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Neural circuit dysfunction in mouse models of neurodevelopmental disorders

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Neuropsychiatric disorders arise from the alteration of normal brain developmental trajectories disrupting the function of specific neuronal circuits. Recent advances in human genetics have greatly accelerated the identification of genes whose variation increases the susceptibility for neurodevelopmental disorders, most notably for autism spectrum disorder (ASD) and schizophrenia. In parallel, experimental studies in animal models — most typically in mice — are beginning to shed light on the role of these genes in the development and function of specific brain circuits. In spite of their limitations, understanding the impact of pathological gene variation in animal models at the level of specific neuronal populations and circuits will likely contribute to orienting human clinical studies in the search for precise disease mechanisms and novel treatments.

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Introduction

Our understanding of the etiology of psychiatric disorders has increased exponentially over the last decade due to massive advances in human genetics and epidemiology studies. These studies suggest that neurodevelopmental disorders such as autism spectrum disorder (ASD) and schizophrenia are highly polygenic, with pleiotropic risk alleles and a complex background of gene-environment interactions underlying the pathophysiology. In this puzzling scenario, where genetic risk and pathogenic mechanisms overlap across multiple conditions [1], an emerging hypothesis is that unrelated genetic abnormalities may lead to similar psychiatric disturbances by altering the function of the same brain circuits. In addition, it has been proposed that neurodevelopmental disorders may primarily segregate by the timing when brain development deviates from a normal trajectory [2,3].

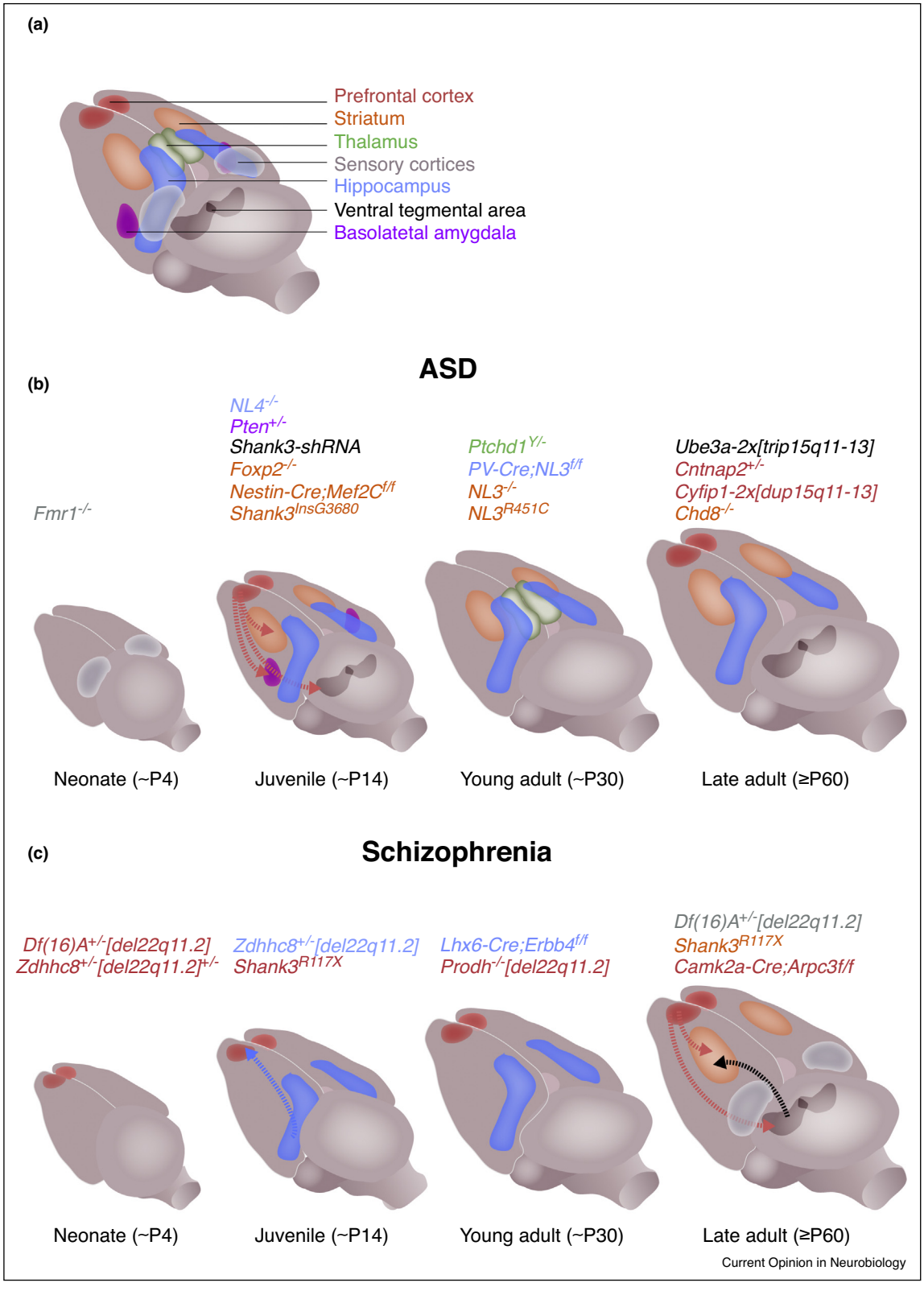
Research on animal models of neurodevelopmental disorders is also progressively shifting from an almost exclusive focus on behavior to the identification of neural circuit alterations linked to specific behavioral traits in an attempt to isolate etiological mechanisms that explain specific symptomatology [4]. Most of these studies concentrate on the analysis of genes whose variation has highly penetrant effects in humans, such as those linked to syndromic conditions, which illustrate the difficulties that exist in the field for the modeling of complex genetic variation. Here, we review recent work on animal models of neurodevelopmental disorders that point to converging defects in brain circuits across multiple conditions. This dissection of specific neural circuit dysfunctions largely concentrates on the analysis of genes linked to autism spectrum disorders (ASD) and schizophrenia. Whenever possible, emphasis is made on the impact of gene variation on developmental trajectories, as opposed to concentrating on the analysis of adult phenotypes.

Cortical circuits

Functional deficits in long-range cortico-cortical circuits are thought to be implicated in the pathophysiology of several neurodevelopmental disorders (Figure 1). For example, cognitive dysfunction is common in schizophrenia and has been associated with deficits in functional connectivity between the hippocampus and the prefrontal cortex (PFC) [5,6]. Consistently, mice modeling a human microdeletion (22q11.2), a well known genetic risk factor for schizophrenia, have profound deficits in the synchronization of PFC and hippocampal networks during working memory demands [7]. Recent work has shown that these defects are likely due to the deficient growth of pyramidal cell axons in the PFC at perinatal stages [8•]. Notably, these functional alterations can be rescued by interfering with the signaling cascades controlling axonal growth during early development [8•,9••].

Functional magnetic resonance imaging (MRI) has been used to consistently identify disturbances in cortico-cortical circuits in ASD patients. In particular, it is suggested that long-range connectivity is reduced in the neocortex, while local connectivity is enhanced [10]. Recent studies in

Figure 1



Summary of neural circuit dysfunctions in mouse models of ASD and schizophrenia during postnatal development. **(a)** Schematic showing brain regions disrupted in mouse models of autism and schizophrenia. **(b, c)** Schematics displaying brain regions and connections disrupted in mouse models of ASD (b) and schizophrenia (c). Brain regions and connections are color-matched to specific mouse strains in which defects have been