

Critical periods and Autism Spectrum Disorders, a role for sleep

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ABSTRACT

Brain development relies on both experience and genetically defined programs. Time windows where certain brain circuits are particularly receptive to external stimuli, resulting in heightened plasticity, are referred to as “critical periods”. Sleep is thought to be essential for normal brain development. Importantly, studies have shown that sleep enhances critical period plasticity and promotes experience-dependent synaptic pruning in the developing mammalian brain. Therefore, normal plasticity during critical periods depends on sleep. Problems falling and staying asleep occur at a higher rate in Autism Spectrum Disorder (ASD) relative to typical development. In this review, we explore the potential link between sleep, critical period plasticity, and ASD. First, we review the importance of critical period plasticity in typical development and the role of sleep in this process. Next, we summarize the evidence linking ASD with deficits in synaptic plasticity in rodent models of high-confidence ASD gene candidates. We then show that the high-confidence rodent models of ASD that show sleep deficits also display plasticity deficits. Given how important sleep is for critical period plasticity, it is essential to understand the connections between synaptic plasticity, sleep, and brain development in ASD. However, studies investigating sleep or plasticity during critical periods in ASD mouse models are lacking. Therefore, we highlight an urgent need to consider developmental trajectory in studies of sleep and plasticity in neurodevelopmental disorders.

1. Introduction

Brain development relies on both experience and genetically defined programs. Brain circuits are established through neuronal proliferation and migration. Experience remodels circuits through both synaptogenesis and pruning, a process referred to as synaptic plasticity (Hübener and Bonhoeffer, 2014). Time windows where certain brain circuits are particularly receptive to external stimuli, resulting in heightened plasticity, are referred to as “critical periods” (Dehorter and Del Pino, 2020; Hensch, 2004; Rice and Barone, 2000). While heightened plasticity allows us to shape neuronal circuits, this also introduces vulnerability. Therefore, disruptions early in life can result in neuronal circuits that respond differently to experiences later on (Hensch, 2003, 2004; Knudsen, 2004; Rice and Barone, 2000). In the last four decades, developmental windows for our brain’s ability to attune to experience have been widely studied, emphasizing the importance of critical periods in the developing brain (Rice and Barone, 2000). During early postnatal development, and while critical periods occur, young mammals spend most of their time sleeping. Sleep is thought to be essential

for normal brain development (Frank and Heller, 1997; Krueger et al., 2016; Ribeiro, 2012; Roffwarg et al., 1966; Shaffery and Roffwarg, 2009). Studies have shown that sleep enhances critical period plasticity (Frank et al., 2001) and promotes experience-dependent synaptic pruning in the developing cortex (Li et al., 2017; Zhou et al., 2020). Therefore, normal plasticity during critical periods depends on adequate amounts of sleep.

Problems falling and staying asleep occur at a higher rate in individuals with Autism Spectrum Disorder (ASD) than in individuals with typical development, affecting up to 93% of individuals (Petruzzelli et al., 2021). Sleep problems in individuals with ASD are predictive of the severity of ASD core symptoms (Cohen et al., 2014) and lead to a reduced quality of life of individuals and caregivers (Hodge et al., 2014). Although sleep problems are often thought of as a co-occurring condition, the fundamental role of sleep in brain development points to sleep problems as a potential core factor in ASD. Recent studies have shown that problems falling asleep in the first year of life precede an ASD diagnosis and are associated with hippocampal overgrowth in infants at high-risk for ASD (MacDuffie et al., 2020b). Recent studies have also shown that problems falling asleep predict impairments in behavior

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Abbreviations

ASD	Autism Spectrum Disorder
NREMS	Non rapid eye movement sleep
REMS	Rapid eye movement sleep
ODP	Ocular dominance plasticity
CNV	Copy Number Variants

regulation later in children with ASD (Tesfaye et al., 2021). However, studies investigating the mechanisms that link sleep early in life and ASD are lacking. ASD is diagnosed behaviorally on average between 4 and 5 years of age based on symptoms in two core domains, social deficits and repetitive behavior (van 't Hof et al., 2021). Altered

trajectories of development in individuals that go on to be diagnosed with ASD can be detected earlier in life (Zwaigenbaum et al., 2015). For example, over-expansion of the cortical surface area between 6 and 12 months of age and subsequent brain volume overgrowth is predictive of later ASD diagnosis in high-risk infants (Hazlett et al., 2017). The high rate of cortical surface and brain volume expansion that occurs after birth in mammals is thought to facilitate the contributions of postnatal experience (Hill et al., 2010). Therefore, alterations in cortical and brain growth early in life can affect how experience molds the brain. The rapid brain growth in the postnatal years is accompanied by high rates of synaptogenesis and pruning, fundamental substrates of synaptic plasticity. Deficits in plasticity early in life are thought to be important contributors to the ASD phenotype (Cohen et al., 2014; LeBlanc and Fagiolini, 2011). Given the relationship between sleep and plasticity, it is reasonable to propose that sleep and plasticity deficits during critical periods of development are inextricably linked in ASD.

