, 48*(6), 459-462.

Chugani, H. T., & Phelps, M. E. (1986). Maturational changes in cerebral function in infants determined by 18FDG positron emission tomography. *Science, 231*(4740), 840-843.

Chugani, H. T., Phelps, M. E., & Mazziotta, J. C. (1987). Positron emission tomography study of human brain functional development. *Ann Neurol, 22*(4), 487-497.

Clancy, B., Darlington, R. B., & Finlay, B. L. (2001). Translating developmental time across mammalian species. *Neuroscience, 105*(1), 7-17.

Clancy, B., Finlay, B. L., Darlington, R. B., & Anand, K. J. (2007a). Extrapolating brain development from experimental species to humans. *Neurotoxicology, 28*(5), 931-937.

Clancy, B., Kersh, B., Hyde, J., Darlington, R. B., Anand, K. J., & Finlay, B. L. (2007b). Web-based method for translating neurodevelopment from laboratory species to humans. *Neuroinformatics, 5*(1), 79-94.

Colonnese, M. T., Phillips, M. A., Constantine-Paton, M., Kaila, K., & Jasanoff, A. (2008). Development of hemodynamic responses and functional connectivity in rat somatosensory cortex. *Nat Neurosci, 11*(1), 72-79.

Costa Dias, T. G., Wilson, V. B., Bathula, D. R., Iyer, S. P., Mills, K. L., Thurlow, B. L., Stevens, C. A., Musser, E. D., Carpenter, S. D., Grayson, D. S., Mitchell, S. H., Nigg, J. T., & Fair, D. A. (2013). Reward circuit connectivity relates to delay discounting in children with attention-deficit/hyperactivity disorder. *Eur Neuropsychopharmacol, 23*(1), 33-45.

Csumitta, K. D., Gotts, S. J., Clasen, L. S., Martin, A., & Raitano Lee, N. (2022). Youth with Down syndrome display widespread increased functional connectivity during rest. *Sci Rep, 12*(1), 9836.

D'Hulst, C., Heulens, I., Van der Aa, N., Goffin, K., Koole, M., Porke, K., Van De Velde, M., Rooms, L., Van Paesschen, W., Van Esch, H., Van Laere, K., & Kooy, R. F. (2015). Positron Emission Tomography (PET) Quantification of GABAA Receptors in the Brain of Fragile X Patients. *PLoS One, 10*(7), e0131486.

del Campo, N., Fryer, T. D., Hong, Y. T., Smith, R., Brichard, L., Acosta-Cabronero, J., Chamberlain, S. R., Tait, R., Izquierdo, D., Regenthal, R., Dowson, J., Suckling, J., Baron, J. C., Aigbirhio, F. I., Robbins, T. W., Sahakian, B. J., & Müller, U. (2013). A positron emission tomography study of nigro-striatal dopaminergic mechanisms underlying attention: implications for ADHD and its treatment. *Brain, 136*(Pt 11), 3252-3270.

Del Casale, A., Ferracuti, S., Alcibiade, A., Simone, S., Modesti, M. N., & Pompili, M. (2022). Neuroanatomical correlates of autism spectrum disorders: A meta-analysis of structural magnetic resonance imaging (MRI) studies. *Psychiatry Res Neuroimaging, 325*, 111516.

Della Rosa, P. A., Canini, M., Marchetta, E., Cirillo, S., Pontesilli, S., Scotti, R., Natali Sora, M. G., Poloniato, A., Barera, G., Falini, A., Scifo, P., & Baldoli, C. (2021). The effects of the functional interplay between the Default Mode and Executive Control Resting State Networks on cognitive outcome in preterm born infants at 6 months of age. *Brain Cogn, 147*, 105669.

Delmonte, S., Gallagher, L., O'Hanlon, E., McGrath, J., & Balsters, J. H. (2013). Functional and structural connectivity of frontostriatal circuitry in Autism Spectrum Disorder. *Front Hum Neurosci, 7*, 430.

Delva, A., Van Weehaeghe, D., Koole, M., Van Laere, K., & Vandenberghe, W. (2020). Loss of Presynaptic Terminal Integrity in the Substantia Nigra in Early Parkinson's Disease. *Mov Disord, 35*(11), 1977-1986.

Di Martino, A. et al. (2014). The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism. *Mol Psychiatry, 19*(6), 659-667.

Dilber, C., Calışkan, M., Sönmezoğlu, K., Nişli, S., Mukaddes, N. M., Tatlı, B., Aydınlı, N., Ekici, B., & Özmen, M. (2013). Positron emission tomography findings in children with infantile spasms and autism. *J Clin Neurosci, 20*(3), 373-376.

Doria, V., Beckmann, C. F., Arichi, T., Merchant, N., Groppo, M., Turkheimer, F. E., Counsell, S. J., Murgasova, M., Aljabar, P., Nunes, R. G., Larkman, D. J., Rees, G., & Edwards, A. D. (2010). Emergence of resting state networks in the preterm human brain. *Proc Natl Acad Sci U S A, 107*(46), 20015-20020.

Dosenbach, N. U., Nardos, B., Cohen, A. L., Fair, D. A., Power, J. D., Church, J. A., Nelson, S. M., Wig, G. S., Vogel, A. C., Lessov-Schlaggar, C. N., Barnes, K. A., Dubis, J. W., Feczko, E., Coalson, R. S., Pruett, J. R., Jr., Barch, D. M., Petersen, S. E., & Schlaggar, B. L. (2010). Prediction of individual brain maturity using fMRI. *Science, 329*(5997), 1358-1361.

Drgon, T., Lin, Z., Wang, G.-J., Fowler, J., Pablo, J., Mash, D. C., Volkow, N., & Uhl, G. R. (2006). Common Human 5′ Dopamine Transporter (SLC6A3) Haplotypes Yield Varying Expression Levels In Vivo. *Cellular and Molecular Neurobiology, 26*(4), 873-887.

Duchesnay, E., Cachia, A., Boddaert, N., Chabane, N., Mangin, J. F., Martinot, J. L., Brunelle, F., & Zilbovicius, M. (2011). Feature selection and classification of imbalanced datasets: application to PET images of children with autistic spectrum disorders. *Neuroimage, 57*(3), 1003-1014.

Emerson, R. W. et al. (2017). Functional neuroimaging of high-risk 6-month-old infants predicts a diagnosis of autism at 24 months of age. *Sci Transl Med, 9*(393).

Emerson, R. W., Gao, W., & Lin, W. (2016). Longitudinal Study of the Emerging Functional Connectivity Asymmetry of Primary Language Regions during Infancy. *J Neurosci, 36*(42), 10883-10892.

Eriksson, P., Buratovic, S., Fredriksson, A., Stenerlöw, B., & Sundell-Bergman, S. (2016). Neonatal exposure to whole body ionizing radiation induces adult neurobehavioural defects: Critical period, dose--response effects and strain and sex comparison. *Behav Brain Res, 304*, 11-19.

Ernst, M., Liebenauer, L. L., King, A. C., Fitzgerald, G. A., Cohen, R. M., & Zametkin, A. J. (1994). Reduced brain metabolism in hyperactive girls. *J Am Acad Child Adolesc Psychiatry, 33*(6), 858-868.

Ernst, M., Zametkin, A. J., Matochik, J. A., Jons, P. H., & Cohen, R. M. (1998). DOPA decarboxylase activity in attention deficit hyperactivity disorder adults. A [fluorine-18]fluorodopa positron emission tomographic study. *J Neurosci, 18*(15), 5901-5907.

Ernst, M., Zametkin, A. J., Matochik, J. A., Pascualvaca, D., Jons, P. H., & Cohen, R. M. (1999). High midbrain [18F]DOPA accumulation in children with attention deficit hyperactivity disorder. *Am J Psychiatry, 156*(8), 1209-1215.

Fair, D. A., Cohen, A. L., Dosenbach, N. U., Church, J. A., Miezin, F. M., Barch, D. M., Raichle, M. E., Petersen, S. E., & Schlaggar, B. L. (2008). The maturing architecture of the brain's default network. *Proc Natl Acad Sci U S A, 105*(10), 4028-4032.

Fair, D. A., Cohen, A. L., Power, J. D., Dosenbach, N. U., Church, J. A., Miezin, F. M., Schlaggar, B. L., & Petersen, S. E. (2009). Functional brain networks develop from a "local to distributed" organization. *PLoS Comput Biol, 5*(5), e1000381.

Fair, D. A., Dosenbach, N. U., Church, J. A., Cohen, A. L., Brahmbhatt, S., Miezin, F. M., Barch, D. M., Raichle, M. E., Petersen, S. E., & Schlaggar, B. L. (2007). Development of distinct control networks through segregation and integration. *Proc Natl Acad Sci U S A, 104*(33), 13507-13512.

Fair, D. A., Posner, J., Nagel, B. J., Bathula, D., Dias, T. G., Mills, K. L., Blythe, M. S., Giwa, A., Schmitt, C. F., & Nigg, J. T. (2010). Atypical default network connectivity in youth with attention-deficit/hyperactivity disorder. *Biol Psychiatry, 68*(12), 1084-1091.

Fan, F., Liao, X., Lei, T., Zhao, T., Xia, M., Men, W., Wang, Y., Hu, M., Liu, J., Qin, S., Tan, S., Gao, J. H., Dong, Q., Tao, S., & He, Y. (2021). Development of the default-mode network during childhood and adolescence: A longitudinal resting-state fMRI study. *Neuroimage, 226*, 117581.

Fang, X. T., Volpi, T., Holmes, S. E., Esterlis, I., Carson, R. E., & Worhunsky, P. D. (2023). Linking resting-state network fluctuations with systems of coherent synaptic density: A multimodal fMRI and (11)C-UCB-J PET study. *Front Hum Neurosci, 17*, 1124254.

Fatemi, S. H., Wong, D. F., Brašić, J. R., Kuwabara, H., Mathur, A., Folsom, T. D., Jacob, S., Realmuto, G. M., Pardo, J. V., & Lee, S. (2018). Metabotropic glutamate receptor 5 tracer [(18)F]-FPEB displays increased binding potential in postcentral gyrus and cerebellum of male individuals with autism: a pilot PET study. *Cerebellum Ataxias, 5*, 3.

