Review

# Resting-State Functional MRI and PET Imaging as Noninvasive Tools to Study (Ab)Normal Neurodevelopment in Humans and Rodents

Charissa Millevert,[1,2,5] Nicholas Vidas-Guscic,[3,5] Liesbeth Vanherp,[5] Elisabeth Jonckers,[3,5] Marleen Verhoye,[3,5] Steven Staelens,[4,5] Daniele Bertoglio,[3,4,5] and Sarah Weckhuysen[1,2,5,6]

[1]Applied & Translational Neurogenomics Group, Vlaams Instituut voor Biotechnologie (VIB) Center for Molecular Neurology, VIB, Antwerp 2610, Belgium, [2]Department of Neurology, University Hospital of Antwerp, Antwerp 2610, Belgium, [3]Bio-Imaging Lab, University of Antwerp, Antwerp 2610, Belgium, [4]Molecular Imaging Center Antwerp (MICA), University of Antwerp, Antwerp 2610, Belgium, [5]µNEURO Research Centre of Excellence, University of Antwerp, Antwerp 2610, Belgium, and [6]Translational Neurosciences, Faculty of Medicine and Health Science, University of Antwerp, Antwerp 2610, Belgium

Neurodevelopmental disorders (NDDs) are a group of complex neurologic 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 noninvasively 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 noninvasive preclinical imaging biomarkers of neurodevelopmental dysfunction, and evaluating treatment-response in disease-specific models.

*Key words:* neurodevelopment; neurodevelopmental disorders; resting-state functional magnetic resonance imaging; positron emission tomography; rodent models

## Introduction

Neurodevelopmental disorders (NDDs) are, according to the DSM-5 (American Psychiatric Association, 2013), a broad group of complex neurologic and psychiatric disorders, including intellectual disability (ID), autism spectrum disorder (ASD), and attention deficit hyperactivity disorder (ADHD; Thapar et al., 2017). Globally, the prevalence numbers of NDDs are highly variable and sparse for individuals living in low-income and middle-income countries (Francés et al., 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 et al., 2022; Yang et al., 2022). Since people with NDDs often suffer from multiple comorbidities, like behavioral disturbances, epilepsy, and cognitive impairments, they represent a major public health problem (Thapar et al., 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 and Shapiro, 2019). These disturbances are thought to occur at early stages of brain development, when the brain is still highly plastic and modifiable (Mohammadi-Nejad et al., 2018). We hypothesize 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 noninvasive way. While in humans this process takes >18 years, rodent models have the advantage of reaching a mature adult brain in only three months (Flurkey et al., 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 et al., 2022; Firouzabadi et al., 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 et al., 2019). Functional and molecular imaging
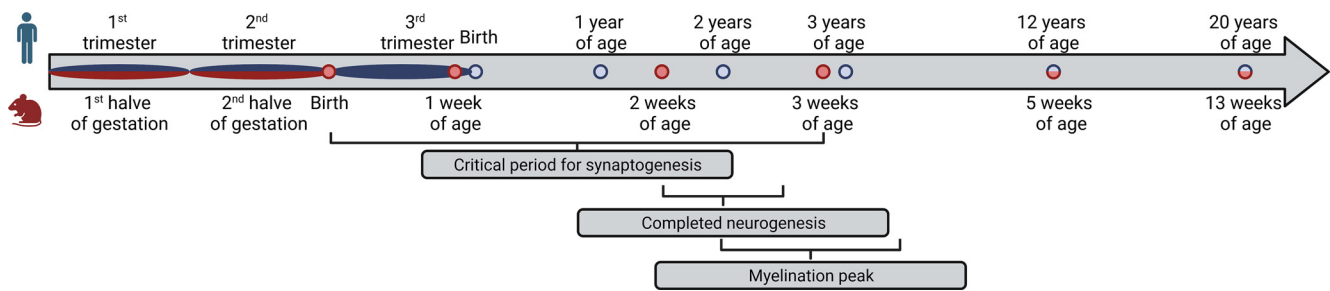
**Figure 1.** Comparison of neurodevelopmental age between humans and mice. Simplified schematic overview of corresponding neurodevelopmental stages in humans and rodents. Data obtained from: Boksa (2010), Clancy et al. (2007a), Nishiyama et al. (2021), and Semple et al. (2013).

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 0.5–2 s within a 5- to 10-min scan period. Spontaneous low-frequency fluctuations (LFFs) in these BOLD signals are an indirect marker of changes in neuronal activity (Biswal et al., 1995). The correlations between the spontaneous LFFs of different voxels can thereby identify their functional connectivity (FC; Biswal et al., 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 and Chugani, 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 and Chugani, 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 healthy human and rodent models. We also give examples of how these two techniques have been used to study abnormal neurodevelopment in both models in specific NDDs (ID with or without epilepsy including genetic syndromes, ASD, and ADHD) and address the limitations of current studies.