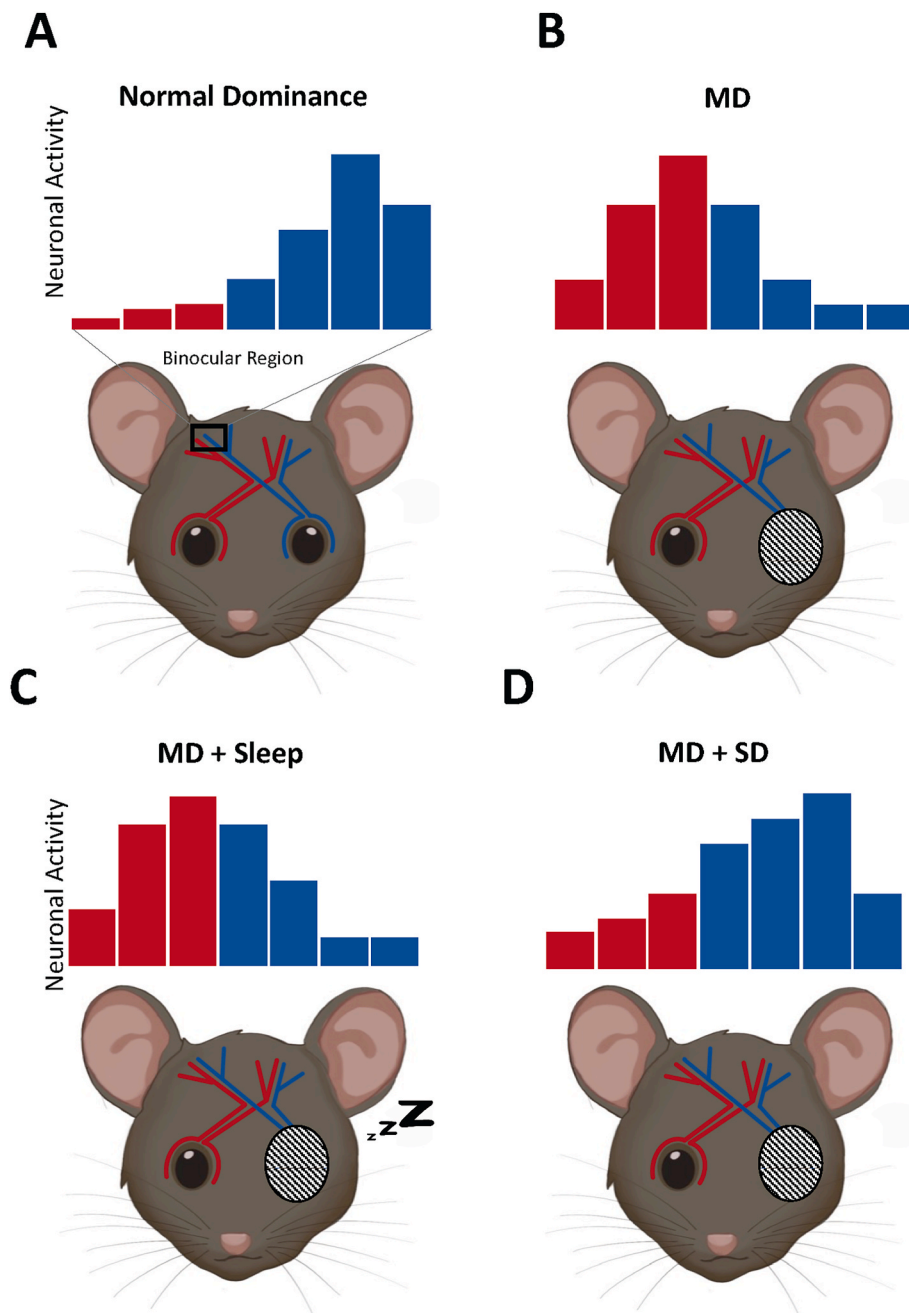


Fig. 1. The Ocular Dominance Plasticity model. A) In the binocular region of the visual cortex most neurons respond to input from the contralateral eye while very few respond to input from the ipsilateral eye input only. Input from eyes is color coded, red represent left, blue represent right. An example of neuronal activity sampled from the left side will receive most input from the contralateral side (blue). B) Monocular deprivation (MD) results in a shift of response from the non-deprived eye C) Sleep is necessary to consolidate the effects of MD. D) When sleep deprivation (SD) follows MD, the shift in response is not seen. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

In this review, we explore the potential link between plasticity, especially during critical periods of development, sleep, and ASD. First, we review the importance of critical period plasticity in typical development and the role of sleep in this process. Next, we summarize the evidence linking ASD with deficits in synaptic plasticity in mouse models of high-confidence ASD gene candidates, and we show that almost all the high-confidence mouse models of ASD (SFARI gene score of 1 or Syndromic) that show sleep deficits also display plasticity deficits. Given how important sleep is in early life, and for critical period plasticity in particular, this review highlights the importance of understanding connections between synaptic plasticity, sleep, and brain development in ASD.

The importance of critical periods in typical brain development.

The brain's typical development relies on multiple processes, such as cell proliferation, migration, circuit formation and maturation, all driven by genetic and environmental stimuli (Dehorter and Del Pino, 2020). Experience promotes rewiring and remodeling through a process known as synaptic plasticity (Hübener and Bonhoeffer, 2014). Synaptic plasticity refers to the ability of synapses to change in numbers, through genesis or pruning, or strength in response to use or disuse. Changes in strength can in turn happen through different mechanisms. Hebbian plasticity is defined as changes in the connection strength (either strengthening or weakening) between two neurons resulting from correlated firing (Hebb, 2005). Long-term potentiation (LTP) and long-term depression (LTD) are two forms of Hebbian plasticity. Homeostatic plasticity, such as synaptic scaling, is a form of plasticity that attempts to stabilize neuron or neuronal circuit activity in the event of a perturbation, such as a change in synapse number or strength that may alter excitability.

Critical periods of development, in which brain circuits are particularly plastic, have been recognized for nearly a century (Levelt and Hübener, 2012). It is important to note that the critical period of plasticity is simply an extreme form of plasticity; while this is elevated in early development, different types of plasticity can occur throughout our lifespan. The timeline for brain development differs across species, but critical periods have been established in both humans and animals. Critical periods also differ in timing based on input modality. During postnatal development, critical periods occur at ages in which other important processes for brain development also occur at a high rate, in particular synaptogenesis and pruning.

The visual system has long been favored as a model for critical period plasticity because experience strongly regulates the maturation of the visual cortex (Espinosa and Stryker, 2012; Levelt and Hübener, 2012). The best-studied example of critical period plasticity is the ocular dominance plasticity model (ODP) in the visual cortex. This model allows for measures of neuronal activity *in vivo* in unanesthetized brains in a system whose cellular processes are well established. In 1959, Hubel and Wiesel discovered that specific neurons in a cat's primary visual cortex were activated through stimuli presented to one eye or the other, termed ocular dominance (Hubel and Wiesel, 1959, 1962). They used monocular deprivation (MD) to deprive one eye of visual experience, which caused a decrease in the cortical neurons' response associated with the deprived eye and increased response to neurons associated with the spared eye in the binocular cortex (example depicted in Fig. 1). MD in a young kitten resulted in the irreversible loss of responsiveness in those cells even though there was no damage to the retina (Hubel and Wiesel, 1970; Wiesel and Hubel, 1963a, 1963b). In contrast, the same MD in an adult cat did not result in a loss of visual acuity. Importantly, this critical period is not a simple age-dependent mechanism, as animals that are only exposed to complete darkness in early life have a delayed onset of this critical period (Cynader, 1983; Mower, 1991). Therefore, the critical period for ODP is both age and experience dependent. The consolidation of ODP is divided into three mechanistically distinct stages. In the first stage, there is a decrease in response to the deprived eye, which is hypothesized to result from the loss of deprived-eye connections or depression in their synaptic efficacy. The dramatic loss of

response to inputs from the deprived eye is thought to occur through Hebbian plasticity. In the second stage of ODP, there is an increase of response to inputs from both eyes, but most notably the open eye. This stage is thought to operate through both homeostatic and Hebbian plasticity. Restoring binocular vision by reopening the deprived eye during the critical period induces a third stage of plasticity, the rapid restoration of both eyes' responses to baseline levels, which is dependent on neurotrophic growth factor signaling. The ODP model has been used to demonstrate the role of sleep on critical period plasticity as described below.