Ferré, J. C., Bannier, E., Raoult, H., Mineur, G., Carsin-Nicol, B., & Gauvrit, J. Y. (2013). Arterial spin labeling (ASL) perfusion: Techniques and clinical use. *Diagnostic and Interventional Imaging, 94*(12), 1211-1223.

Firouzabadi, F. D., Ramezanpour, S., Firouzabadi, M. D., Yousem, I. J., Puts, N. A. J., & Yousem, D. M. (2022). Neuroimaging in Attention-Deficit/Hyperactivity Disorder: Recent Advances. *AJR Am J Roentgenol, 218*(2), 321-332.

Flurkey, K., Currer, J., & Harrison, D. (2007). The Mouse in Aging Research. *The Mouse in Biomedical Research, 3*.

Forssberg, H., Fernell, E., Waters, S., Waters, N., & Tedroff, J. (2006). Altered pattern of brain dopamine synthesis in male adolescents with attention deficit hyperactivity disorder. *Behav Brain Funct, 2*, 40.

Francés, L., Quintero, J., Fernández, A., Ruiz, A., Caules, J., Fillon, G., Hervás, A., & Soler, C. V. (2022). Current state of knowledge on the prevalence of neurodevelopmental disorders in childhood according to the DSM-5: a systematic review in accordance with the PRISMA criteria. *Child Adolesc Psychiatry Ment Health, 16*(1), 27.

Fransson, P., Skiöld, B., Horsch, S., Nordell, A., Blennow, M., Lagercrantz, H., & Aden, U. (2007). Resting-state networks in the infant brain. *Proc Natl Acad Sci U S A, 104*(39), 15531-15536.

Fröhlich, F. (2016). Chapter 13 - Imaging Functional Networks With MRI. In F. Fröhlich (Ed.), *Network Neuroscience* (pp. 177-185). San Diego: Academic Press.

Fung, L. K., Flores, R. E., Gu, M., Sun, K. L., James, D., Schuck, R. K., Jo, B., Park, J. H., Lee, B. C., Jung, J. H., Kim, S. E., Saggar, M., Sacchet, M. D., Warnock, G., Khalighi, M. M., Spielman, D., Chin, F. T., & Hardan, A. Y. (2021). Thalamic and prefrontal GABA concentrations but not GABAA receptor

densities are altered in high-functioning adults with autism spectrum disorder. *Molecular Psychiatry, 26*(5), 1634-1646.
Fusar-Poli, P., Rubia, K., Rossi, G., Sartori, G., & Balottin, U. (2012). Striatal dopamine transporter alterations in ADHD: pathophysiology or adaptation to psychostimulants? A meta-analysis. *Am J Psychiatry, 169*(3), 264-272.
Gao, W., Alcauter, S., Elton, A., Hernandez-Castillo, C. R., Smith, J. K., Ramirez, J., & Lin, W. (2015). Functional Network Development During the First Year: Relative Sequence and Socioeconomic Correlations. *Cereb Cortex, 25*(9), 2919-2928.
Gao, W., Gilmore, J. H., Giovanello, K. S., Smith, J. K., Shen, D., Zhu, H., & Lin, W. (2011). Temporal and spatial evolution of brain network topology during the first two years of life. *PLoS One, 6*(9), e25278.
Gao, W., Gilmore, J. H., Shen, D., Smith, J. K., Zhu, H., & Lin, W. (2013). The synchronization within and interaction between the default and dorsal attention networks in early infancy. *Cereb Cortex, 23*(3), 594-603.
Gao, W., Lin, W., Grewen, K., & Gilmore, J. H. (2017). Functional Connectivity of the Infant Human Brain: Plastic and Modifiable. *Neuroscientist, 23*(2), 169-184.
Gao, W., Zhu, H., Giovanello, K. S., Smith, J. K., Shen, D., Gilmore, J. H., & Lin, W. (2009). Evidence on the emergence of the brain's default network from 2-week-old to 2-year-old healthy pediatric subjects. *Proc Natl Acad Sci U S A, 106*(16), 6790-6795.
Gardiner, K., Herault, Y., Lott, I. T., Antonarakis, S. E., Reeves, R. H., & Dierssen, M. (2010). Down syndrome: from understanding the neurobiology to therapy. *J Neurosci, 30*(45), 14943-14945.
Gendry Meresse, I., Zilbovicius, M., Boddaert, N., Robel, L., Philippe, A., Sfaello, I., Laurier, L., Brunelle, F., Samson, Y., Mouren, M. C., & Chabane, N. (2005). Autism severity and temporal lobe functional abnormalities. *Ann Neurol, 58*(3), 466-469.
Gilmore, J. H., Knickmeyer, R. C., & Gao, W. (2018). Imaging structural and functional brain development in early childhood. *Nat Rev Neurosci, 19*(3), 123-137.
Girgis, R. R., Slifstein, M., Xu, X., Frankle, W. G., Anagnostou, E., Wasserman, S., Pepa, L., Kolevzon, A., Abi-Dargham, A., Laruelle, M., & Hollander, E. (2011). The 5-HT(2A) receptor and serotonin transporter in Asperger's disorder: A PET study with [^{11}C]MDL 100907 and [^{11}C]DASB. *Psychiatry Res, 194*(3), 230-234.
Graham, A. M., Buss, C., Rasmussen, J. M., Rudolph, M. D., Demeter, D. V., Gilmore, J. H., Styner, M., Entringer, S., Wadhwa, P. D., & Fair, D. A. (2016). Implications of newborn amygdala connectivity for fear and cognitive development at 6-months-of-age. *Dev Cogn Neurosci, 18*, 12-25.
Graham, A. M., Marr, M., Buss, C., Sullivan, E. L., & Fair, D. A. (2021). Understanding Vulnerability and Adaptation in Early Brain Development using Network Neuroscience. *Trends Neurosci, 44*(4), 276-288.
Grandjean, J., Schroeter, A., Batata, I., & Rudin, M. (2014). Optimization of anesthesia protocol for resting-state fMRI in mice based on differential effects of anesthetics on functional connectivity patterns. *Neuroimage, 102 Pt 2*, 838-847.
Green, R. R., Bigler, E. D., Froehlich, A., Prigge, M. B. D., Zielinski, B. A., Travers, B. G., Anderson, J. S., Alexander, A., Lange, N., & Lainhart, J. E. (2019). Beery VMI and Brain Volumetric Relations in Autism Spectrum Disorder. *J Pediatr Neuropsychol, 5*(3), 77-84.
Guadagno, A., Kang, M. S., Devenyi, G. A., Mathieu, A. P., Rosa-Neto, P., Chakravarty, M., & Walker, C. D. (2018). Reduced resting-state functional connectivity of the basolateral amygdala to the medial prefrontal cortex in preweaning rats exposed to chronic early-life stress. *Brain Struct Funct, 223*(8), 3711-3729.

Ha, S., Lee, H., Choi, Y., Kang, H., Jeon, S. J., Ryu, J. H., Kim, H. J., Cheong, J. H., Lim, S., Kim, B. N., & Lee, D. S. (2020). Maturational delay and asymmetric information flow of brain connectivity in SHR model of ADHD revealed by topological analysis of metabolic networks. *Sci Rep, 10*(1), 3197.

Haginoya, K., Togashi, N., Kaneta, T., Hino-Fukuyo, N., Ishitobi, M., Kakisaka, Y., Uematsu, M., Inui, T., Okubo, Y., Sato, R., Miyabayashi, T., Arai, A., Ogiwara, I., Mazaki, E., Yamakawa, K., Iinuma, K., & Kure, S. (2018). [(18)F]fluorodeoxyglucose-positron emission tomography study of genetically confirmed patients with Dravet syndrome. *Epilepsy Res, 147*, 9-14.

Haznedar, M. M., Buchsbaum, M. S., Hazlett, E. A., LiCalzi, E. M., Cartwright, C., & Hollander, E. (2006). Volumetric analysis and three-dimensional glucose metabolic mapping of the striatum and thalamus in patients with autism spectrum disorders. *Am J Psychiatry, 163*(7), 1252-1263.

Haznedar, M. M., Buchsbaum, M. S., Metzger, M., Solimando, A., Spiegel-Cohen, J., & Hollander, E. (1997). Anterior cingulate gyrus volume and glucose metabolism in autistic disorder. *Am J Psychiatry, 154*(8), 1047-1050.

Hickman, D. L., & Swan, M. P. (2011). Effects of age of pups and removal of existing litter on pup survival during cross-fostering between multiparous outbred mice. *J Am Assoc Lab Anim Sci, 50*(5), 641-646.

Hoekzema, E., Carmona, S., Ramos-Quiroga, J. A., Richarte Fernández, V., Bosch, R., Soliva, J. C., Rovira, M., Bulbena, A., Tobeña, A., Casas, M., & Vilarroya, O. (2014). An independent components and functional connectivity analysis of resting state fMRI data points to neural network dysregulation in adult ADHD. *Hum Brain Mapp, 35*(4), 1261-1272.

Hogart, A., Nagarajan, R. P., Patzel, K. A., Yasui, D. H., & Lasalle, J. M. (2007). 15q11-13 GABAA receptor genes are normally biallelically expressed in brain yet are subject to epigenetic dysregulation in autism-spectrum disorders. *Hum Mol Genet, 16*(6), 691-703.

Holopainen, I. E., Metsähonkala, E. L., Kokkonen, H., Parkkola, R. K., Manner, T. E., Någren, K., & Korpi, E. R. (2001). Decreased binding of [11C]flumazenil in Angelman syndrome patients with GABA(A) receptor beta3 subunit deletions. *Ann Neurol, 49*(1), 110-113.

Hong, S. B., Harrison, B. J., Fornito, A., Sohn, C. H., Song, I. C., & Kim, J. W. (2015). Functional dysconnectivity of corticostriatal circuitry and differential response to methylphenidate in youth with attention-deficit/hyperactivity disorder. *J Psychiatry Neurosci, 40*(1), 46-57.