## Extrapolating Timing of Brain Development from Rodent Models to Humans

Rodent models are often used as proxies for human biological processes. When using rodent models in neurodevelopmental research, the ability to extrapolate the timing of brain development from rodents to humans is critical (Clancy et al., 2007b). Compared with humans, rodents have a shorter lifespan and, therefore neurodevelopment takes place in a shorter period of time. After an average gestation period of 19 d in mice and 22 d

in rats, rodents are born with less mature brains than full-term infants (Clancy et al., 2001). Consequently, the critical period for synaptogenesis in human fetuses starts already *in utero*, whereas in rodents it occurs completely *ex utero* during the first three postnatal weeks (Semple et al., 2013). It has been suggested that approximately around postnatal day (P)7 to P13, the rat brain reaches a stage of development equivalent to that of a full-term human newborn in terms of white matter development and axonal outgrowth (Boksa, 2010; Semple et al., 2013; Fig. 1). In rodents, neurogenesis is complete by around P15, whereas in humans it can continue until 2.5 years of age (Semple et al., 2013). Myelination peaks at around P20 in rodents and between two and five years of age in humans, and continues into adulthood (Semple et al., 2013; Nishiyama et al., 2021). In addition, a rodent brain reaches 90–95% of its adult weight between P21 and P28. A similar plateau is reached in humans at two to three years of age (Semple et al., 2013). Although it is an oversimplification to translate developmental milestones by age between species using a linear scale, the first and second halves of rodent gestation and the first postnatal week roughly correspond to the first, second, and third trimesters of human pregnancy, respectively (Clancy et al., 2007a). Overall, the period from fetal age to three 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 fiber tracts, whereas in rodents this period encompasses the first three postnatal weeks.

## Functional Connectivity Networks Using Resting-State Functional MRI Provide Insight into Normal Brain Development

### 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 et al., 2017; Mohammadi-Nejad et al., 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 fetuses between 20 and 26 weeks of gestation. They showed the presence of immature RSNs and interhemispheric (long-range) FC (Schöpf et al., 2012; Thomason et al., 2013; Jakab et al., 2014; van den Heuvel et al., 2018). This is followed by a period of expansion, leading to an increase in the proportion and strength of interhemispheric and intrahemispheric (e.g., between frontal and temporal lobes) FC, and in
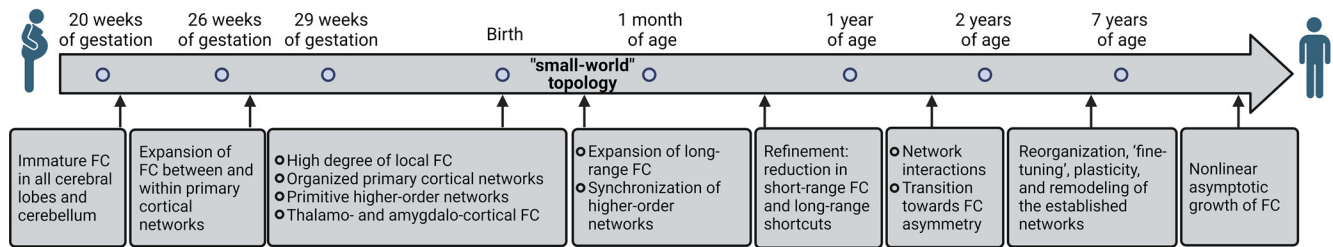
**Figure 2.** Timeline of development of functional connectivity in the human brain as derived from rs-fMRI from 20 weeks of gestation until adulthood. FC: functional connectivity.

short-range connections (e.g., within frontal and parietal lobes; Thomason et al., 2013; Jakab et al., 2014). Interestingly, fetuses 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 fetuses, reduced FC between the motor network and anterior cingulate, insula, and lateral cerebellar regions was also associated with advanced motor skills at four months of age (Thomason et al., 2018). Both findings support the idea that an earlier FC formation, as well as more active and earlier specialization 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 synchronized and resemble adult-like topologies soon after birth (Fransson et al., 2007; Lin et al., 2008; Doria et al., 2010; Smyser et al., 2010; Alcauter et al., 2014; Toulmin et al., 2015). Higher-order networks, on the other hand, are only primitively present at birth (Table 1; Doria et al., 2010; Gao et al., 2013; Alcauter et al., 2014). 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 et al., 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 six months of age (Della Rosa et al., 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 et al., 2014; Toulmin et al., 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 et al., 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 six months of age (Graham et al., 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 et al., 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 et al., 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 (Gao et al., 2013; Alcauter et al., 2014). This refinement leads to a significant reduction in short-range FC and the creation of long-

range shortcuts (Gao et al., 2011). It is also known as functional specialization and enables global and efficient information transfer (Gao et al., 2011). For example, the DMN is well synchronized by one year of age, and that has an adult-like topology by two years of age (Gao et al., 2009). Like the DMN, the salience network develops relatively early, reflecting the rapid emergence of self-awareness in the first year of life (Alcauter et al., 2015). This is thought to lay the foundation for the development of other higher-order networks (Alcauter et al., 2015). The executive control network, on the other hand, is still in an immature state at one year of age (Gao et al., 2015).

From the age of one 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 et al., 2013). Thalamus-salience connections also develop, and the strength of this FC can significantly predict working memory performance and intelligence quotient (IQ; Alcauter et al., 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 four years of age (Emerson et al., 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 specialization 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 characterized by reorganization, "fine-tuning," plasticity, and remodeling of the established networks (Gilmore et al., 2018). Small-world topology does not change significantly from childhood to adulthood in terms of path length ($\lambda$) and clustering coefficient ($\gamma$; Fair et al., 2009; Supekar et al., 2009). Nevertheless, the architecture of RSN connectivity is changing. They become more lateralised and form additional connections with other networks (Fair et al., 2007; Kelly et al., 2009). Functional specialization, characterized by a decrease in short-range FC and an increase in long-range FC, continues into adulthood (Fair et al., 2007, 2009; Kelly et al., 2009). This leads not only to an increase in overall FC strength, but also to an increase in global and local network efficiency (Fan et al., 2021).