1.1. The role of sleep in the consolidation of plasticity

Sleep is a naturally reoccurring and reversible brain state (Sun et al., 2020). Sleep or sleep-like states occur in all vertebrates and are widely present in invertebrates (Sun et al., 2020). Sleep states in mammals are traditionally defined using electroencephalographic recordings (EEG) and are categorized into two major stages: rapid-eye-movement (REM) sleep and non-rapid-eye movement (NREM) sleep. NREMS is characterized by high amplitude, slow frequency oscillations in the EEG (slow waves, less than 1 Hz), spindles (0.5–2s bursts of 10–16 Hz), a relaxed EMG, and a decrease in body temperature. Slow-wave activity (SWA) or the synchronization of low frequency (<4 Hz) membrane potentials of many neurons in the cortical membrane, is a major component of NREMS (Siegel, 2009). SWA is homeostatically regulated, as it is enhanced across the brain after prolonged periods of wake. REMS is characterized by low amplitude, fast frequency EEG, muscle atonia and increased body temperature (Siegel, 2009).

Scientists have yet to reach a universal consensus on the function of sleep and it is likely that it serves multiple functions. Nonetheless, we know sleep is important for cognitive function. Acute sleep loss can lead to impairments in learning, attention, and emotional regulation (Krause et al., 2017). Chronic sleep disturbances are common in neurodevelopmental disorders such as ASD (Cohen et al., 2014). The complexity of the molecular mechanism of sleep provides evidence for multiple functions leading to multiple hypotheses. One such theory supported by many sleep researchers is that sleep is essential for the connectivity or plasticity of the brain (Krueger et al., 2016). While the function of sleep is not fully understood, several functional and morphological studies *in vivo* provide direct evidence that sleep is important for synaptic plasticity during development and into adulthood (Frank, 2015; Renouard et al., 2022). The mechanisms underlying this relationship are less clear.

During early postnatal development, and while critical periods occur, mammals spend most of their time sleeping (Roffwarg et al., 1966). Sleep states in rodents cannot be identified using EEG until approximately postnatal (P) day 12 (Frank and Heller, 2003; Rensing et al., 2018), which corresponds to approximately a 40 day old human infant (Workman et al., 2013, <https://www.translatingtime.org>). Early in development REMS is the predominant sleep state. Gradually REMS decreases, while wake and NREMS amount increase (Frank et al., 2017; Medina et al., 2022; Rensing et al., 2018). In rodents, the decrease of REMS stabilizes around P20 while NREMS continues to increase until P30 (Frank et al., 2017), which correspond to 7–16 months in humans (Workman et al., 2013, <https://www.translatingtime.org>). REMS deprivation in P28 rodents prolonged the critical period for synaptic plasticity in the visual cortex (Shaffery et al., 2002). Most of the work regarding to role of sleep in ODP, however, has been done in kittens during the peak of their critical period (~P30, corresponding to a 4-month-old human infant). Those studies have shown that sleep enhances plasticity during the critical period for ODP, while REMS deprivation inhibits experience-dependent plasticity in the cortex while (Dumoulin Bridi et al., 2015; Frank et al., 2001). Sleep can both strengthen and weaken different synapses in response to experience during wake (Aton et al., 2009; Frank et al., 2001; Frank, 2015; Puentes-Mestriil and Aton, 2017; Zhou et al., 2020). In addition, REM sleep

has been shown to be required for phosphorylation of kinases involved in plasticity following MD, such as ERK (Aton et al., 2009; Dumoulin Bridi et al., 2015; Renouard et al., 2018). Overall, these studies provide evidence that sleep, and in particular REM sleep, are essential for the consolidation of plasticity, especially during critical periods of development. Therefore, sleep alterations during early life may have long lasting effects on experience-dependent synapse remodeling.

1.2. Autism spectrum disorders and underlying mechanisms

Autism spectrum disorder (ASD) is the most prevalent neurodevelopmental disorder in the United States (Scandurra et al., 2019). ASD is called a spectrum disorder, as individuals on the spectrum display a wide range of symptoms; however, many impairments occur in the first two years of life which includes the critical period for normal brain development (Meredith, 2015). ASD diagnosis is challenging as it is behaviorally diagnosed and therefore often relies on the identification of symptomatic behaviors and professional clinical judgement. These behaviors may not be displayed until the disorder is well established. The current diagnostic criteria for ASD require symptoms in two core domains: deficits in social interactions and restrictive/repetitive behaviors. The average age of diagnosis in the United States is four years old (Zuckerman et al., 2016). Evidence suggests that early diagnosis and intervention can significantly improve treatment outcomes and, therefore, individuals' quality of life (Cohen et al., 2014; Verhoeff et al., 2018). While there is a genetic basis for ASD, most ASD cases occur for unknown reasons. Therefore, identifying biomarkers may aid in early detection and diagnosis is crucial.

Critical period dysregulation may pinpoint the key developmental stages at which synaptic abnormalities are present in neurodevelopmental disorders such as ASD. Some research supports that neurodevelopmental disorders are caused by the deregulation of critical periods for synaptic brain circuitry, leading to disruptions in proper development, and altered behavior. At the synaptic level, embryonic and early postnatal spine dysmorphology present in some ASD mouse models (Cruz-Martín et al., 2010; Galvez and Greenough, 2005) supports the hypothesis that abnormal circuitry may not be a consequence of impaired cognitive and behavioral impairment. This suggests that abnormalities in mechanisms that regulate synaptic circuitry are present before significant cognitive and behavioral abnormalities are detectable. The ability to measure molecular abnormalities in early postnatal development would give rise to the possibility of earlier intervention, thereby increasing the therapeutic potential for individuals with ASD.

ASD encompasses a set of highly heterogeneous neurodevelopmental disorders that share common behavioral abnormalities. One common underlying theme in ASD is the functional alteration of both excitatory and inhibitory synapses. Brain function relies on informational transfer between excitatory and inhibitory networks. A dysfunctional balance between excitatory and inhibitory networks can lead to alterations in structural processes leading to electrophysiological changes that then lead to behavioral abnormalities. A mutation in a single gene can play a major role in cellular processes leading to complex effects in network phenotypes. Multiple ASD-associated genes are thought to influence plasticity in different cell types and at different levels, as they encode proteins involved in synaptic plasticity, neuronal excitability, and connectivity; as well as chromatin remodelers that allow changes brought upon by experience to be encoded long-term through epigenetic changes.