Horder, J. et al. (2018). GABA(A) receptor availability is not altered in adults with autism spectrum disorder or in mouse models. *Sci Transl Med, 10*(461).

Huang, S.-C. (2000). Anatomy of SUV. *Nuclear Medicine and Biology, 27*(7), 643-646.

Huang, S. M., Wu, Y. L., Peng, S. L., Peng, H. H., Huang, T. Y., Ho, K. C., & Wang, F. N. (2016). Inter-Strain Differences in Default Mode Network: A Resting State fMRI Study on Spontaneously Hypertensive Rat and Wistar Kyoto Rat. *Sci Rep, 6*, 21697.

Hulbert, S. W., & Jiang, Y. H. (2016). Monogenic mouse models of autism spectrum disorders: Common mechanisms and missing links. *Neuroscience, 321*, 3-23.

Hull, J. V., Dokovna, L. B., Jacokes, Z. J., Torgerson, C. M., Irimia, A., & Van Horn, J. D. (2016). Resting-State Functional Connectivity in Autism Spectrum Disorders: A Review. *Front Psychiatry, 7*, 205.

Ibrahim, G. M., Morgan, B. R., Lee, W., Smith, M. L., Donner, E. J., Wang, F., Beers, C. A., Federico, P., Taylor, M. J., Doesburg, S. M., Rutka, J. T., & Snead, O. C., 3rd. (2014). Impaired development of intrinsic connectivity networks in children with medically intractable localization-related epilepsy. *Hum Brain Mapp, 35*(11), 5686-5700.

Ismail, F. Y., & Shapiro, B. K. (2019). What are neurodevelopmental disorders? *Curr Opin Neurol, 32*(4), 611-616.

Itomi, K., Okumura, A., Negoro, T., Watanabe, K., Natsume, J., Takada, H., Tadokoro, M., & Ishigaki, T. (2002). Prognostic value of positron emission tomography in cryptogenic West syndrome. *Dev Med Child Neurol, 44*(2), 107-111.

Jakab, A., Schwartz, E., Kasprian, G., Gruber, G. M., Prayer, D., Schöpf, V., & Langs, G. (2014). Fetal functional imaging portrays heterogeneous development of emerging human brain networks. *Front Hum Neurosci, 8*, 852.

Jansson, L. C., & Åkerman, K. E. (2014). The role of glutamate and its receptors in the proliferation, migration, differentiation and survival of neural progenitor cells. *Journal of Neural Transmission, 121*(8), 819-836.

Janz, R., Goda, Y., Geppert, M., Missler, M., & Südhof, T. C. (1999). SV2A and SV2B function as redundant Ca2+ regulators in neurotransmitter release. *Neuron, 24*(4), 1003-1016.

Jiang, D., Lu, X., Li, Z., Rydberg, N., Zuo, C., Peng, F., Hua, F., Guan, Y., & Xie, F. (2018). Increased Vesicular Monoamine Transporter 2 (VMAT2) and Dopamine Transporter (DAT) Expression in Adolescent Brain Development: A Longitudinal Micro-PET/CT Study in Rodent. *Front Neurosci, 12*, 1052.

Jiang, D., Qiu, X., Ren, S., Hua, F., Kong, Y., Guan, Y., & Xie, F. (2020). Maturation of topological organization of brain networks in male adolescent rats: A longitudinal FDG-PET study. *Neuroscience Letters, 723*, 134864.

Jucaite, A., Fernell, E., Halldin, C., Forssberg, H., & Farde, L. (2005). Reduced midbrain dopamine transporter binding in male adolescents with attention-deficit/hyperactivity disorder: association between striatal dopamine markers and motor hyperactivity. *Biol Psychiatry, 57*(3), 229-238.

Jucaite, A., Forssberg, H., Karlsson, P., Halldin, C., & Farde, L. (2010). Age-related reduction in dopamine D1 receptors in the human brain: from late childhood to adulthood, a positron emission tomography study. *Neuroscience, 167*(1), 104-110.

Kang, E., Lee, D. S., Kang, H., Lee, J. S., Oh, S. H., Lee, M. C., & Kim, C. S. (2004). Age-associated changes of cerebral glucose metabolic activity in both male and female deaf children: parametric analysis using objective volume of interest and voxel-based mapping. *Neuroimage, 22*(4), 1543-1553.

Kelly, A. M., Di Martino, A., Uddin, L. Q., Shehzad, Z., Gee, D. G., Reiss, P. T., Margulies, D. S., Castellanos, F. X., & Milham, M. P. (2009). Development of anterior cingulate functional connectivity from late childhood to early adulthood. *Cereb Cortex, 19*(3), 640-657.

Kim, H. G., Lee, J. H., Choi, J. W., Han, M., Gho, S. M., & Moon, Y. (2018). Multidelay Arterial Spin-Labeling MRI in Neonates and Infants: Cerebral Perfusion Changes during Brain Maturation. *AJNR Am J Neuroradiol, 39*(10), 1912-1918.

Kinnala, A., Suhonen-Polvi, H., Aärimaa, T., Kero, P., Korvenranta, H., Ruotsalainen, U., Bergman, J., Haaparanta, M., Solin, O., Nuutila, P., & Wegelius, U. (1996). Cerebral metabolic rate for glucose during the first six months of life: an FDG positron emission tomography study. *Arch Dis Child Fetal Neonatal Ed, 74*(3), F153-157.

Kowalewska, B., Drozdz, W., & Kowalewski, L. (2021). Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) in autism research: literature review. *Ir J Psychol Med*, 1-15.

Kozberg, M. G., Chen, B. R., DeLeo, S. E., Bouchard, M. B., & Hillman, E. M. (2013). Resolving the transition from negative to positive blood oxygen level-dependent responses in the developing brain. *Proc Natl Acad Sci U S A, 110*(11), 4380-4385.

Kubota, M. et al. (2020). Binding of Dopamine D1 Receptor and Noradrenaline Transporter in Individuals with Autism Spectrum Disorder: A PET Study. *Cereb Cortex, 30*(12), 6458-6468.

Kumar, A., & Chugani, H. T. (2008). PET in the Assessment of Pediatric Brain Development and Developmental Disorders. *PET Clin, 3*(4), 487-515.

Kumar, A., Juhász, C., Luat, A., Govil-Dalela, T., Behen, M. E., Hicks, M. A., & Chugani, H. T. (2018). Evolution of Brain Glucose Metabolic Abnormalities in Children With Epilepsy and SCN1A Gene Variants. *J Child Neurol, 33*(13), 832-836.

Larsen, B., Olafsson, V., Calabro, F., Laymon, C., Tervo-Clemmens, B., Campbell, E., Minhas, D., Montez, D., Price, J., & Luna, B. (2020). Maturation of the human striatal dopamine system revealed by PET and quantitative MRI. *Nat Commun, 11*(1), 846.

Leurquin-Sterk, G., Van den Stock, J., Crunelle, C. L., de Laat, B., Weerasekera, A., Himmelreich, U., Bormans, G., & Van Laere, K. (2016). Positive Association Between Limbic Metabotropic Glutamate Receptor 5 Availability and Novelty-Seeking Temperament in Humans: An 18F-FPEB PET Study. *J Nucl Med, 57*(11), 1746-1752.

Li, C. L., Deng, Y. J., He, Y. H., Zhai, H. C., & Jia, F. C. (2019). The development of brain functional connectivity networks revealed by resting-state functional magnetic resonance imaging. *Neural Regen Res, 14*(8), 1419-1429.

Li, X., Zhang, K., He, X., Zhou, J., Jin, C., Shen, L., Gao, Y., Tian, M., & Zhang, H. (2021). Structural, Functional, and Molecular Imaging of Autism Spectrum Disorder. *Neurosci Bull, 37*(7), 1051-1071.

Liao, W. (2019). Psychomotor Dysfunction in Rett Syndrome: Insights into the Neurochemical and Circuit Roots. *Dev Neurobiol, 79*(1), 51-59.

Lin, W., Zhu, Q., Gao, W., Chen, Y., Toh, C. H., Styner, M., Gerig, G., Smith, J. K., Biswal, B., & Gilmore, J. H. (2008). Functional connectivity MR imaging reveals cortical functional connectivity in the developing brain. *AJNR Am J Neuroradiol, 29*(10), 1883-1889.

Liska, A., Bertero, A., Gomolka, R., Sabbioni, M., Galbusera, A., Barsotti, N., Panzeri, S., Scattoni, M. L., Pasqualetti, M., & Gozzi, A. (2018). Homozygous Loss of Autism-Risk Gene CNTNAP2 Results in Reduced Local and Long-Range Prefrontal Functional Connectivity. *Cereb Cortex, 28*(4), 1141-1153.

Loepke, A. W., McCann, J. C., Kurth, C. D., & McAuliffe, J. J. (2006). The physiologic effects of isoflurane anesthesia in neonatal mice. *Anesth Analg, 102*(1), 75-80.

London, K., & Howman-Giles, R. (2014). Normal cerebral FDG uptake during childhood. *Eur J Nucl Med Mol Imaging, 41*(4), 723-735.

London, K., & Howman-Giles, R. (2015). Voxel-based analysis of normal cerebral [18F]FDG uptake during childhood using statistical parametric mapping. *Neuroimage, 106*, 264-271.

López-Picón, F. R., Kirjavainen, A. K., Forsback, S., Takkinen, J. S., Peters, D., Haaparanta-Solin, M., & Solin, O. (2019). In vivo characterization of a novel norepinephrine transporter PET tracer [(18)F]NS12137 in adult and immature Sprague-Dawley rats. *Theranostics, 9*(1), 11-19.

Lu, H., Rea, W., Stein, E. A., & Yang, Y. (2006). Resting state functional connectivity in rat brain. *In Proceedings 14th Scientific Meeting, International Society for Magnetic Resonance in Medicine, Seattle*.

Lu, H., Zuo, Y., Gu, H., Waltz, J. A., Zhan, W., Scholl, C. A., Rea, W., Yang, Y., & Stein, E. A. (2007). Synchronized delta oscillations correlate with the resting-state functional MRI signal. *Proc Natl Acad Sci U S A, 104*(46), 18265-18269.