In particular higher-order networks undergo a prolonged period of developmental maturation into adulthood (C.L. Li et al., 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,

**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, para-hippocampal gyrus | Prefrontal, orbitofrontal and prelimbic cortex, cingulate cortex, retrosplenial cortex, parietal and temporal association cortex, entorhinal cortex, hippocampus | ● Primitive at birth<br>● Synchronized at 1 year<br>● From 1 year anticorrelation with DAN<br>● Adult-like topology at 2 years<br>● FC strengthening until adulthood | ID +/− epilepsy (Ibrahim et al., 2014; Ofer et al., 2018), ASD (Uddin et al., 2013; Washington et al., 2014; Zerbi et al., 2018), ADHD (Castellanos et al., 2008; Uddin et al., 2008; Fair et al., 2010; Qiu et al., 2011; S.M. Huang et al., 2016) |
| 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 behavior, communication, and self-awareness) | 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<br>● FC with thalamus at birth<br>● Synchronized at 1y | Down syndrome (Pujol et al., 2015), ASD (Uddin et al., 2013; Zerbi et al., 2018; Oldehinkel et al., 2019), ADHD (C. Wang et al., 2018) |
| 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 (Uddin et al., 2013; Oldehinkel et al., 2019) |
| 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 1 year<br>● Synchronized at 3 years<br>● FC strengthening until adulthood | ADHD (Posner et al., 2013) |
| Ventral attention network (VAN) | Task-positive network; detects salient or unexpected stimuli and redirects attention toward 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 1 year<br>● Synchronized at 3 years<br>● FC strengthening until adulthood | ADHD (Marcos-Vidal et al., 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 1 year<br>● Synchronized at 3 years<br>● FC strengthening until adulthood | Down syndrome (Pujol et al., 2015), ADHD (C. Wang et al., 2018) |

ADHD: attention deficit hyperactivity disorder; ASD: autism spectrum disorder; FC: functional connectivity; ID: intellectual disability; NDDs: neurodevelopmental disorders.

are only sparsely functionally connected during the first decade (Fair et al., 2008; Kelly et al., 2009; Supekar et al., 2010). These FCs develop into a cohesive, interconnected network by adulthood (Fair et al., 2008; Kelly et al., 2009; Supekar et al., 2010). Overall FC increases from childhood to adulthood following a nonlinear 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 et al., 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 et al., 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 specialized, enabling efficient information processing.

## Rs-fMRI in normally developing rodents

In the mid-2000s, several research groups have successfully performed rs-fMRI in rodents (Lu et al., 2006, 2007; Williams et al., 2006; Pawela et al., 2008; Zhao et al., 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 et al., 2007; Pawela et al., 2008; Zhao et al., 2008). Subsequent studies confirmed the presence of FC in (young) adult mice (Mechling et al., 2014; Stafford et al., 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 et al., 2014; Stafford et al., 2014).

Zoratto et al. (2018) performed rs-fMRI in anesthetized Wistar rats during the juvenile period at P21–P25, P28–P32, and P35–P39. They showed an increase in FC between the three time periods, particularly between the hippocampus and striatum (Zoratto et al., 2018). Another study characterized the developmental changes in FC from juvenile (P30) to adult (P70–P90) age in awake rats (Ma et al., 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 specialization. Functional specialization 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 et al., 2018). In conclusion, neurodevelopment continues at a slow pace during the juvenile period, with findings similar to those described in humans (Fair et al., 2007, 2009; Kelly et al., 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.
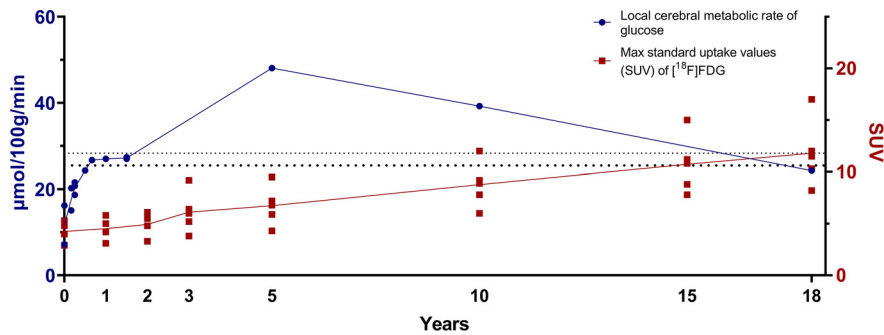
**Figure 3.**    Normal brain metabolism from birth until adulthood derived from [¹⁸F]-FDG PET: conflicting results between older and more recent studies. The blue line represents the mean local cerebral metabolic rate of glucose in the whole brain, derived from studies published before 2000 (H.T. Chugani and Phelps, 1986; H.T. Chugani et al., 1987; Kinnala et al., 1996). The red line represents the mean maximum standard uptake value (SUV) in different brain regions, derived from studies published between 2014 and 2018 (London and Howman-Giles, 2014; Barber et al., 2018). The horizontal line with large and small dots represents the adult values of mean local cerebral metabolic rate of glucose and SUV, respectively.