1.3. Prevalence of sleep problems in ASD

Sleep problems occur at a much higher rate in children with ASD. It is estimated that sleep problems affect 40–93% of children with ASD, compared to 11%–37% of typically developing children (Petruzzelli et al., 2021). Three key features characterize ASD sleep problems: problems falling asleep, problems staying asleep, and overall less sleep

(Hodge et al., 2014). Sleep problems predict the severity of ASD core diagnostic symptoms and associated challenging behaviors (Cohen et al., 2014), and often increase with age (Hodge et al., 2014), which imposes a severe burden on caregivers. Recent studies using parent reports of sleep on a cohort of baby siblings of individuals with ASD (who are at a higher risk for a diagnosis) found that problems falling asleep in the first year of life precede an autism diagnosis and are associated with altered patterns of brain development, specifically hippocampal overgrowth (MacDuffie et al., 2020b). Baby-sibling studies have also shown that sleep problems in autistic children as young as four years old are associated with increased 'higher-order' restricted and repetitive behaviors later in childhood (MacDuffie et al., 2020a). This suggests that sleep problems early in life are predictive of symptom severity across the lifespan. This view is supported by recent studies showing that problems falling asleep predict impairments in behavior regulation later in children with ASD (Tefaye et al., 2021). However, whether there is a causal mechanism linking sleep problems and brain dysfunction during development remains unknown.

There are several monogenic syndromes associated with ASD. The recapitulation of these syndromes in animal models has provided insights into mechanisms associated with the disorder. Genes linked to ASD and available mouse models can be found in the Simons Foundation Autism Research Initiative (SFARI) gene database. In that database genes are categorized according to the strength of evidence linking them to ASD based on human genetic studies as follows: S (Syndromic), 1 (High Confidence), 2 (Strong Candidate), 3 (Suggestive Evidence), 4 (Minimal Evidence), 5 (Hypothesized). Few of the mouse ASD models have been studied in regard to sleep and whether they recapitulate all features of the clinical sleep phenotype, which are: reduced sleep time, sleep fragmentation, and increased latency to fall asleep (Wintler et al., 2020). Some ASD mouse models display reduced sleep, even fewer also display sleep fragmentation. The *Shank3^{4C}* mouse model is the only high-confidence ASD mouse model, so far, to also display increased sleep latency.

Sleep patterns across development including the response to sleep loss have been investigated in only one mouse model, *Shank3^{4C}* mice. Studies show that *Shank3^{4C}* mice sleep less throughout their lifespan and show reduced NREM sleep compared to wildtype littermates but paradoxically display dramatically increased levels of REM sleep at postnatal day 23 (Medina et al., 2022). At this age mice have achieved 70% of their maximal brain growth and are roughly equivalent to 9–10 month-old human infants based on brain volume (Workman et al., 2013) *Shank3^{4C}* mice at P23 also show EEG spectral signatures during wake that may be indicative of cortical overgrowth (Medina et al., 2022). This time in rodents coincides with critical periods when the brain is exquisitely sensitive to changes in the environment. Therefore, studies in young mice, although limited, support the hypothesis from infant studies that sleep may be altered early in life and be a core feature of the ASD phenotype. In turn this predicts that sleep problems early in life may be highly correlated and perhaps predictive of alterations in brain plasticity such as an imbalance of excitation and inhibitory networks which are well documented in ASD (Bagni and Zukin, 2019).

1.4. Deficits in synaptic plasticity in ASD

Syndromic mouse models of ASD that recapitulate the human phenotype provide valuable insights into general mechanisms underlying ASD. To establish the number of ASD mouse models that have also been associated with deficits in synaptic plasticity we reviewed studies within the SFARI gene database (January 2021 release). The original dataset included copy number variants (CNV) and genes that were either syndromic (S) or had an evidence score of 1 (high confidence) and encompassed 105 genes and 438 related articles. Based on primary research articles we determined which genes or genomic regions influenced plasticity. We defined an effect on plasticity based on whether a mutation in the gene or a CNV produced one or more of the following

Table 1

High-Confidence ASD Genes and CNVs associated with neuroplasticity. Summary of genes and CNVs extracted from the SFARI gene database (January 13th, 2021, release) for which mutations are associated with deficits in plasticity based on mouse model studies. Only copy number variants (CNV) or ASD genes that were either syndromic (S) or had an evidence score of 1 (high confidence) were considered. Column 1: gene symbol; column 2: brief description of the gene; column 3: Articles supporting a role for the gene/CNV in neuroplasticity; columns 4–6: “Yes” indicates a change in neuroplasticity reported in the literature in either: 1) dendritic spine morphology, 2) electrophysiological measures of plasticity (LTD, LTP, EPSC, IPSC, EPSP, IPSP), or 3) learning/memory behavioral task. “No” indicates article looked at and/or measured neuroplasticity but found no change between control and gene (i.e., enhancement or deficit was not indicated in the article). “N/a” indicates no article addressed measured plasticity in this manner; column 7: list articles that investigate sleep in a mouse model of the gene/CNV, “No” indicates it has not yet been investigated.