Lucignani, G., Panzacchi, A., Bosio, L., Moresco, R. M., Ravasi, L., Coppa, I., Chiumello, G., Frey, K., Koeppe, R., & Fazio, F. (2004). GABA A receptor abnormalities in Prader-Willi syndrome assessed with positron emission tomography and [11C]flumazenil. *Neuroimage, 22*(1), 22-28.

Ludolph, A. G., Kassubek, J., Schmeck, K., Glaser, C., Wunderlich, A., Buck, A. K., Reske, S. N., Fegert, J. M., & Mottaghy, F. M. (2008). Dopaminergic dysfunction in attention deficit hyperactivity disorder (ADHD), differences between pharmacologically treated and never treated young adults: a 3,4-dihdroxy-6-[18F]fluorophenyl-l-alanine PET study. *Neuroimage, 41*(3), 718-727.

Ma, Z., Ma, Y., & Zhang, N. (2018). Development of brain-wide connectivity architecture in awake rats. *Neuroimage, 176*, 380-389.

Marcos-Vidal, L., Martínez-García, M., Pretus, C., Garcia-Garcia, D., Martínez, K., Janssen, J., Vilarroya, O., Castellanos, F. X., Desco, M., Sepulcre, J., & Carmona, S. (2018). Local functional connectivity

suggests functional immaturity in children with attention-deficit/hyperactivity disorder. *Hum Brain Mapp, 39*(6), 2442-2454.
Mecca, A. P., Rogers, K., Jacobs, Z., McDonald, J. W., Michalak, H. R., DellaGioia, N., Zhao, W., Hillmer, A. T., Nabulsi, N., Lim, K., Ropchan, J., Huang, Y., Matuskey, D., Esterlis, I., Carson, R. E., & van Dyck, C. H. (2021). Effect of age on brain metabotropic glutamate receptor subtype 5 measured with [(18)F]FPEB PET. *Neuroimage, 238*, 118217.
Mechling, A. E., Hübner, N. S., Lee, H. L., Hennig, J., von Elverfeldt, D., & Harsan, L. A. (2014). Fine-grained mapping of mouse brain functional connectivity with resting-state fMRI. *Neuroimage, 96*, 203-215.
Mendez, M. A., Horder, J., Myers, J., Coghlan, S., Stokes, P., Erritzoe, D., Howes, O., Lingford-Hughes, A., Murphy, D., & Nutt, D. (2013). The brain GABA-benzodiazepine receptor alpha-5 subtype in autism spectrum disorder: a pilot [(11)C]Ro15-4513 positron emission tomography study. *Neuropharmacology, 68*, 195-201.
Mills, K. L., Bathula, D., Dias, T. G., Iyer, S. P., Fenesy, M. C., Musser, E. D., Stevens, C. A., Thurlow, B. L., Carpenter, S. D., Nagel, B. J., Nigg, J. T., & Fair, D. A. (2012). Altered cortico-striatal-thalamic connectivity in relation to spatial working memory capacity in children with ADHD. *Front Psychiatry, 3*, 2.
Miranda, A., Glorie, D., Bertoglio, D., Vleugels, J., De Bruyne, G., Stroobants, S., Staelens, S., & Verhaeghe, J. (2019). Awake (18)F-FDG PET Imaging of Memantine-Induced Brain Activation and Test-Retest in Freely Running Mice. *J Nucl Med, 60*(6), 844-850.
Mitelman, S. A., Bralet, M. C., Mehmet Haznedar, M., Hollander, E., Shihabuddin, L., Hazlett, E. A., & Buchsbaum, M. S. (2018). Positron emission tomography assessment of cerebral glucose metabolic rates in autism spectrum disorder and schizophrenia. *Brain Imaging Behav, 12*(2), 532-546.
Mody, M., Petibon, Y., Han, P., Kuruppu, D., Ma, C., Yokell, D., Neelamegam, R., Normandin, M. D., Fakhri, G. E., & Brownell, A. L. (2021). In vivo imaging of mGlu5 receptor expression in humans with Fragile X Syndrome towards development of a potential biomarker. *Sci Rep, 11*(1), 15897.
Mohammadi-Nejad, A. R., Mahmoudzadeh, M., Hassanpour, M. S., Wallois, F., Muzik, O., Papadelis, C., Hansen, A., Soltanian-Zadeh, H., Gelovani, J., & Nasiriavanaki, M. (2018). Neonatal brain resting-state functional connectivity imaging modalities. *Photoacoustics, 10*, 1-19.
Moody, J. F., Adluru, N., Alexander, A. L., & Field, A. S. (2021). The Connectomes: Methods of White Matter Tractography and Contributions of Resting State fMRI. *Semin Ultrasound CT MR, 42*(5), 507-522.
Murayama, C., Iwabuchi, T., Kato, Y., Yokokura, M., Harada, T., Goto, T., Tamayama, T., Kameno, Y., Wakuda, T., Kuwabara, H., Senju, A., Nishizawa, S., Ouchi, Y., & Yamasue, H. (2022). Extrastriatal dopamine D2/3 receptor binding, functional connectivity, and autism socio-communicational deficits: a PET and fMRI study. *Mol Psychiatry*.
Nakamura, K., Sekine, Y., Ouchi, Y., Tsujii, M., Yoshikawa, E., Futatsubashi, M., Tsuchiya, K. J., Sugihara, G., Iwata, Y., Suzuki, K., Matsuzaki, H., Suda, S., Sugiyama, T., Takei, N., & Mori, N. (2010). Brain serotonin and dopamine transporter bindings in adults with high-functioning autism. *Arch Gen Psychiatry, 67*(1), 59-68.
Natsume, J., Maeda, N., Itomi, K., Kidokoro, H., Ishihara, N., Takada, H., Okumura, A., Kubota, T., Miura, K., Aso, K., Morikawa, T., Kato, K., Negoro, T., & Watanabe, K. (2014). PET in infancy predicts long-term outcome during adolescence in cryptogenic West syndrome. *AJNR. American journal of neuroradiology, 35*(8), 1580-1585.
Nebel, M. B., Joel, S. E., Muschelli, J., Barber, A. D., Caffo, B. S., Pekar, J. J., & Mostofsky, S. H. (2014). Disruption of functional organization within the primary motor cortex in children with autism. *Hum Brain Mapp, 35*(2), 567-580.

Nieminen-von Wendt, T. S., Metsähonkala, L., Kulomäki, T. A., Aalto, S., Autti, T. H., Vanhala, R., Eskola, O., Bergman, J., Hietala, J. A., & von Wendt, L. O. (2004). Increased presynaptic dopamine function in Asperger syndrome. *Neuroreport, 15*(5), 757-760.

Nishiyama, A., Shimizu, T., Sherafat, A., & Richardson, W. D. (2021). Life-long oligodendrocyte development and plasticity. *Seminars in Cell & Developmental Biology, 116*, 25-37.

Ofer, I., Jacobs, J., Jaiser, N., Akin, B., Hennig, J., Schulze-Bonhage, A., & LeVan, P. (2018). Cognitive and behavioral comorbidities in Rolandic epilepsy and their relation with default mode network's functional connectivity and organization. *Epilepsy Behav, 78*, 179-186.

Oldehinkel, M. et al. (2019). Altered Connectivity Between Cerebellum, Visual, and Sensory-Motor Networks in Autism Spectrum Disorder: Results from the EU-AIMS Longitudinal European Autism Project. *Biol Psychiatry Cogn Neurosci Neuroimaging, 4*(3), 260-270.

Pagani, M., Bertero, A., Liska, A., Galbusera, A., Sabbioni, M., Barsotti, N., Colenbier, N., Marinazzo, D., Scattoni, M. L., Pasqualetti, M., & Gozzi, A. (2019). Deletion of Autism Risk Gene Shank3 Disrupts Prefrontal Connectivity. *J Neurosci, 39*(27), 5299-5310.

Paldino, M. J., Golriz, F., Chapieski, M. L., Zhang, W., & Chu, Z. D. (2017). Brain Network Architecture and Global Intelligence in Children with Focal Epilepsy. *AJNR Am J Neuroradiol, 38*(2), 349-356.

Paniukov, D., Lebel, R. M., Giesbrecht, G., & Lebel, C. (2020). Cerebral blood flow increases across early childhood. *Neuroimage, 204*, 116224.

Pasqual, E., Bosch de Basea, M., López-Vicente, M., Thierry-Chef, I., & Cardis, E. (2020). Neurodevelopmental effects of low dose ionizing radiation exposure: A systematic review of the epidemiological evidence. *Environment International, 136*, 105371.

Pawela, C. P., Biswal, B. B., Cho, Y. R., Kao, D. S., Li, R., Jones, S. R., Schulte, M. L., Matloub, H. S., Hudetz, A. G., & Hyde, J. S. (2008). Resting-state functional connectivity of the rat brain. *Magn Reson Med, 59*(5), 1021-1029.

Picci, G., Gotts, S. J., & Scherf, K. S. (2016). A theoretical rut: revisiting and critically evaluating the generalized under/over-connectivity hypothesis of autism. *Dev Sci, 19*(4), 524-549.

Pilli, V. K., Jeong, J. W., Konka, P., Kumar, A., Chugani, H. T., & Juhász, C. (2019). Objective PET study of glucose metabolism asymmetries in children with epilepsy: Implications for normal brain development. *Hum Brain Mapp, 40*(1), 53-64.

Pizoli, C. E., Shah, M. N., Snyder, A. Z., Shimony, J. S., Limbrick, D. D., Raichle, M. E., Schlaggar, B. L., & Smyth, M. D. (2011). Resting-state activity in development and maintenance of normal brain function. *Proc Natl Acad Sci U S A, 108*(28), 11638-11643.

Poirier, G. L., Huang, W., Tam, K., DiFranza, J. R., & King, J. A. (2017). Awake whole-brain functional connectivity alterations in the adolescent spontaneously hypertensive rat feature visual streams and striatal networks. *Brain Struct Funct, 222*(4), 1673-1683.