## Three Molecular Imaging with PET Provides Insight into Normal Brain Development

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

*Glucose metabolism*
Brain maturation is thought to be associated with regional changes in cerebral metabolism (Kinnala et al., 1996). 2-Deoxy-2[¹⁸F]-fluoro-D-glucose ([¹⁸F]-FDG) PET allows the visualization and quantification of cerebral glucose metabolism (H.T. Chugani and Phelps, 1986). Studies using [¹⁸F]-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 et al., 1996), extracranial malignancy (London and Howman-Giles, 2014, 2015), epilepsy (H.T. Chugani and Phelps, 1986; H.T. Chugani et al., 1987; Van Bogaert et al., 1998; Trotta et al., 2016; Pilli et al., 2019), or deafness (Kang et al., 2004). Earlier studies quantified the local cerebral metabolic rate of glucose (H.T. Chugani and Phelps, 1986; H.T. Chugani et al., 1987; Kinnala et al., 1996), whereas more recent studies calculated standard uptake values (SUV) of [¹⁸F]-FDG (London and Howman-Giles, 2014; Barber et al., 2018) or used statistical parametric methods (Van Bogaert et al., 1998; Kang et al., 2004; London and Howman-Giles, 2015; Trotta et al., 2016).

During the neonatal period, glucose metabolism is higher in subcortical than in cortical structures, and then gradually increases to reach adult levels by two years of age (H.T. Chugani and Phelps, 1986; H.T. Chugani et al., 1987; Kinnala et al., 1996). H.T. Chugani et al. (1987) also included older individuals (5 d to 15 years). They showed that glucose metabolism continues to increase, exceeding adult values by more than twofold at three years of age. The rate of glucose metabolism then remains stable until approximately nine years of age, after which it declines and returns to adult levels by the end of the second decade (Fig. 3; H.T. Chugani et al., 1987). In contrast, more recent studies have calculated SUVs, and have shown a progressive increase in [¹⁸F]-FDG uptake in different brain regions into adulthood (London and Howman-Giles, 2014; Barber et al., 2018). The SUV is the dimensionless ratio of the image-derived radioactivity concentration to a normalization 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 et al., 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 signaling because of myelination and synaptic pruning.

Some studies used statistical parametric mapping to calculate the regional glucose metabolism adjusted for global activity (Van Bogaert et al., 1998; Kang et al., 2004; Trotta et al., 2016). Kang et al. (2004) included deaf children aged 1–15 years. The authors showed a linear increase in adjusted glucose metabolism with age in the frontal lobes (Kang et al., 2004). The other two studies included participants aged 6–38 years (Van Bogaert et al., 1998) and 6–50 years (Trotta et al., 2016). They showed that adjusted metabolic glucose metabolism followed a nonlinear 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 (Van Bogaert et al., 1998; Trotta et al., 2016). 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 et al., 2019). However, other studies have shown little or no asymmetry between contralateral brain regions (London and Howman-Giles, 2014; Barber et al., 2018). Asymmetric [¹⁸F]-FDG uptake may also be sex-specific, as the rate of increase and absolute values of FDG uptake differ between females and males (Kang et al., 2004).

*Cerebral blood flow*

CBF rates can be used as a surrogate measure of local energy demand, as the two are closely related (Kumar and Chugani, 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 et al., 1988; Takahashi et al., 1999; Andersen et al., 2019). In the neonatal period, CBF values are low but variable. Andersen et al. (2019) measured whole brain CBF in four healthy children within the first 3 d of life. CBF rate in these children ranged from 15 to 22.2 ml/100 g/min (mean: 17.8 ml/100 g/min; Andersen et al., 2019). In another study, CBF values ranged from 13 to 55 ml/100 g/min (mean: 23.6 ml/100 g/min) in five term born healthy neonates aged 3–14 d (Altman et al., 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 approximately eight years of age. More specifically, between three and eight years of age, CBF values peak at 140% to 175% of adult values. After eight 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 H.T. Chugani and Phelps (1986).

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

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 labeling MRI.

*Neurotransmitters*

PET can also be used to visualize and measure different neurotransmitters using specific radiotracers (Sander and Hesse, 2017). 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 et al., 2019). Changes in $GABA_A$ neurotransmission in response to sensory stimuli are thought to lead to synaptic plasticity (Kumar and Chugani, 2008; Andersson et al., 2019). 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 et al., 2001; H.T. Chugani et al., 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 et al., 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 et al., 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 and Åkerman, 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 et al., 2016; Mecca et al., 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 behavior, motor control, and control of hormone release, and is therefore thought to be a driving factor in adolescent behavior (Wahlstrom et al., 2010). The earliest dopamine PET study was conducted in children aged 10 years (Jucaite et al., 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 et al., 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 (Wong et al., 1984; Suhara et al., 1991; Y. Wang et al., 1998; Larsen et al., 2020). 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 and Chugani, 2008). *In utero* serotonin depletion leads to microcephaly, delayed neurogenesis, and disruption of synaptic connectivity in sensory cortices (Kumar and Chugani, 2008). Serotonin has indeed been shown to be a driver of neurodevelopment (D.C. Chugani et al., 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 two and five years of age with normal neurodevelopment is twice that of adults. This is followed by a decline toward 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 et al., 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.