Gene/CNV	Description	Citations	Dendritic spine morphology	Electro-physiology	Behavior	Sleep
m7qF3	<i>16p11.2 duplication</i>	Arbogast et al. (2016)	N/A	No	Yes	No
m7qF3	<i>16p11.2 deletion</i>	Arbogast et al. (2016); Bertero et al. (2018); Grissom et al. (2018); Horev et al. (2011); Portmann et al. (2014); Stoppel et al. (2018); Tian et al. (2015); Yang et al. (2015)	Yes	Yes	Yes	Angelakos et al. (2017); Lu et al. (2019)
m7qC	<i>15q13.3 deletion</i>	Fejgin et al. (2014); Uddin et al. (2018)	Yes	Yes	Yes	No
m7qB5-qC	<i>15q11-q13 duplication</i>	Isshiki et al. (2014); Kloth et al. (2015); Nakai et al. (2017); Piochon et al. (2014)	Yes	Yes	Yes	No
M11qB1.3-qB2	<i>17p11.2 duplication</i>	Lacaria et al. (2012)	N/A	N/A	Yes	No
<i>Actl6b</i>	Actin like 6B	Wenderski et al. (2020)	N/A	N/A	Yes	No
<i>Adnp</i>	Activity-dependent neuroprotector homeobox	Hacohen-Kleiman et al. (2018)	Yes	N/A	Yes	No
<i>Ahi1</i>	Abelson helper integration site 1	Sacai et al. (2020)	N/a	Yes	No	No
<i>Ank2</i>	Ankyrin 2, neuronal	Yang et al. (2019)	No	Yes	Yes	No
<i>Arid1b</i>	AT-rich interaction domain 1B	Jung et al. (2017); Shibutani et al. (2017); Smith et al. (2020)	Yes	Yes	Yes	No
<i>Arx</i>	Aristaless related homeobox	Dubos et al. (2018)	N/A	Yes	Yes	No
<i>Auts2</i>	Activator of transcription and developmental regulator	Hori et al. (2020)	Yes	Yes	Yes	No
<i>Cacna1c</i>	Calcium voltage-gated channel subunit alpha1 C	Langwieser et al. (2010); Moosmang et al. (2005)	No	Yes	Yes	Kumar et al. (2015)
<i>Camk2a</i>	Calcium/calmodulin dependent protein kinase II alpha	Stephenson et al. (2017)	Yes	Yes	No	No
<i>Caprin1</i>	RNA granule protein 105 (Caprin 1)	Ohashi et al. (2016)	N/A	N/A	Yes	No
<i>Cdkl5</i>	Cyclin-dependent kinase-like 5	Tang et al. (2019)	Yes	Yes	Yes	No
<i>Chd2</i>	Chromodomain helicase DNA binding protein 2	Kim et al. (2018)	N/a	Yes	Yes	No
<i>Chd8</i>	Chromodomain helicase DNA binding protein 8	Durak et al. (2016); Ellingford et al. (2021); Gompers et al. (2017); Jung et al. (2018); Katayama et al. (2016); Kawamura et al. (2021); Platt et al. (2017)	Yes	Yes	Yes	No
<i>Cntnap2</i>	Contactin associated protein-like 2	Antoine et al. (2019); Brunner et al. (2015); Kloth et al. (2015); Peñagarikano et al. (2011); Sacai et al. (2020)	Yes	Yes	Yes	Thomas et al. (2017)
<i>Ctnnb1</i>	Catenin (cadherin associated protein), beta 1	Dong et al. (2016)	N/A	N/A	Yes	No
<i>Cul3</i>	Cullin 3	Z. Dong et al. (2020); Rapanelli et al. (2021)	Yes	Yes	No	No
<i>Deaf1</i>	Transcription factor	Vulto-van Silfhout et al. (2014)	N/A	N/A	Yes	No
<i>Dip2a</i>	Disco interacting protein 2 homolog A	Ma et al. (2019)	Yes	Yes	No	No
<i>Dlg4</i>	Discs, large homolog 4 (Drosophila)	Feyder et al. (2010)	Yes	N/A	Yes	No
<i>Dmd</i>	Dystrophin	Daoud et al. (2008)	Yes	Yes	Yes	No
<i>Dscam</i>	DS cell adhesion molecule	Maynard and Stein (2012)	Yes	N/A	N/A	No
<i>Dyrk1a</i>	Dual specificity tyrosine-Y-phosphorylation regulated kinase 1A	Altafaj et al. (2001); Arranz et al. (2019); Fotaki et al. (2002)	Yes	N/A	Yes	No
<i>Fmr1</i>	Fragile X mental retardation protein 1	Antoine et al. (2019); Bhattacharya et al. (2012); Comery et al. (1997); Costa et al. (2012); Koekkoek et al. (2005); Lim et al. (2014); Padmashri et al. (2013); Qin et al. (2011); Shang et al. (2009); Testa-Silva et al. (2012)	Yes	Yes	Yes	Boone et al. (2018)
<i>Foxp1</i>	Forkhead box P1	Araujo et al. (2017); Bacon et al. (2015)	Yes	Yes	Yes	No
<i>Foxp2</i>	Forkhead box P2	Enard et al. (2009)	Yes	Yes	N/a	No
<i>Gabrb3</i>	Gamma-aminobutyric acid type A receptor beta 3 subunit	DeLorey et al. (1998)	N/A	N/A	Yes	Wisor et al. (2002)
<i>Gria2</i>	Glutamate receptor, ionotropic, AMPA 2	Chung et al. (2003)	N/A	Yes	N/A	No
<i>Grin2b</i>	Glutamate receptor, ionotropic, N-methyl D-aspartate 2B	Brigman et al. (2010)	Yes	Yes	Yes	No
<i>Iqsec2</i>	IQ motif and Sec7 domain 2	Rogers et al. (2019)	N/A	Yes	Yes	No
<i>Kmt2a</i>	Lysine methyltransferase 2A	Shen et al. (2016)	Yes	Yes	Yes	No

(continued on next page)

Table 1 (continued)