Posner, J., Park, C., & Wang, Z. (2014). Connecting the dots: a review of resting connectivity MRI studies in attention-deficit/hyperactivity disorder. *Neuropsychol Rev, 24*(1), 3-15.

Posner, J., Rauh, V., Gruber, A., Gat, I., Wang, Z., & Peterson, B. S. (2013). Dissociable attentional and affective circuits in medication-naïve children with attention-deficit/hyperactivity disorder. *Psychiatry Res, 213*(1), 24-30.

Pujol, J., del Hoyo, L., Blanco-Hinojo, L., de Sola, S., Macià, D., Martínez-Vilavella, G., Amor, M., Deus, J., Rodríguez, J., Farré, M., Dierssen, M., & de la Torre, R. (2015). Anomalous brain functional connectivity contributing to poor adaptive behavior in Down syndrome. *Cortex, 64*, 148-156.

Qin, L., Jiang, W., Zheng, J., Zhou, X., Zhang, Z., & Liu, J. (2020). Alterations Functional Connectivity in Temporal Lobe Epilepsy and Their Relationships With Cognitive Function: A Longitudinal Resting-State fMRI Study. *Front Neurol, 11*, 625.

Qiu, M. G., Ye, Z., Li, Q. Y., Liu, G. J., Xie, B., & Wang, J. (2011). Changes of brain structure and function in ADHD children. *Brain Topogr, 24*(3-4), 243-252.

Radonjic, M., Cappaert, N. L., de Vries, E. F., de Esch, C. E., Kuper, F. C., van Waarde, A., Dierckx, R. A., Wadman, W. J., Wolterbeek, A. P., Stierum, R. H., & de Groot, D. M. (2013). Delay and impairment in brain development and function in rat offspring after maternal exposure to methylmercury. *Toxicol Sci, 133*(1), 112-124.

Rane, P., Cochran, D., Hodge, S. M., Haselgrove, C., Kennedy, D. N., & Frazier, J. A. (2015). Connectivity in Autism: A Review of MRI Connectivity Studies. *Harv Rev Psychiatry, 23*(4), 223-244.

Ricobaraza, A., Mora-Jimenez, L., Puerta, E., Sanchez-Carpintero, R., Mingorance, A., Artieda, J., Nicolas, M. J., Besne, G., Bunuales, M., Gonzalez-Aparicio, M., Sola-Sevilla, N., Valencia, M., & Hernandez-Alcoceba, R. (2019). Epilepsy and neuropsychiatric comorbidities in mice carrying a recurrent Dravet syndrome SCN1A missense mutation. *Sci Rep, 9*(1), 14172.

Robertson, J., Hatton, C., Emerson, E., & Baines, S. (2015). Prevalence of epilepsy among people with intellectual disabilities: A systematic review. *Seizure, 29*, 46-62.

Rosa-Neto, P., Lou, H. C., Cumming, P., Pryds, O., Karrebaek, H., Lunding, J., & Gjedde, A. (2005). Methylphenidate-evoked changes in striatal dopamine correlate with inattention and impulsivity in adolescents with attention deficit hyperactivity disorder. *Neuroimage, 25*(3), 868-876.

Rossano, S., Toyonaga, T., Berg, E., Lorence, I., Fowles, K., Nabulsi, N., Ropchan, J., Li, S., Ye, Y., Felchner, Z., Kukis, D., Huang, Y., Benveniste, H., Tarantal, A. F., Groman, S., & Carson, R. E. (2022). Imaging the fetal nonhuman primate brain with SV2A positron emission tomography (PET). *Eur J Nucl Med Mol Imaging*.

Rumsey, J. M., Duara, R., Grady, C., Rapoport, J. L., Margolin, R. A., Rapoport, S. I., & Cutler, N. R. (1985). Brain Metabolism in Autism: Resting Cerebral Glucose Utilization Rates as Measured With Positron Emission Tomography. *Archives of General Psychiatry, 42*(5), 448-455.

Sander, C. Y., & Hesse, S. (2017). News and views on in-vivo imaging of neurotransmission using PET and MRI. *Q J Nucl Med Mol Imaging, 61*(4), 414-428.

Sanefuji, M., Craig, M., Parlatini, V., Mehta, M. A., Murphy, D. G., Catani, M., Cerliani, L., & Thiebaut de Schotten, M. (2017). Double-dissociation between the mechanism leading to impulsivity and inattention in Attention Deficit Hyperactivity Disorder: A resting-state functional connectivity study. *Cortex, 86*, 290-302.

Schalbroeck, R., de Geus-Oei, L. F., Selten, J. P., Yaqub, M., Schrantee, A., van Amelsvoort, T., Booij, J., & van Velden, F. H. P. (2021a). Cerebral [(18)F]-FDOPA Uptake in Autism Spectrum Disorder and Its Association with Autistic Traits. *Diagnostics (Basel), 11*(12).

Schalbroeck, R., van Velden, F. H. P., de Geus-Oei, L. F., Yaqub, M., van Amelsvoort, T., Booij, J., & Selten, J. P. (2021b). Striatal dopamine synthesis capacity in autism spectrum disorder and its relation with social defeat: an [(18)F]-FDOPA PET/CT study. *Transl Psychiatry, 11*(1), 47.

Scheffer, I. E., & Liao, J. (2020). Deciphering the concepts behind "Epileptic encephalopathy" and "Developmental and epileptic encephalopathy". *Eur J Paediatr Neurol, 24*, 11-14.

Schöpf, V., Kasprian, G., Brugger, P. C., & Prayer, D. (2012). Watching the fetal brain at 'rest'. *Int J Dev Neurosci, 30*(1), 11-17.

Schweitzer, J. B., Lee, D. O., Hanford, R. B., Tagamets, M. A., Hoffman, J. M., Grafton, S. T., & Kilts, C. D. (2003). A positron emission tomography study of methylphenidate in adults with ADHD: alterations in resting blood flow and predicting treatment response. *Neuropsychopharmacology, 28*(5), 967-973.

Semple, B. D., Blomgren, K., Gimlin, K., Ferriero, D. M., & Noble-Haeusslein, L. J. (2013). Brain development in rodents and humans: Identifying benchmarks of maturation and vulnerability to injury across species. *Progress in neurobiology, 106-107*, 1-16.

Shen, X., Dong, Y., Xu, Z., Wang, H., Miao, C., Soriano, S. G., Sun, D., Baxter, M. G., Zhang, Y., & Xie, Z. (2013). Selective anesthesia-induced neuroinflammation in developing mouse brain and cognitive impairment. *Anesthesiology, 118*(3), 502-515.

Shi, Y., Jin, R.-b., Zhao, J.-n., Tang, S.-f., Li, H.-q., & Li, T.-y. (2009). Brain positron emission tomography in preterm and term newborn infants. *Early Human Development, 85*(7), 429-432.

Shofty, B., Bergmann, E., Zur, G., Asleh, J., Bosak, N., Kavushansky, A., Castellanos, F. X., Ben-Sira, L., Packer, R. J., Vezina, G. L., Constantini, S., Acosta, M. T., & Kahn, I. (2019). Autism-associated Nf1 deficiency disrupts corticocortical and corticostriatal functional connectivity in human and mouse. *Neurobiol Dis, 130*, 104479.

Smyser, C. D., Inder, T. E., Shimony, J. S., Hill, J. E., Degnan, A. J., Snyder, A. Z., & Neil, J. J. (2010). Longitudinal analysis of neural network development in preterm infants. *Cereb Cortex, 20*(12), 2852-2862.

Snoeijen-Schouwenaars, F. M., Young, C., Rowe, C., van Ool, J. S., Schelhaas, H. J., & Shankar, R. (2021). People with epilepsy and intellectual disability: More than a sum of two conditions. *Epilepsy & Behavior, 124*, 108355.

Songjiang, L., Tijiang, Z., Heng, L., Wenjing, Z., Bo, T., Ganjun, S., Maoqiang, T., & Su, L. (2021). Impact of Brain Functional Network Properties on Intelligence in Children and Adolescents with Focal Epilepsy: A Resting-state MRI Study. *Acad Radiol, 28*(2), 225-232.

Spencer, T. J., Biederman, J., Madras, B. K., Dougherty, D. D., Bonab, A. A., Livni, E., Meltzer, P. C., Martin, J., Rauch, S., & Fischman, A. J. (2007). Further Evidence of Dopamine Transporter Dysregulation in ADHD: A Controlled PET Imaging Study Using Altropane. *Biological Psychiatry, 62*(9), 1059-1061.

Stafford, J. M., Jarrett, B. R., Miranda-Dominguez, O., Mills, B. D., Cain, N., Mihalas, S., Lahvis, G. P., Lattal, K. M., Mitchell, S. H., David, S. V., Fryer, J. D., Nigg, J. T., & Fair, D. A. (2014). Large-scale topology and the default mode network in the mouse connectome. *Proc Natl Acad Sci U S A, 111*(52), 18745-18750.

Stokes, J., Freed, A., Bornstein, R., Su, K. N., Snell, J., Pan, A., Sun, G. X., Park, K. Y., Jung, S., Worstman, H., Johnson, B. M., Morgan, P. G., Sedensky, M. M., & Johnson, S. C. (2021). Mechanisms underlying neonate-specific metabolic effects of volatile anesthetics. *Elife, 10*.

Struck, A. F., Boly, M., Hwang, G., Nair, V., Mathis, J., Nencka, A., Conant, L. L., DeYoe, E. A., Raghavan, M., Prabhakaran, V., Binder, J. R., Meyerand, M. E., & Hermann, B. P. (2021). Regional and global resting-state functional MR connectivity in temporal lobe epilepsy: Results from the Epilepsy Connectome Project. *Epilepsy Behav, 117*, 107841.

Suhara, T., Fukuda, H., Inoue, O., Itoh, T., Suzuki, K., Yamasaki, T., & Tateno, Y. (1991). Age-related changes in human D1 dopamine receptors measured by positron emission tomography. *Psychopharmacology (Berl), 103*(1), 41-45.