**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 et al., 2015; Jiang et al., 2018, 2020; Xue et al., 2022). Consistent with human studies (London and Howman-Giles, 2014; Barber et al., 2018), [$^{18}$F]-FDG SUV increased in the striatum from two (juvenile) to four (adult) months of age (Jiang et al., 2018). Choi et al. (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 nonlinear inverted U-shaped pattern resembles the adjusted glucose metabolism pattern detected in humans from

6 to 50 years of age (Trotta et al., 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 (Van Bogaert et al., 1998; Trotta et al., 2016), rats showed a decrease in both brain regions between 5 and 10 weeks of age (Choi et al., 2015).

Three of the four longitudinal studies examined metabolic correlations (connections) between brain regions (Choi et al., 2015; Jiang et al., 2020; Xue et al., 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 normalized FDG uptake of each brain region, was found in the retrosplenial cortex and medial prefrontal cortex with increasing age (Choi et al., 2015). This increased energy efficiency was also demonstrated by Jiang et al. (2020).

A small-world topology was found in two-month-old (adolescent) rats (Jiang et al., 2020). Xue et al. (2022) found no change in normalized path length from adolescence (two months) to adulthood (18 months) in rats (Xue et al., 2022). Both of these findings are similar to the rs-fMRI findings in humans (Fair et al., 2009; Supekar et al., 2009). In contrast, Jiang et al. (2020) found a decrease in normalized path length ($\lambda$), and an increase in the small-world index from two to nine months of age in rats, indicating more efficient information transfer between long-distance nodes (Jiang et al., 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 et al., 2015; Jiang et al., 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.

## 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).

### Intellectual disability with or without epilepsy
*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 (American Psychiatric Association, 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 et al., 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 characterized 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 et al., 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 with controls, demonstrating that the deleted GABR genes result in a reduced number of GABA$_A$ receptors (Lucignani et al., 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 (two to six years) with a maternal 15q11-q13 deletion (Holopainen et al., 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 (D'Hulst et al., 2015; Mody et al., 2021; Brašić et al., 2022).

Down syndrome, also known as trisomy 21, is caused by a third copy of chromosome 21, and is characterized by ID and dysmorphic features (Gardiner et al., 2010). Down syndrome has been studied using rs-fMRI, and these studies have generally shown a mixed pattern of both hyperconnectivity and hypoconnectivity (Pujol et al., 2015; Wilson et al., 2019; Csumitta et al., 2022). 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 et al., 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 et al., 2022).

Some genetic syndromes, such as Dravet syndrome and Rett syndrome, are characterized by an initial normal neurodevelopment followed by a neurodevelopmental arrest or regression (Haginoya et al., 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 et al., 2018; Kumar et al., 2018; Villemagne et al., 2002). For example, while the glucose metabolism patterns were still normal in children with Dravet syndrome under the age of three years, a profound reduction in glucose uptake was observed in the cortex of older patients (Haginoya et al., 2018; Kumar et al., 2018). Next, an infantile glucose pattern, characterized by relatively increased glucose metabolism in the frontal cortex and cerebellum and decreased glucose metabolism in the occipital cortex, was observed in 3- to eight-year-old children with Rett syndrome (Villemagne et al., 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

**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 et al., 2002), Dravet syndrome (Haginoya et al., 2018; Kumar et al., 2018; Ricobaraza et al., 2019), ID +/− epilepsy (Itomi et al., 2002; Natsume et al., 2014), ASD (Rumsey et al., 1985; Haznedar et al., 1997; Haznedar et al., 2006; H.T. Chugani et al., 2007; Dilber et al., 2013; Chivate et al., 2016; Anil Kumar et al., 2017; Mitelman et al., 2018), ADHD (Zametkin et al., 1990; Ernst et al., 1994; Ha et al., 2020) |
| GABA 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 et al., 2004), Angelman syndrome (Holopainen et al., 2001), Fragile X syndrome (D'Hulst et al., 2015; Horder et al., 2018) |
| | $[^{11}C]$-Ro15-4513 | $GABA_A$ $\alpha5$ | ASD (Mendez et al., 2013) |
| Glutamate major excitatory neurotransmitter, critical for brain development and function | $[^{18}F]$-FPEB | $mGluR_5$ | Fragile X syndrome (Brašić et al., 2021; Mody et al., 2021; Afshar et al., 2022; Brašić et al., 2022), ASD (Fatemi et al., 2018; Cai et al., 2019; Brašić et al., 2021) |
| Dopamine neurotransmitter, involved in the motivational component of reward-motivated behavior, motor control, and control of hormone release | $[^{11}C]$-NMSP | D2 dopamine receptor | Rett syndrome (Wong et al., 2018) |
| | $[^{11}C]$-raclopride | D2/D3 dopamine receptor | Rett syndrome (Wong et al., 2018), ADHD (Rosa-Neto et al., 2005; Volkow et al., 2007b; Brown et al., 2011) |
| | $[^{11}C]$-WIN-35428 | Dopamine transport | ASD (Nakamura et al., 2010) |
| | $[^{11}C]$-cocaine | Dopamine transport | ADHD (Volkow et al., 2007b) |
| | $[^{11}C]$-altropane | Dopamine transport | ADHD (Spencer et al., 2007) |
| | $[^{11}C]$-FLB457 | D2/D3 dopamine receptor | ASD (Murayama et al., 2022) |
| | $[^{18}F]$-DOPA | L-DOPA analogue | ASD (Nieminen-von Wendt et al., 2004), ADHD (Ernst et al., 1998; Ludolph et al., 2008) |
| | L-$[^{11}C]$-DOPA | L-DOPA analogue | ADHD (Forssberg et al., 2006) |
| | $[^{11}C]$-PE2I | Dopamine transport | ADHD (Jucaite et al., 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) | $\alpha[^{11}C]$-AMT | Tryptophan (precursor) | ASD (D.C. Chugani et al., 1997; Chandana et al., 2005) |
| | $[^{11}C](+)$McN-5652 | Serotonin receptor | ASD (Nakamura et al., 2010) |
| | $[^{18}F]$-setoperone | Serotonin receptor | ASD (Beversdorf et al., 2012) |