Gene/CNV	Description	Citations	Dendritic spine morphology	Electro-physiology	Behavior	Sleep
<i>Mecp2</i>	Methyl-CpG binding protein 2	Jentarra et al. (2010); Na et al. (2012); Wood et al. (2009); Wood and Shepherd (2010)	Yes	Yes	Yes	Dong et al. (2020); Johnston et al. (2014)
<i>Mef2c</i>	Myocyte Enhancer Factor 2C	Barbosa et al. (2008); Harrington et al. (2016)	Yes	Yes	Yes	Bjorness et al. (2020)
<i>mTor</i>	Mechanistic target of rapamycin kinase	Rial et al. (2020)	Yes	Yes	N/A	No
<i>Nbea</i>	Neurobeachin	Medrihan et al. (2009); Muellerleile et al. (2020); Nuytens et al. (2013)	Yes	Yes	Yes	No
<i>Nf1</i>	Neurofibromin 1	Costa et al. (2001); Molosh et al. (2014)	N/A	Yes	Yes	Anastasaki et al. (2019)
<i>Nlgn3</i>	Neuroigin 3	Baudouin et al. (2012); Etherton et al. (2011); Isshiki et al. (2014); Martella et al. (2018); Pizzarelli and Cherubini (2013); Tabuchi et al. (2007); Zhang et al. (2015)	Yes	Yes	Yes	Liu et al. (2017)
<i>Nr2f1</i>	Nuclear receptor subfamily 2 group F member 1	K. Zhang et al. (2020)	N/A	Yes	Yes	No
<i>Nr3c2</i>	Nuclear receptor subfamily 3, group C, member 2	Berger et al. (2006)	No	No	Yes	No
<i>Nrxn1</i>	Neurexin 1	Etherton et al. (2009)	N/A	Yes	Yes	No
<i>Nrxn2</i>	Neurexin2	Born et al. (2015)	No	Yes	No	No
<i>Pogz</i>	Pogo transposable element derived with ZNF domain	Matsumura et al. (2020)	Yes	Yes	Yes	No
<i>Ptchd1</i>	Patched domain containing 1	Ung et al. (2018); Wells et al. (2016)	Yes	Yes	Yes	No
<i>Pten</i>	Phosphatase and tensin homolog	Sánchez-Puelles et al. (2020); Takeuchi et al. (2013); Williams et al. (2015)	Yes	Yes	Yes	No
<i>Rai1</i>	Retinoic acid induced 1	W.-H. L. Huang et al. (2018)	Yes	N/A	N/A	Diessler et al. (2017)
<i>Reln</i>	Reelin	Rice et al. (2001)	Yes	N/A	N/A	No
<i>Rims1</i>	Regulating synaptic membrane exocytosis 1	Powell et al. (2004); Schoch et al. (2002); Wang et al. (2018)	No	Yes	Yes	Lonart et al. (2008)
<i>Rps6ka3</i>	Ribosomal protein s6 kinase, 90 kDa, polypeptide 3	Morice et al. (2013)	Yes	Yes	Yes	No
<i>Scn1a</i>	Sodium channel, voltage-gated, type 1, alpha subunit	Bahceci et al. (2020); Han et al. (2012); Kalume et al. (2015); Rubinstein et al. (2015); Tai et al. (2020)	N/A	Yes	Yes	Kalume et al. (2015); Papale et al. (2013)
<i>Scn2a</i>	Sodium voltage-gated channel alpha subunit 2	Middleton et al. (2018); Shin et al. (2019)	N/A	Yes	Yes	Ma et al. (2022)
<i>Scn8a</i>	Sodium voltage-gated channel alpha subunit 8	Papale et al. (2013); Woodruff-Pak et al. (2006)	N/A	Yes	Yes	Papale et al. (2010)
<i>Setd5</i>	SET domain containing 5	Deliu et al. (2018, p. 5); Moore et al. (2019)	Yes	Yes	Yes	No
<i>Shank2</i>	SH3 and multiple ankyrin repeat domains 2	Ha et al. (2016); Lim et al. (2017); Won et al. (2012)	Yes	Yes	Yes	No
<i>Shank3</i>	SH3 and multiple ankyrin repeat domains 3	Bozdagi et al. (2010, 2013); Jaramillo et al. (2016, pp. 4-, 2017, p. 3); Kabitzke et al. (2018); Kouser et al. (2013); Mei et al. (2016); Speed et al. (2015, p. 21); Tatavarty et al. (2020); Wang et al. (2011, 2016, 2020)	Yes	Yes	Yes	Bian et al. (2022); Ingiosi et al. (2019); Medina et al. (2022)
<i>Slc1a2</i>	Solute carrier family 1 (glial high affinity glutamate transporter), member 2	Aida et al. (2015)	N/A	Yes	N/A	No
<i>Slc6a1</i>	Solute carrier family 6, member 1	Gong et al. (2009)	No	Yes	Yes	Xu et al. (2013)
<i>Slc9a6</i>	Solute carrier family 9, subfamily A	Ouyang et al. (2013)	Yes	N/A	N/A	No
<i>Syngap1</i>	Synaptic Ras GTPase activating protein 1a	Clement et al. (2012); Kim et al. (2003); Muhia et al. (2012)	Yes	Yes	Yes	Sullivan et al. (2020)
<i>Tbr1</i>	T-box, brain 1	Fazel Darbandi et al. (2018, 2020); Huang et al. (2014, 2019); Lee et al. (2015); Yook et al. (2019)	Yes	Yes	Yes	No
<i>Tbx1</i>	T-box 1	Hiramoto et al. (2011)	N/A	N/A	Yes	No
<i>Tcf4</i>	Transcription factor 4	Kennedy et al. (2016, p. 4); Li et al. (2019)	Yes	Yes	Yes	No
<i>Trio</i>	Trio Rho guanine nucleotide exchange factor	Katrancha et al. (2019)	Yes	Yes	N/A	No
<i>Tsc1</i>	Tuberous sclerosis 1	Haji et al. (2020)	Yes	N/A	Yes	Rensing et al. (2020); K. Zhang et al. (2020)
<i>Tsc2</i>	Tuberous sclerosis 2	Antoine et al. (2019); Tang et al. (2014)	Yes	Yes	N/A	No
<i>Tshz3</i>	Teashirt zinc finger homeobox 3	Caubit et al. (2016)	N/A	Yes	N/A	No
<i>Ube3a</i>	Ubiquitin protein ligase E3A	Greer et al. (2010); Jiang et al. (1998); Kaphzan et al. (2012); Smith et al. (2011); Sun et al. (2015); Yashiro et al. (2009)	Yes	Yes	Yes	Colas et al. (2005); Copping and Silverman (2021); Ehlen et al. (2015)
<i>Upf3b</i>	Regulator of nonsense mediated mRNA decay	L. W.-H. Huang et al. (2018)	Yes	N/A	Yes	No

phenotypes in mice: 1) change in dendritic spine morphology or number, 2) change in plasticity measured by electrophysiology, 3) change in learning/memory behavioral task and 4) whether a sleep phenotype has been investigated. The results are displayed in Table 1 and include 5

CNVs and 66 genes.

While ASD encompasses a wide range of neurodevelopmental disorders, identifying common pathways may aid the understanding and treatment of ASD core features. ASD risk genes identified so far belong to

Table 2

High-Confidence ASD Genes and CNVs associated with neuroplasticity and sleep deficits. Additional details for genes in [Table 1](#) for which mouse mode studies also display a sleep deficit. We restricted ourselves only to published studies that measure sleep *in vivo* with methods that allow differentiation between sleep state to quantify sleep amounts and quality of sleep. A reduction in sleep amount was defined as reduction in either NREMS or REMS or total sleep. Deficits in sleep quality were defined as fragmented sleep or altered spectral power in the EEG during sleep states. Deficits in the response to sleep loss were defined as either increases in latency to fall asleep or altered buildup of sleep pressure after sleep deprivation. Mice over 8 weeks were considered as adults. [Table 2](#) includes 19 high-confidence ASD mouse models for which mutations have been implicated in both plasticity and sleep deficits (16p.11.2, *Cacna1c*, *Cntnap2*, *Fmr1*, *Gabrb3*, *Mecp2*, *Mef2c*, *Nf1*, *Nlgn3*, *Rims1*, *Rai1*, *Scn1a*, *Scn2a*, *Scn8a*, *Shank3*, *Slc6a1*, *Syngap1*, *Tsc1*, *Ube3a*).