Sun, L., Cao, Q., Long, X., Sui, M., Cao, X., Zhu, C., Zuo, X., An, L., Song, Y., Zang, Y., & Wang, Y. (2012). Abnormal functional connectivity between the anterior cingulate and the default mode network in drug-naïve boys with attention deficit hyperactivity disorder. *Psychiatry Res, 201*(2), 120-127.

Supekar, K., Musen, M., & Menon, V. (2009). Development of large-scale functional brain networks in children. *PLoS Biol, 7*(7), e1000157.

Supekar, K., Uddin, L. Q., Prater, K., Amin, H., Greicius, M. D., & Menon, V. (2010). Development of functional and structural connectivity within the default mode network in young children. *Neuroimage, 52*(1), 290-301.

Takahashi, T., Shirane, R., Sato, S., & Yoshimoto, T. (1999). Developmental changes of cerebral blood flow and oxygen metabolism in children. *AJNR Am J Neuroradiol, 20*(5), 917-922.

Tan, Z., Wei, H., Song, X., Mai, W., Yan, J., Ye, W., Ling, X., Hou, L., Zhang, S., Yan, S., Xu, H., & Wang, L. (2022). Positron Emission Tomography in the Neuroimaging of Autism Spectrum Disorder: A Review. *Front Neurosci, 16*, 806876.

Tang, F. R., Loke, W. K., & Khoo, B. C. (2017). Low-dose or low-dose-rate ionizing radiation-induced bioeffects in animal models. *J Radiat Res, 58*(2), 165-182.

Telias, M. (2019). Molecular Mechanisms of Synaptic Dysregulation in Fragile X Syndrome and Autism Spectrum Disorders. *Front Mol Neurosci, 12*, 51.

Thapar, A., Cooper, M., & Rutter, M. (2017). Neurodevelopmental disorders. *Lancet Psychiatry, 4*(4), 339-346.

Thomason, M. E., Dassanayake, M. T., Shen, S., Katkuri, Y., Alexis, M., Anderson, A. L., Yeo, L., Mody, S., Hernandez-Andrade, E., Hassan, S. S., Studholme, C., Jeong, J. W., & Romero, R. (2013). Cross-hemispheric functional connectivity in the human fetal brain. *Sci Transl Med, 5*(173), 173ra124.

Thomason, M. E., Hect, J., Waller, R., Manning, J. H., Stacks, A. M., Beeghly, M., Boeve, J. L., Wong, K., van den Heuvel, M. I., Hernandez-Andrade, E., Hassan, S. S., & Romero, R. (2018). Prenatal neural origins of infant motor development: Associations between fetal brain and infant motor development. *Dev Psychopathol, 30*(3), 763-772.

Tian, L., Jiang, T., Liang, M., Zang, Y., He, Y., Sui, M., & Wang, Y. (2008). Enhanced resting-state brain activities in ADHD patients: A fMRI study. *Brain and Development, 30*(5), 342-348.

Toulmin, H., Beckmann, C. F., O'Muircheartaigh, J., Ball, G., Nongena, P., Makropoulos, A., Ederies, A., Counsell, S. J., Kennea, N., Arichi, T., Tusor, N., Rutherford, M. A., Azzopardi, D., Gonzalez-Cinca, N., Hajnal, J. V., & Edwards, A. D. (2015). Specialization and integration of functional thalamocortical connectivity in the human infant. *Proc Natl Acad Sci U S A, 112*(20), 6485-6490.

Trotta, N., Archambaud, F., Goldman, S., Baete, K., Van Laere, K., Wens, V., Van Bogaert, P., Chiron, C., & De Tiège, X. (2016). Functional integration changes in regional brain glucose metabolism from childhood to adulthood. *Hum Brain Mapp, 37*(8), 3017-3030.

Uddin, L. Q., Kelly, A. M., Biswal, B. B., Margulies, D. S., Shehzad, Z., Shaw, D., Ghaffari, M., Rotrosen, J., Adler, L. A., Castellanos, F. X., & Milham, M. P. (2008). Network homogeneity reveals decreased integrity of default-mode network in ADHD. *J Neurosci Methods, 169*(1), 249-254.

Uddin, L. Q., Supekar, K., Lynch, C. J., Khouzam, A., Phillips, J., Feinstein, C., Ryali, S., & Menon, V. (2013). Salience network-based classification and prediction of symptom severity in children with autism. *JAMA Psychiatry, 70*(8), 869-879.

Van Bogaert, P., Wikler, D., Damhaut, P., Szliwowski, H. B., & Goldman, S. (1998). Regional changes in glucose metabolism during brain development from the age of 6 years. *Neuroimage, 8*(1), 62-68.

van den Heuvel, M. I., Turk, E., Manning, J. H., Hect, J., Hernandez-Andrade, E., Hassan, S. S., Romero, R., van den Heuvel, M. P., & Thomason, M. E. (2018). Hubs in the human fetal brain network. *Dev Cogn Neurosci, 30*, 108-115.

Verreet, T., Quintens, R., Van Dam, D., Verslegers, M., Tanori, M., Casciati, A., Neefs, M., Leysen, L., Michaux, A., Janssen, A., D'Agostino, E., Vande Velde, G., Baatout, S., Moons, L., Pazzaglia, S., Saran, A., Himmelreich, U., De Deyn, P. P., & Benotmane, M. A. (2015). A multidisciplinary approach unravels early and persistent effects of X-ray exposure at the onset of prenatal neurogenesis. *J Neurodev Disord, 7*(1), 3.

Villemagne, P. M., Naidu, S., Villemagne, V. L., Yaster, M., Wagner, H. N., Jr., Harris, J. C., Moser, H. W., Johnston, M. V., Dannals, R. F., & Wong, D. F. (2002). Brain glucose metabolism in Rett Syndrome. *Pediatr Neurol, 27*(2), 117-122.

Volkow, N. D., Wang, G.-J., Newcorn, J., Fowler, J. S., Telang, F., Solanto, M. V., Logan, J., Wong, C., Ma, Y., Swanson, J. M., Schulz, K., & Pradhan, K. (2007a). Brain dopamine transporter levels in treatment and drug naïve adults with ADHD. *Neuroimage, 34*(3), 1182-1190.

Volkow, N. D., Wang, G. J., Newcorn, J., Telang, F., Solanto, M. V., Fowler, J. S., Logan, J., Ma, Y., Schulz, K., Pradhan, K., Wong, C., & Swanson, J. M. (2007b). Depressed dopamine activity in caudate and preliminary evidence of limbic involvement in adults with attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry, 64*(8), 932-940.

Volkow, N. D., Wang, G. J., Newcorn, J. H., Kollins, S. H., Wigal, T. L., Telang, F., Fowler, J. S., Goldstein, R. Z., Klein, N., Logan, J., Wong, C., & Swanson, J. M. (2011). Motivation deficit in ADHD is associated with dysfunction of the dopamine reward pathway. *Molecular Psychiatry, 16*(11), 1147-1154.

Wahlstrom, D., Collins, P., White, T., & Luciana, M. (2010). Developmental changes in dopamine neurotransmission in adolescence: behavioral implications and issues in assessment. *Brain Cogn, 72*(1), 146-159.

Wang, C., Yang, B., Fang, D., Zeng, H., Chen, X., Peng, G., Cheng, Q., & Liang, G. (2018). The impact of SNAP25 on brain functional connectivity density and working memory in ADHD. *Biol Psychol, 138*, 35-40.

Wang, Y., Chan, G. L., Holden, J. E., Dobko, T., Mak, E., Schulzer, M., Huser, J. M., Snow, B. J., Ruth, T. J., Calne, D. B., & Stoessl, A. J. (1998). Age-dependent decline of dopamine D1 receptors in human brain: a PET study. *Synapse, 30*(1), 56-61.

Wang, Z., Fernández-Seara, M., Alsop, D. C., Liu, W.-C., Flax, J. F., Benasich, A. A., & Detre, J. A. (2008). Assessment of functional development in normal infant brain using arterial spin labeled perfusion MRI. *Neuroimage, 39*(3), 973-978.

Washington, S. D., Gordon, E. M., Brar, J., Warburton, S., Sawyer, A. T., Wolfe, A., Mease-Ference, E. R., Girton, L., Hailu, A., Mbwana, J., Gaillard, W. D., Kalbfleisch, M. L., & VanMeter, J. W. (2014). Dysmaturation of the default mode network in autism. *Hum Brain Mapp, 35*(4), 1284-1296.

Wiers, C. E., Lohoff, F. W., Lee, J., Muench, C., Freeman, C., Zehra, A., Marenco, S., Lipska, B. K., Auluck, P. K., Feng, N., Sun, H., Goldman, D., Swanson, J. M., Wang, G. J., & Volkow, N. D. (2018). Methylation of the dopamine transporter gene in blood is associated with striatal dopamine transporter availability in ADHD: A preliminary study. *Eur J Neurosci, 48*(3), 1884-1895.

Williams, K., Peltier, S., LaConte, S., & Keilholz, S. D. (2006). MRI evidence of resting state connectivity in rodent brain. *In Proceedings 14th Scientific Meeting, International Society for Magnetic Resonance in Medicine, Seattle*.

Wilson, L. R., Vatansever, D., Annus, T., Williams, G. B., Hong, Y. T., Fryer, T. D., Nestor, P. J., Holland, A. J., & Zaman, S. H. (2019). Differential effects of Down's syndrome and Alzheimer's neuropathology on default mode connectivity. *Hum Brain Mapp, 40*(15), 4551-4563.

Wong, D. F., Blue, M. E., Brašić, J. R., Nandi, A., Valentine, H., Stansfield, K. H., Rousset, O., Bibat, G., Yablonski, M. E., Johnston, M. V., Gjedde, A., & Naidu, S. (2018). Are dopamine receptor and transporter changes in Rett syndrome reflected in Mecp2-deficient mice? *Exp Neurol, 307*, 74-81.

Wong, D. F., Wagner, H. N., Jr., Dannals, R. F., Links, J. M., Frost, J. J., Ravert, H. T., Wilson, A. A., Rosenbaum, A. E., Gjedde, A., Douglass, K. H., & et al. (1984). Effects of age on dopamine and serotonin receptors measured by positron tomography in the living human brain. *Science, 226*(4681), 1393-1396.