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

aged 3–18 years (Yoshikawa et al., 1991). Villemagne et al. (2002) propose that mitochondrial dysfunction is the underlying cause of the uncoupling between brain glucose utilization and CBF in Rett syndrome (Villemagne et al., 2002).

In >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 et al., 2018).

People with ID often have epilepsy, and vice versa (Snoeijen-Schouwenaars et al., 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 and Liao, 2020). While many studies have investigated FC changes in the context of epilepsy (Abela et al., 2014; Moody et al., 2021), a more limited number of studies have investigated the association between FC and cognitive impairment in this patient population (Paldino et al., 2017). In a case report of a five-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 et al., 2011). Furthermore, in children with childhood epilepsy with centrotemporal spikes (7–13 years), abnormal FC organization within the DMN was shown to correlate with cognitive and socio-emotional development (Ofer et al., 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 et al., 2014). Finally, some studies have shown an association between FC patterns and intelligence in children, adolescents, and adults with focal epilepsy (Qin et al., 2020; Songjiang et al., 2021; Struck et al., 2021).

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

*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 (Wong et al., 2018; Ricobaraza et al., 2019; Afshar et al., 2022). Two showed results similar to those in humans (Wong, 2018; Afshar, 2022). 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 et al., 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 et al., 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 (one to eight months; Ricobaraza et al., 2019), while children older than three years with Dravet syndrome have reduced cortical glucose uptake (Haginoya et al., 2018; Kumar et al., 2018). The authors suggested that the influence of anti-seizure medication in patients and different normalization methods could be a possible explanation for these conflicting results (Ricobaraza et al., 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-matched and genotype-matched monogenic rodent models and humans are warranted to support this hypothesis further.

**Autism spectrum disorder**
*rs-fMRI and PET in humans with ASD*
Individuals with ASD have persistent deficits in social communication and interaction combined with restricted, repetitive behaviors that are evident before the age of three years (American Psychiatric Association, 2013). A large number of studies have used rs-fMRI or PET to investigate changes in individuals with ASD (for rs-fMRI review, see Rane et al., 2015; Hull et al., 2016; Picci et al., 2016; for PET review, see Zürcher et al., 2015; Kowalewska et al., 2022; X. Li et al., 2021; Tan et al., 2022).

Many, but not all, rs-fMRI studies have shown long-range cortico-cortical hypoconnectivity, combined with cortico-subcortical hyperconnectivity (Delmonte et al., 2013; Di Martino et al., 2014; Cerliani et al., 2015; Oldehinkel et al., 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 et al., 2019). These FC alternations are thought to reflect impaired visual-motor and multisensory integration (Oldehinkel et al., 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 et al., 2013; Washington et al., 2014). These findings have been associated with more severe autistic traits (Uddin

et al., 2013; Washington et al., 2014; Oldehinkel et al., 2019). 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 behavior scores (Uddin et al., 2013).

[$^{18}$F]-FDG PET studies in individuals with ASD show conflicting results. Glucose metabolism patterns of global increase (Rumsey et al., 1985), local decrease in temporal lobes (H.T. Chugani et al., 2007; Dilber et al., 2013), anterior cingulate cortex (Haznedar et al., 1997) or striatum and thalamus (Haznedar et al., 2006), and mixed patterns (Chivate et al., 2016; Anil Kumar et al., 2017; Mitelman et al., 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 with controls (Zilbovicius et al., 2000; Boddaert et al., 2002; Duchesnay et al., 2011). 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 et al., 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$_A$ ($\alpha$5; Horder et al., 2018; Fung et al., 2021), 5-HT2 serotonin (Girgis et al., 2011), and D1 or D2/3 dopamine receptor availability (Kubota et al., 2020; Schalbroeck et al., 2021a, b) between individuals with ASD and controls. Others have shown decreased GABA$_A$ $\alpha$5 receptor binding (Mendez et al., 2013), increased mGluR5 expression (Fatemi et al., 2018; Brašić et al., 2021), decreased serotonin synthesis (D.C. Chugani et al., 1997; Chandana et al., 2005) and 5-HT2 receptor binding (Nakamura et al., 2010; Beversdorf et al., 2012), increased striatal presynaptic dopamine synthesis (Nieminen-von Wendt, 2004), and increased dopamine transporter binding (Nakamura et al., 2010) in adults with ASD. These findings have been correlated with more severe autistic traits (Nakamura et al., 2010; Fatemi et al., 2018; Kubota et al., 2020). Interestingly, Murayama et al. (2022) performed both [$^{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 et al., 2022).