Gene/CNV	Citation	Reduced Sleep Amounts	Reduced Sleep Quality	Deficits in Response to Sleep Loss	Sex	Age
16p11.2 (<i>m7qF3</i>)	Angelakos et al. (2017)	Yes	Abnormal EEG spectral power	Not assessed	Male and Female	Adult
	Lu et al. (2019)	Yes	Fragmented, abnormal EEG spectral power	Not assessed	Male	Young (6–7 wks)
<i>Cacna1c</i>	Kumar et al. (2015)	Yes	Fragmented, abnormal EEG spectral power	Alterations in REMS rebound	Male	Not specified
<i>Cntnap2</i>	Thomas et al. (2017)	No	Fragmented	No difference in sleep pressure accumulation or sleep latency	Male	Adult
<i>Fmr1</i>	Boone et al. (2018)	Yes	Fragmented	Not assessed	Male	Adult
	Wisor et al. (2002)	Yes	Fragmented, abnormal EEG spectral power	Not assessed	Male and Female	Adult
<i>Mecp2</i>	Johnston et al. (2014)	Yes	Fragmented, abnormal EEG spectral power	Not assessed	Male and Female	Young (6–7 wks)
	H.-W. Dong et al. (2020)	Yes	Fragmented	Not assessed	Female	Young (5–8 wks) Old (20–24 wks)
<i>Mef2c</i>	Bjorness et al. (2020)	No	Abnormal EEG spectral power (modest)	Deficits in sleep pressure accumulation	Male	Adult
<i>Nf1</i>	Anastasaki et al. (2019)	No	Fragmented, abnormal EEG spectral power	Not assessed	Male and Female	Adult
<i>Nlgn3</i>	Liu et al. (2017)	No	Abnormal EEG spectral power	Not assessed	Male	Adult
<i>Rai1</i>	Diessler et al. (2017)	No	Abnormal EEG spectral power	No	Male	Adult
<i>Rims1</i>	Lonart et al. (2008)	Yes	Fragmented	Alterations in REMS rebound	Male	Adult
	Kalume et al. (2015)	No	Fragmented	Deficits in sleep pressure accumulation	Not specified	Young (P30-33)
<i>Scn2a</i>	Papale et al. (2013)	Yes	No	No	Male	Adult
	Ma et al. (2022)	Yes	Fragmented, abnormal EEG spectral power	Not assessed	Male and Female	Not specified
<i>Scn8a</i>	Papale et al. (2010)	Yes	Fragmented	No difference in sleep pressure accumulation	Male	Adult
<i>Shank3</i>	Bian et al. (2022)	Yes	Abnormal EEG spectral power	Not assessed	Male and Female	Young (P35-42)
	Ingiosi et al. (2019)	Yes	Fragmented, abnormal EEG spectral power	Increased sleep latency, no difference in sleep pressure accumulation	Male	Adult
	Medina et al. (2022)	Yes	Fragmented, abnormal EEG spectral power	Increased sleep latency, no difference in sleep pressure accumulation	Male	Longitudinal (P23–P60)
<i>Slc6a1</i>	Xu et al. (2013)	Yes	Abnormal EEG power	Deficits in sleep pressure accumulation	Male	Not specified
	Sullivan et al. (2020)	Yes	Abnormal EEG power	Not assessed	Male and Female	Adult
<i>Tsc1</i>	Rensing et al. (2020)	Yes, age dependent	Fragmented, abnormal EEG spectral power	Not assessed	Male and Female	Young (P9-21)
	B. Zhang et al. (2020)	Yes	No	Not assessed	Male and Female	Young (4 wks)
<i>Ube3a</i>	Ehlen et al. (2015)	Yes	Fragmented, abnormal EEG spectral power	Deficits in sleep pressure accumulation	Not specified	Adult (6–8 wks)
	Colas et al. (2005)	Yes	Fragmented	Deficits in sleep pressure accumulation	Female	Adult
	Copping and Silverman (2021)	Yes	Fragmented, abnormal EEG spectral power	Not assessed	Male and Female	Adult

convergent biological pathways relating to transcription, chromatin structure, and synaptic function. Although the earliest ASD risk genes to be identified were known to function at the synapse, it has become clear that a distinct subset of ASD genes are chromatin-modifiers and RNA-binding proteins. Of the 66 ASD risk genes we identified to have a role in synaptic plasticity based on animal model studies, 14 are associated with the cell membrane and known to function at the synapse (e.g.: *Ctnnb1*, *Dscam*, *Shank2*, *Shank3*, *Ank2*, *Camk2a*, *Dlg4*, *Dmd*, *Fmr1*, *Gria2*, *Grin2b*, *Nrxn1*, *Nlgn3*, *Rims1*). In addition, a large fraction of genes in [Table 1](#) act in the nucleus as transcription/chromatin regulators e.g., *Pogz*, *Ube3a*, *Nr3c2*, *Foxp2*, *Adnp*, *Mecp2*, *Chd2*, *Foxp1*, *Tcf4*, *Fmr1*, *Tsc1*. Some genes have both a role at the synapse and in the nucleus (*Ctnnb1*, *Shank3*). This likely reflects the fact that synaptic plasticity requires changes at the synapse to be stabilized through changes in transcription,

translation, and epigenetic modifications (Hegde and Smith, 2019).

1.5. Abnormal sleep in ASD and its potential impact on plasticity

Abnormal sleep in ASD and deficits in synaptic plasticity are not mutually exclusive phenotypes. [Table 2](#) provides additional details for genes in [Table 1](#) for which mouse mode studies also display a sleep deficit. A reduction in sleep amount is defined as reduction in either NREMS, REMS or total sleep. Deficits in sleep quality are defined as fragmented sleep or altered spectral power in the EEG during sleep states. Deficits in the response to sleep loss are defined as either increases in latency to fall asleep or altered buildup of sleep pressure after sleep deprivation. Mice over 8 weeks were considered as adults. [Table 2](#) includes 1 CNV and 18 high-confidence genes (SFARI gene score of 1 or