Xue, X., Wu, J. J., Huo, B. B., Xing, X. X., Ma, J., Li, Y. L., Zheng, M. X., Hua, X. Y., & Xu, J. G. (2022). Age-related alterations of brain metabolic network based on [18F]FDG-PET of rats. *Aging (Albany NY), 14*(2), 923-942.

Yang, Y., Zhao, S., Zhang, M., Xiang, M., Zhao, J., Chen, S., Wang, H., Han, L., & Ran, J. (2022). Prevalence of neurodevelopmental disorders among US children and adolescents in 2019 and 2020. *Front Psychol, 13*, 997648.

Yoshikawa, H., Fueki, N., Suzuki, H., Sakuragawa, N., & Masaaki, I. (1991). Cerebral Blood Flow and Oxygen Metabolism in Rett Syndrome. *Journal of Child Neurology, 6*(3), 237-242.

Zametkin, A. J., Liebenauer, L. L., Fitzgerald, G. A., King, A. C., Minkunas, D. V., Herscovitch, P., Yamada, E. M., & Cohen, R. M. (1993). Brain metabolism in teenagers with attention-deficit hyperactivity disorder. *Arch Gen Psychiatry, 50*(5), 333-340.

Zametkin, A. J., Nordahl, T. E., Gross, M., King, A. C., Semple, W. E., Rumsey, J., Hamburger, S., & Cohen, R. M. (1990). Cerebral glucose metabolism in adults with hyperactivity of childhood onset. *N Engl J Med, 323*(20), 1361-1366.

Zerbi, V., Ielacqua, G. D., Markicevic, M., Haberl, M. G., Ellisman, M. H., A, A. B., Frick, A., Rudin, M., & Wenderoth, N. (2018). Dysfunctional Autism Risk Genes Cause Circuit-Specific Connectivity Deficits With Distinct Developmental Trajectories. *Cereb Cortex, 28*(7), 2495-2506.

Zerbi, V., Pagani, M., Markicevic, M., Matteoli, M., Pozzi, D., Fagiolini, M., Bozzi, Y., Galbusera, A., Scattoni, M. L., Provenzano, G., Banerjee, A., Helmchen, F., Basson, M. A., Ellegood, J., Lerch, J. P., Rudin, M., Gozzi, A., & Wenderoth, N. (2021). Brain mapping across 16 autism mouse models reveals a spectrum of functional connectivity subtypes. *Mol Psychiatry*.

Zhao, F., Zhao, T., Zhou, L., Wu, Q., & Hu, X. (2008). BOLD study of stimulation-induced neural activity and resting-state connectivity in medetomidine-sedated rat. *Neuroimage, 39*(1), 248-260.

Zilbovicius, M., Boddaert, N., Belin, P., Poline, J. B., Remy, P., Mangin, J. F., Thivard, L., Barthélémy, C., & Samson, Y. (2000). Temporal lobe dysfunction in childhood autism: a PET study. Positron emission tomography. *Am J Psychiatry, 157*(12), 1988-1993.

Zilbovicius, M., Garreau, B., Samson, Y., Remy, P., Barthélémy, C., Syrota, A., & Lelord, G. (1995). Delayed maturation of the frontal cortex in childhood autism. *Am J Psychiatry, 152*(2), 248-252.

Zoratto, F., Altabella, L., Tistarelli, N., Laviola, G., Adriani, W., & Canese, R. (2018). Inside the Developing Brain to Understand Teen Behavior From Rat Models: Metabolic, Structural, and Functional-Connectivity Alterations Among Limbic Structures Across Three Pre-adolescent Stages. *Front Behav Neurosci, 12*, 208.

Zoratto, F., Palombelli, G. M., Ruocco, L. A., Carboni, E., Laviola, G., Sadile, A. G., Adriani, W., & Canese, R. (2017). Enhanced limbic/impaired cortical-loop connection onto the hippocampus of NHE rats: Application of resting-state functional connectivity in a preclinical ADHD model. *Behav Brain Res, 333*, 171-178.

Zürcher, N. R., Bhanot, A., McDougle, C. J., & Hooker, J. M. (2015). A systematic review of molecular imaging (PET and SPECT) in autism spectrum disorder: current state and future research opportunities. *Neurosci Biobehav Rev, 52*, 56-73.

Figures

Figure 1: Comparison of neurodevelopmental age between humans and mice

Simplified schematic overview of corresponding neurodevelopmental stages in humans and rodents. Data obtained from: (Boksa, 2010; Clancy, 2007a; Nishiyama, 2021; Semple, 2013).

Figure 2: Timeline of development of functional connectivity in the human brain as derived from resting-state functional MRI from 20 weeks of gestation until adulthood.

FC: functional connectivity

Figure 3: Normal brain metabolism from birth until adulthood derived from [^{18}F]-FDG PET: conflicting results between older and more recent studies.

The blue line represents the mean local cerebral metabolic rate of glucose in the whole brain, derived from studies published before 2000 (H. T. Chugani, 1986; H. T. Chugani, 1987; Kinnala, 1996). The red line represents the mean maximum standard uptake value (SUV) in different brain regions, derived from studies published between 2014 and 2018 (Barber, 2018; London, 2014). The horizontal line with large and small dots represents the adult values of mean local cerebral metabolic rate of glucose and SUV, respectively.

Table 1: Information about function, development, and resting-state functional connectivity alterations of higher-order networks derived from resting-stage fMRI studies in humans and rodents

Higher order networks	Function	Anatomical brain regions involved in humans	Anatomical brain regions involved in rodents	Development of higher-order in humans	NDDs in which altered FC of higher-order networks has been reported
Default-mode network (DMN)	Task-negative network; daydreaming, mind-wandering, internal evaluation, retrieving memories, theory of mind	Medial prefrontal cortex, anterior/posterior cingulate cortex, precuneus, retrosplenial cortex, and inferior parietal cortex (angular gyrus), entorhinal cortex, parahippocampal gyrus	Prefrontal, orbitofrontal and prelimbic cortex, cingulate cortex, retrosplenial cortex, parietal and temporal association cortex, entorhinal cortex, hippocampus	• Primitive at birth • Synchronized at 1y • From 1y anticorrelation with DAN • Adult-like topology at 2y • FC strengthening until adulthood	ID +/- epilepsy (Ibrahim, 2014; Ofer, 2018), ASD (Uddin, 2013; Washington, 2014; Zerbi, 2018), ADHD (Castellanos, 2008; Fair, 2010; S. M. Huang, 2016; Qiu, 2011; Uddin, 2008)
Salience network	Identifying key biological and cognitive events and redirecting attention, intercepting feelings associated with reward, and recruiting other networks to contribute to complex functions (e.g., social behaviour,	Anterior insula and anterior cingulate cortex, amygdala, ventral striatum, substantia nigra, and ventral tegmental region	Anterior insula and anterior cingulate cortex, ventral striatum	• Primitive at birth • FC with thalamus at birth • Synchronized at 1y	Down syndrome (Pujol, 2015), ASD (Oldehinkel, 2019; Uddin, 2013; Zerbi, 2018), ADHD (C. Wang, 2018)

	communication, and self-awareness)				
Lateral visual network	Visual association area, feature extraction, shape recognition and face perception	Peristriate area (lateral part of occipital lobe), lateral and superior occipital gyrus	Occipital, parietal and retrosplenial cortex	No developmental rs-fMRI data available	ASD (Oldehinkel, 2019; Uddin, 2013)
Dorsal attention network (DAN)	Task-positive network; sustained, and voluntary (top-down) guided reorientation of attention to locations or features	Intraparietal sulcus, and lateral frontal cortex (frontal eye fields)	/	• Primitive at 1y • Synchronized at 3y • FC strengthening until adulthood	ADHD (Posner, 2013)
Ventral attention network (VAN)	Task-positive network; detects salient or unexpected stimuli and redirects attention towards these stimuli (bottom-up), inhibited during focused attention (top-down)	Temporo-parietal junction (inferior parietal lobule/superior temporal gyrus), and ventral frontal cortex (inferior frontal gyrus/middle frontal gyrus), often more lateralized in the right hemisphere	/	• Primitive at 1y • Synchronized at 3y • FC strengthening until adulthood	ADHD (Marcos-Vidal, 2018)
Executive control network	Cognitive control network, performance of high-level cognitive tasks, rule-based problem solving and decision making, working memory	Dorsolateral prefrontal cortex and the lateral posterior parietal cortex	Lateral cortical network: frontal association cortex (prefrontal cortex + secondary motor cortex), primary motor cortex	• Primitive at 1y • Synchronized at 3y • FC strengthening until adulthood	Down syndrome (Pujol, 2015), ADHD (C. Wang, 2018)

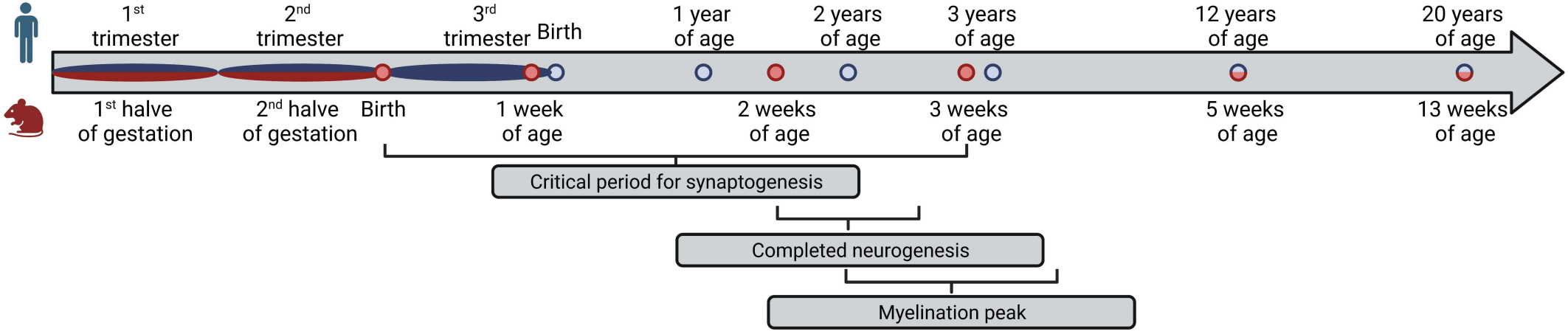
ADHD: attention deficit hyperactivity disorder; ASD: autism spectrum disorder; ID: intellectual disability; NDDs: neurodevelopmental disorders; Y: year(s) of age