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

In conclusion, the results of the rs-fMRI and PET studies in ASD are often inconsistent and inconclusive. Differences in the age of participants is one factor that could influence the results, as functional and molecular brain patterns change during development. First, FC abnormalities have been shown to already emerge before the onset of clinical symptoms, as early as six months of age, and may predict the diagnosis of ASD (Emerson et al., 2017). Second, some abnormalities emerge or progress after the onset of

ASD symptoms (Washington et al., 2014). Finally, both PET and rs-fMRI studies have shown delayed maturation patterns in young children with ASD, which eventually develop into a normal pattern at a later age (Zilbovicius et al., 1995; D.C. Chugani et al., 1999; Nebel et al., 2014). We argue that other possible factors contributing to the inconsistencies include the often small number of participants, the clinical heterogeneity of ASD, and differences in study design and study population.

*rs-fMRI and PET in rodent models of ASD*
Rodent studies typically model specific monogenic forms of ASD (Hulbert and Jiang, 2016). This circumvents the problem of clinical and etiological heterogeneity that is present in many of the human cohort studies. Indeed, a comparison of 16 different transgenic mouse models of ASD showed that all individual models were characterized by distinct, spatially distributed FC changes, and that there was no abnormal FC pattern that was common to all etiologies (Zerbi et al., 2021). This finding argues against the existence of a specific resting-state FC-based biomarker for ASD (Zerbi et al., 2021). For example, longitudinal rs-fMRI assessment was performed at juvenile (≈P34), young-adult (≈P58), and adult (≈P112) ages in two different transgenic mouse models of ASD. They showed reduced FC between sensory-processing areas from juvenile to adult age in the *fmr1* KO mice compared with controls, whereas reduced FC in the DMN, salience network, and hippocampal areas became apparent only between adolescence and adulthood in the contactin-associated protein 2 KO (*Cntnap2* KO) mice. Interestingly, the timing of the abnormal FC coincides with the expression profile of both genes (Zerbi et al., 2018). In adult *Cntnap2* KO mice, hypoconnectivity between DMN nodes was shown to be associated with reduced social behavior (Liska et al., 2018). Administration of oxytocin to *Cntnap2* KO mice normalized FC patterns and rescued social deficits, illustrating the potential use of rs-fMRI-based biomarkers to assess treatment effects in the context of neurodevelopmental dysfunction (Choe et al., 2022).

Adult Shank3B KO mice are a widely used model of ASD. The mouse model showed reduced prefrontal FC, and this reduction was associated with impaired social communication (Pagani et al., 2019). Second, increased subcortical mGluR$_5$ receptor availability was observed in this mouse model (Cai et al., 2019). Both findings were similar to those seen in studies of humans with ASD, although here the increased mGluR$_5$ receptor availability was found in cortical brain regions (Fatemi et al., 2018; Brašić et al., 2021). To the best of our knowledge, neither imaging study has ever been performed in the specific subset of individuals with pathogenic variants in the *SHANK3* gene, precluding a direct comparison with the human situation.

In another study, the availability of GABA$_A$ and GABA$_A$ $\alpha$5 subunits was measured by autoradiography using the tracers [$^{11}$C]-FMZ and [$^{11}$C]-Ro15-4513 in three different adult ASD mouse models (*Cntnap2* KO, *Shank3B* KO, 16p11.2 deletion; Horder et al., 2018). GABA$_A$ and GABA$_A$ $\alpha$5 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 et al., 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 synchronization between prefrontal and associative cortical areas were found in both children with 16p11.2 deletion and in adult 16p11.2$^{+/−}$

mice (Bertero et al., 2018). One study compared FC findings in awake children with neurofibromatosis type 1 because of a heterozygous pathogenic variant in the *NF1* gene with awake, head-fixed *Nf1*$^{+/−}$ adult mice (Shofty et al., 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 et al., 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 etiology dependent, highlighting the importance of using homogeneous study populations in both rodent and human imaging studies.

## Attention deficit hyperactivity disorder
*Rs-fMRI and PET in humans with ADHD*
ADHD is an NDD characterized by hyperactivity-impulsivity and/or inattention (American Psychiatric Association, 2013). In rs-fMRI studies, a delay in the maturation of higher-order networks such as the DMN is a consistent finding (Castellanos et al., 2008; Uddin et al., 2008; Fair et al., 2010; Qiu et al., 2011). 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 et al., 2008; Uddin et al., 2008; Fair et al., 2010; Qiu et al., 2011; Sun et al., 2012; Hoekzema et al., 2014; Marcos-Vidal et al., 2018). The reduced anticorrelation has been suggested to explain inattention, as activation of the DMN would interfere with sustained attention (Posner et al., 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 et al., 2018). These findings correlated with poor working memory performance (C. Wang et al., 2018). In addition to reduced prefrontal FC, reduced glucose metabolism in the prefrontal cortex has been shown in individuals with ADHD (Zametkin et al., 1990; Ernst et al., 1994). 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 (Tian et al., 2008; Costa Dias et al., 2013; Sanefuji et al., 2017) and decreased (Cao et al., 2009; Mills et al., 2012; Posner et al., 2013; Hong et al., 2015) in people with ADHD. These inconsistent findings may be because of 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 et al., 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 (Rosa-Neto et al., 2005; Volkow et al., 2007b; del Campo et al., 2013), decrease subcortical dopamine synthesis (Ludolph, 2008), and increase regional CBF in the cerebellar vermis (Schweitzer et al., 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 behavior and in the control of mood and movement, dopamine dysfunction has been implicated in the pathogenesis of ADHD (Volkow et al., 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 et al., 2006; Ludolph et al., 2008), midbrain (Ludolph et al., 2008), and prefrontal cortex (Ernst et al., 1998), regardless of treatment status. However, an older study failed to find presynaptic dopamine differences in the subcortex or prefrontal cortex, and found a nonsignificant increase in midbrain dopamine synthesis in adolescent ADHD patients, even when treated with a psychostimulant (Ernst et al., 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 et al., 2007b), whereas other studies showed no differences (Jucaite et al., 2005; del Campo et al., 2013) or even an increase (Rosa-Neto et al., 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 et al., 2007) and another found lower DAT in the left caudate nucleus and nucleus accumbens (Volkow et al., 2007a) compared with healthy controls. These differences have been explained by differences in the 5'DAT (*SLC6A3*) haplotype (Drgon et al., 2006), the degree of methylation of the *DAT1* promoter (Wiers et al., 2018), and medication status (Fusar-Poli et al., 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 (Zametkin et al., 1993; Ernst et al., 1994, 1998).