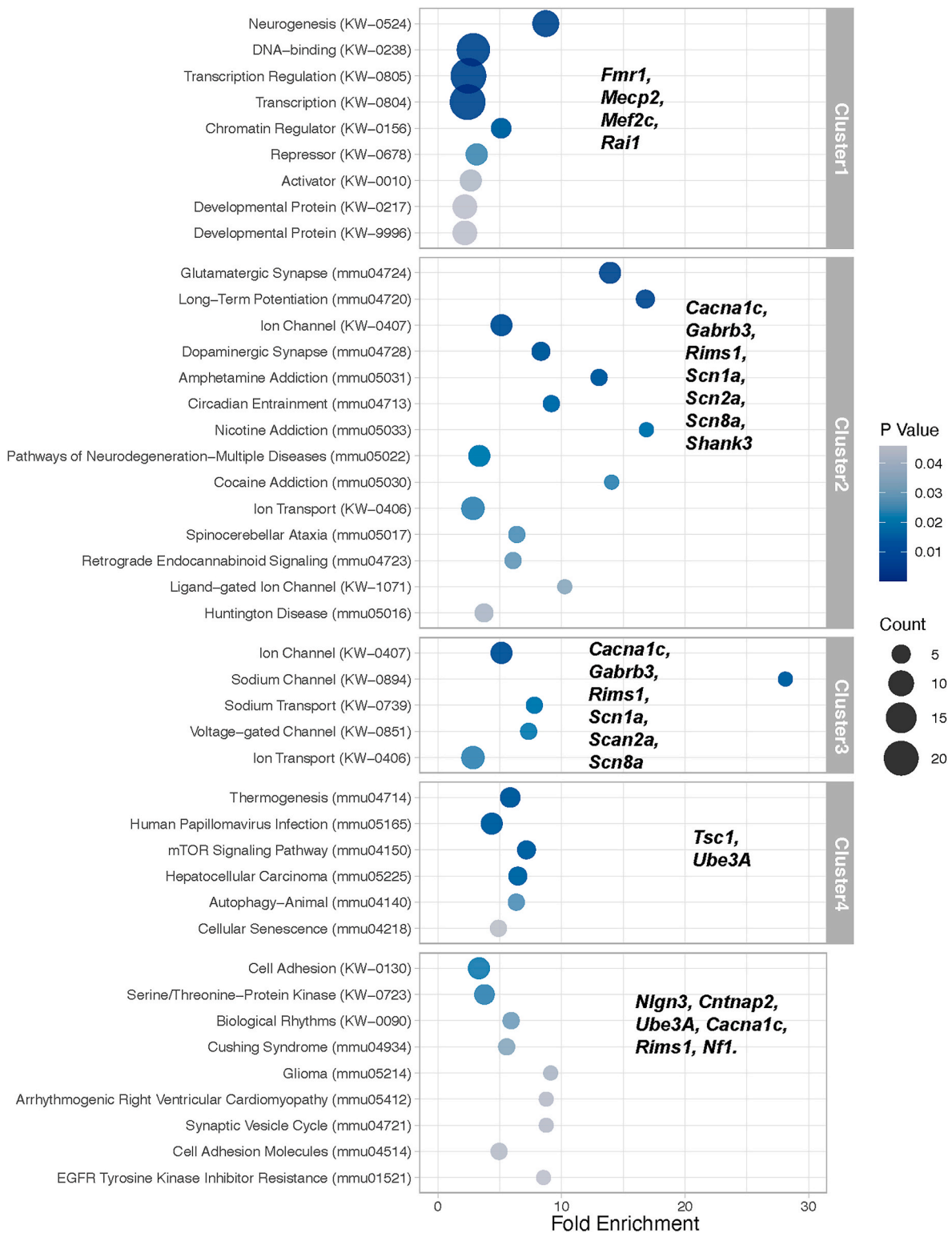


Fig. 2. Summary of biological processes and pathways affected by ASD genes at the intersection of sleep and plasticity. Functional Annotation Enrichment analysis and subsequent clustering of genes in Table 1. Genes highlighted in bold are those for which mutations also affect sleep as outlined in Table 2. KW: KEGG pathway identifier, mmu: Uniprot biological process or molecular function identifier.

Syndromic) for which mutations have been implicated in both plasticity and sleep deficits using mouse models (*16p.11.2*, *Cacna1c*, *Cntnap2*, *Fmr1*, *Gabrb3*, *Mecp2*, *Mef2c*, *Nf1*, *Nlgn3*, *Rims1*, *Rai1*, *Shank3*, *Scn1a*, *Scn2a*, *Scn8a*, *Slc6a1*, *Syngap1*, *Tsc1*, *Ube3a*).

To summarize the relationship between the ASD mouse models displaying plasticity deficits outlined in Table 1 and those also displaying

sleep deficits outlined in Table 2, we performed a functional enrichment analysis using Database for Annotation, Visualization and Integrated Discovery (DAVID, <https://david.ncicrf.gov>) and data from the following databases: Uniprot and KEGG. We first determined which biological processes, molecular functions or pathways were statistically overrepresented among genes in Table 1 compared to what is expected

by chance from the whole mouse genome. Significant statistical enrichment was defined as $p < 0.05$ and was found in several categories. As expected several genes mapped to multiple enriched biological processes, molecular functions and pathways. Subsequently we clustered the enriched terms to find common broad biological functions. Despite the small list of genes, this analysis resulted in four main clusters: transcription/chromatin regulation, synapse function, voltages gated ion channels and mTOR signaling; as well as a handful of pathways or processes that did not cluster. We then mapped the identity of ASD mouse models displaying sleep deficits outlined in Table 2 to these functional clusters. Fig. 2 shows the results of the enrichment and clustering and provide a summary of the functions of the genes that lie at the intersection between plasticity, sleep and ASD. These biological processes are well-known be affected in ASD as well and plasticity. However, the role of sleep in these processes, especially in the larger cluster involving transcription and chromatin regulation is less understood.

Synapse formation and chromatin regulation are processes well-known to influence brain development. Therefore, the convergence of ASD genetic models that show plasticity and sleep deficits on these biological processes may explain why sleep has such a profound effect on critical period plasticity. It is also likely that in ASD a sleep deficit may cause or contribute to deficits in synaptic plasticity from very early on. Nonetheless, very few studies have evaluated the role of ASD-associated genes on either sleep or plasticity early in life. The *Shank3* mouse model is the only one in which sleep, and the impact of sleep loss has been examined early in life and in adults. *Shank3*^{ΔC-/-} have been shown to develop an abnormal response to sleep loss during the early developmental period (Medina et al., 2022), while early-life sleep disruption in *Shank3*^{ΔC-/+} has been shown to affect behavior in adulthood (Lord et al., 2022). Mutations in *Shank3* have also been shown to lead to deficits in homeostatic plasticity during the critical period, although those studies were done in a different mutant line (*Shank3B*) from the sleep studies (Tatavarty et al., 2020). There are currently no studies that have concurrently examined sleep and synaptic plasticity deficits early in life using an ASD mouse model. Recent studies demonstrate that sleep loss during development leads to long lasting impairments on social behavior and that increasing the quality of sleep during adolescence in a mouse model of ASD rescues social deficits in adulthood (Bian et al., 2022). The effect of early-life sleep disruption on social behavior and cognition has also been demonstrated in prairie voles in the absence of any genetic mutations (Jones et al., 2019, 2021). Therefore, it is likely the effects of sleep loss are more pronounced at earlier developmental stages in which sleep is the predominant brain state. Overall, further examination of the interaction between sleep and plasticity during early life in ASD is necessary.

2. Concluding remarks

Animal models have been proven useful to understand mechanisms underlying deficits in ASD. In this review, we support the known link between the genetic basis of ASD and deficits in synaptic plasticity and provide a comprehensive table of ASD mouse models that show plasticity deficits (Table 1). We also highlight that there is a considerable overlap between the ASD mouse models that show deficits in sleep and those that show deficits in plasticity (Table 2). This suggest that the genetic basis of both sleep and plasticity deficits in ASD is overlapping. This overlap may be particularly prominent during critical periods of brain development in which both plasticity and sleep are maximal. Recent studies suggest that sleep problems in ASD arise early in the postnatal period and are predictive of the severity of ASD core symptoms. Therefore, sleep problems: 1) may serve as an early biomarker for ASD and 2) may have functional consequences on plasticity during brain development. Further research is needed to understand the interaction between sleep and plasticity in ASD. Specifically, it is important to look early in life for the functional consequences of both sleep and plasticity

deficits. Investigating sleep and plasticity during critical periods of development may be key to understanding long-term consequences of abnormal sleep on synaptic plasticity during both typical and atypical brain development.

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Elizabeth Medina: Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Sarah Peterson:** Conceptualization, Data curation, Writing – review & editing. **Kaitlyn Ford:** Data curation. Visualization. **Kristan Singletary:** Writing – review & editing, Visualization. **Lucia Peixoto:** Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing, Visualization.

Declaration of competing interest

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