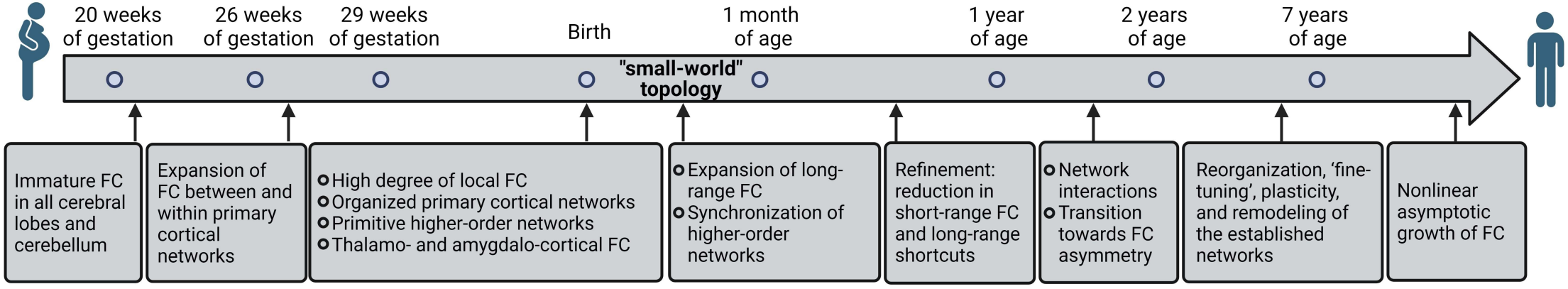
1686 Table 2: Overview of different PET tracers used to study glucose and neurotransmitters in neurodevelopmental disorders.

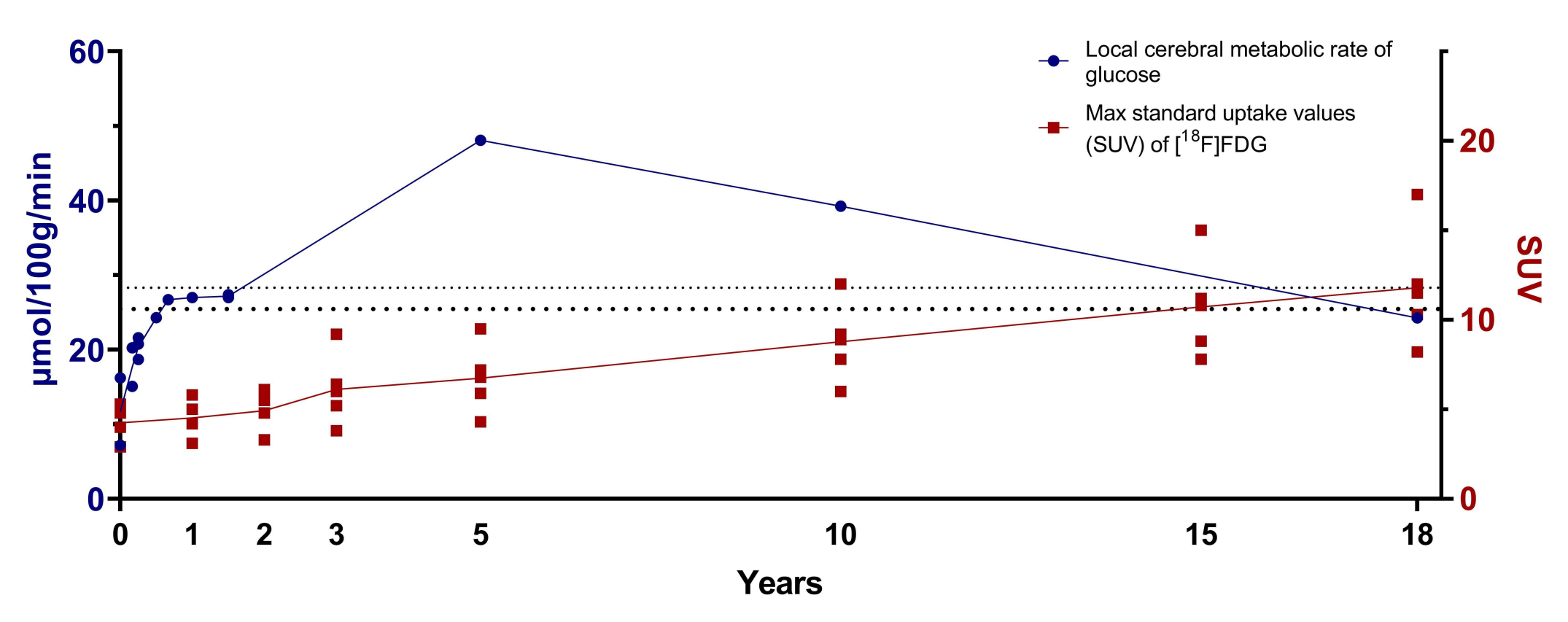
	Tracer	Tracer binding	NDDs in which molecular changes have been reported
Glucose Main source of energy for the brain, critical for brain functions, such as memory and learning, and precursor for neurotransmitter synthesis	[^{18}F]-FDG		Rett syndrome (Villemagne, 2002), Dravet syndrome (Haginoya, 2018; Kumar, 2018; Ricobaraza, 2019), ID +/- epilepsy (Itomi, 2002; Natsume, 2014), ASD (Anil Kumar, 2017; Chivate, 2016; H. T. Chugani, 2007; Dilber, 2013; Haznedar, 2006; Haznedar, 1997; Mitelman, 2018; Rumsey, 1985), ADHD (Ernst, 1994; Ha, 2020; Zametkin, 1990)
GABA (Gamma-aminobutyric acid) Major inhibitory neurotransmitter, excitatory effects during development, critical role in brain development and in physiological processes such as memory, attention, and stress reactivity	[^{11}C]-FMZ	$GABA_A$	Prader-Willi syndrome (Lucignani, 2004), Angelman syndrome (Holopainen, 2001), Fragile X syndrome (D'Hulst, 2015; Horder, 2018)
	[^{11}C]-Ro15-4513	$GABA_A$ α5	ASD (Mendez, 2013)
Glutamate Major excitatory neurotransmitter, critical for brain development and function	[^{18}F]-FPEB	$mGluR_5$	Fragile X syndrome (Afshar, 2022; Brašić, 2022; Brašić, 2021; Mody, 2021), ASD (Brašić, 2021; Cai, 2019; Fatemi, 2018)
Dopamine Neurotransmitter, involved in the motivational component of reward-motivated behaviour, motor control, and control of hormone release	[^{11}C]-NMSP	D2 dopamine receptor	Rett syndrome (Wong, 2018)
	[^{11}C]-raclopride	D2/D3 dopamine receptor	Rett syndrome (Wong, 2018), ADHD (Brown, 2011; Rosa-Neto, 2005; Volkow, 2007b)
	[^{11}C]-WIN-35,428	Dopamine transport	ASD (Nakamura, 2010)

	[^{11}C]-cocaine	Dopamine transport	ADHD (Volkow, 2007b)
	[^{11}C]-altropane	Dopamine transport	ADHD (Spencer, 2007)
	[^{11}C]-FLB457	D2/D3 dopamine receptor	ASD (Murayama, 2022)
	[^{18}F]-DOPA	L-DOPA analogue	ASD (Nieminen-von Wendt, 2004), ADHD (Ernst, 1998; Ludolph, 2008)
	L-[^{11}C]-DOPA	L-DOPA analogue	ADHD (Forssberg, 2006)
	[^{11}C]-PE2I	Dopamine transport	ADHD (Jucaite, 2005)
Serotonin (5-hydroxytryptamine (5-HT)) Role in neuronal proliferation, migration, and development, role in mood, emotions, appetite and digestion, precursor of melatonin (role in sleep-wake cycle)	α[^{11}C]-AMT	Tryptophan (precursor)	ASD (Chandana, 2005; D. C. Chugani, 1997)
	[^{11}C](+)McN-5652	Serotonin receptor	ASD (Nakamura, 2010)
	[^{18}F]-setoperone	Serotonin receptor	ASD (Beversdorf, 2012)

ADHD: attention deficit hyperactivity disorder; ASD: autism spectrum disorder; ID: intellectual disability; $mGluR_5$: Metabotropic glutamate receptor subtype 5; NDDs: neurodevelopmental disorders


1st trimester
2nd trimester
3rd trimester
Birth
1 year of age
2 years of age
3 years of age
12 years of age
20 years of age
1st halve of gestation
2nd halve of gestation
Birth
1 week of age
2 weeks of age
3 weeks of age
5 weeks of age
13 weeks of age
Critical period for synaptogenesis
Completed neurogenesis
Myelination peak


20 weeks of gestation
26 weeks of gestation
29 weeks of gestation
Birth
1 month of age
1 year of age
2 years of age
7 years of age
"small-world" topology
Immature FC in all cerebral lobes and cerebellum
Expansion of FC between and within primary cortical networks
High degree of local FC
Organized primary cortical networks
Primitive higher-order networks
Thalamo- and amygdalo-cortical FC
Expansion of long-range FC
Synchronization of higher-order networks
Refinement: reduction in short-range FC and long-range shortcuts
Network interactions
Transition towards FC asymmetry
Reorganization, 'fine-tuning', plasticity, and remodeling of the established networks
Nonlinear asymptotic growth of FC


Local cerebral metabolic rate of glucose
Max standard uptake values (SUV) of [18F]FDG
µmol/100g/min
SUV
Years
60
40
20
0
20
10
0
0
1
2
3
5
10
15
18