In summary, similar to ASD, ADHD is a very heterogeneous disorder, and variable imaging results may be because of 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.

*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 et al., 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 et al., 2011; S.M. Huang et al., 2016; Poirier et al., 2017; Zoratto et al., 2017; Ha et al., 2020).

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 et al., 2017). In contrast, the six-week-old spontaneously hypertensive (SHR) rat model, a model with phenotypic features similar to the hyperactive/impulsive ADHD subtype, showed stronger cortico-striato-thalamocortical connections compared with controls (S.M. Huang et al., 2016). Poirier et al. (2017) also found evidence for a stronger cortico-stratal network in awake six-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 et al., 2017). The inconsistent findings between the two rat models (NHE vs SHR) are similar to what has been demonstrated in humans and may be because of the different subtypes of ADHD (Sanefuji et al., 2017).

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

Ha et al. (2020) used the same SHR rat model to investigate the metabolic connections using $[^{18}F]$-FDG PET at four and six weeks of age. The authors showed delayed maturation of limbic and (sub)cortical connections together with reduced right fronto-striatal connections at six weeks of age. The latter is inconsistent with the study by S.M. Huang et al. (2016), which may be because of a different imaging technique (awake $[^{18}F]$-FDG PET vs rs-fMRI under anesthesia) 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 with wild-type controls (Brown et al., 2011). Upon initiation of methylphenidate, striatal $[^{11}C]$-raclopride binding was restored to wild-type levels (Brown et al., 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 (Rosa-Neto et al., 2005; Volkow et al., 2007b; del Campo et al., 2013).

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

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

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

Second, there is uncertainty about the effects of the anesthesia on infant rodents, which may differ from those in older animals. It is well known that the depth of anesthesia and the pharmacological effects of different anesthetics influence BOLD signals, and hence FC patterns (Grandjean et al., 2014). While the combination of vasodilating low-dose isoflurane and intravenous 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 anesthesia protocol would result in suppressed FC, but the authors argued that it was sufficient to perform a seed-based analysis (Guadagno et al., 2018). To avoid the confounding factor of anesthesia, methods to perform rs-fMRI in awake (young) adult rodents have been explored (Becerra et al., 2011). However, preschool 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 anesthesia is similar.

Finally, hemodynamic responses may differ at different ages, which would result in different BOLD signals affecting the FC quantification (Colonnese et al., 2008; Kozberg et al., 2013). Colonnese et al. (2008) investigated differences in BOLD responses after forepaw stimulation in rats of different ages (P10–P12, P13–P15, P20–P30, and adult; Colonnese et al., 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 hemodynamic response, mainly because of 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 et al., 2008). When performing rs-fMRI in infants and young children, the same factors that may influence the hemodynamic response should be considered.

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

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

Second, the radioactive tracer used in PET imaging must be administered intravenously through a tail vein catheter. The small tail size of infant rodents, especially mice, can make it difficult to perform PET imaging within the first few weeks of life. Third, since the rodents need to be scanned at a preweaning 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 because of urine loss from the scanned pup. In addition, rejection by the mother after the pups return to the cage has been described (Hickman and Swan, 2011).

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

anesthetic challenges, efforts are being made to perform awake PET in freely moving rodents (Miranda et al., 2019). However, sedation would also be required in preschool children.

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

In recent years, several PET radiotracers have been developed to visualize synaptic vesicle glycoprotein 2A (SV2A) *in vivo* (Carson et al., 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 et al., 2020, 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 et al., 1999). Therefore, SV2A quantification has been proposed as a surrogate marker for synaptic density. SV2A PET has been used to detect pathologic changes in synaptic density in humans and animal models of neurodegenerative disorders and spinal cord injury (Delva et al., 2020; Bertoglio et al., 2021, 2022a; Chen et al., 2021). 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 fetal brain of pregnant rhesus monkeys (Rossano et al., 2022). In addition, individual component analysis (ICA) on SV2A PET can be used to identify presynaptic density networks (Akkermans et al., 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 et al., 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 noninvasive preclinical imaging biomarkers of neurodevelopmental dysfunction, and assessing treatment response.

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