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Neurodevelopmental Perspectives on Wnt Signaling in Psychiatry

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Abstract

Mounting evidence indicates that Wnt signaling is relevant to pathophysiology of diverse mental illnesses including schizophrenia, bipolar disorder, and autism spectrum disorder. In the 35 years since Wnt ligands were first described, animal studies have richly explored how downstream Wnt signaling pathways affect an array of neurodevelopmental processes and how their disruption can lead to both neurological and behavioral phenotypes. Recently, human induced pluripotent stem cell (hiPSC) models have begun to contribute to this literature while pushing it in increasingly translational directions. Simultaneously, large-scale human genomic studies are providing evidence that sequence variation in Wnt signal pathway genes contributes to pathogenesis in several psychiatric disorders. This article reviews neurodevelopmental and postneurodevelopmental functions of Wnt signaling, highlighting mechanisms, whereby its disruption might contribute to psychiatric illness, and then reviews the most reliable recent genetic evidence supporting that mutations in Wnt pathway genes contribute to psychiatric illness. We are proponents of the notion that studies in animal and hiPSC models informed by the human genetic data combined with the deep knowledge base and tool kits generated over the last several decades of basic neurodevelopmental research will yield near-term tangible advances in neuropsychiatry.

Introduction

The importance of uncovering the molecular etiologies of psychiatric disorders cannot be overstated. Millions of people in the US suffer from mental illness, corresponding to an annual economic cost of over USD 300 billion [1], and rates and proportional economic burden in other countries are likely to be similar. Although psychiatric disorders have complex multifactorial etiologies, mounting evidence indicates Wnt signaling as one mechanistic link between symptomatologically diverse mental illnesses, including schizophrenia (Scz), bipolar disorder (BD), and autism spectrum disorder (ASD). The idea that altered Wnt signaling contributes to mental illness originated in part from the discovery approximately 2 decades ago that the mood-stabilizing drug lithium inhibits glycogen synthase kinase 3 (GSK3) to mimic activation of the Wnt/β-catenin signaling pathway [2]. Even before

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that and increasingly since, animal studies have revealed how Wnt proteins and pathways govern a wide variety of neurodevelopmental processes and how their disruption can lead to both neurological and behavioral phenotypes. The advent of human induced pluripotent stem cell (hiPSC) models is contributing to further expansion of knowledge in this area. Simultaneously, recent large-scale human genomic studies in several psychiatric disorders, most notably ASD, provide strong genetic support for the participation of Wnt signaling in psychiatric pathophysiology.

While the general significance of Wnt signaling in psychiatry is now hard to deny, relating specific neurodevelopmental pathway roles to the pathogenesis of specific psychiatric disorders remains challenging. To start with, there is the heterogeneity of Wnt signaling itself: There are 19 separately encoded Wnt ligand loci within the genomes of mammals, encoding secreted proteins that activate either canonical or noncanonical Wnt pathways (explained further below) depending on the receptor and intracellular molecular context of responding cells. Wnt signals are transduced through diverse intracellular signaling proteins to affect transcription of target genes, cytoskeletal dynamics, and other cellular processes. Wnt signaling is active in the central nervous system (CNS) from its earliest developmental stages into adulthood, orchestrating a broad range of neurodevelopmental and some postneurodevelopmental processes including CNS regionalization, neural progenitor differentiation, neuronal migration, axon guidance, dendrite development, synaptogenesis, adult neurogenesis, and neural plasticity. Moreover, the heterogeneity of Wnt signaling intersects with the heterogeneity of psychiatric pathogenesis. In the preceding list, every neurodevelopmental and neuroplastic process has been suggested, if not empirically implicated, as a potential pathogenic factor in behavioral illnesses [3, 4]. Given the broad array of Wnt pathway-influenced neurodevelopmental and postneurodevelopmental processes that could theoretically affect psychiatric pathology, it is understandable to feel daunted by the task of linking specific roles to pathogenesis in a way that can lead to therapeutic progress. But we believe that such pessimism is unwarranted. Instead, we believe that strategies combining contemporary human genomic findings with empirical studies in animal and hiPSC models, building on prior decades of basic research on Wnt signaling in neurodevelopment, can produce tangible, near-term advances in neuropsychiatry. The intent of this review is to facilitate this by framing Wnt signaling in the context of its various neurodevelopmental and postneurodevelopmental functions, highlighting mechanisms whereby its disruption might contribute to psychiatric illness.

Brief Overview of WNT Signaling

In this section, we will provide a general overview of Wnt pathways (Fig. 1), although greater detail can be found in reviews dedicated to pathway mechanisms [5–9]. Wnt proteins are secreted, cysteine-rich glycolipoproteins that function as paracrine signaling molecules to affect target cells [6, 10]. Signaling pathways activated by Wnts govern diverse developmental processes and regulate adult tissue homeostasis through many cellular responses, including proliferation, differentiation, migration, and apoptosis. Although often discussed as linear pathways and referred to as either "canonical" (β-catenin-dependent) or "noncanonical" (β-catenin-independent), Wnt signaling can also be thought of more holistically as a network of interconnected biochemical cascades; that is, Wnt-receptor binding may simultaneously activate several cross-regulated intracellular pathways to elicit a coordinated change in cellular state [11–13].

The originally described, and still molecularly best-characterized, "canonical" Wnt/β-catenin pathway hinges on regulated proteolysis of cytoplasmic β-catenin (Fig. 1a). In the absence of Wnt pathway activation, the vast majority of β-catenin protein in a cell is localized to the submembranous space where it complexes stably with cadherin proteins involved in cell adhesion at adherens junctions and synapses; free cytoplasmic β-catenin levels are kept low through constitutive activity of a multiprotein "β-catenin destruction complex" composed of the scaffold proteins axin and adenomatous polyposis coli (APC) plus the kinases casein kinase 1α (CK1α) and GSK3[1]. Once bound to the complex, β-catenin is sequentially phosphorylated by CK1α and GSK3, leading to its ubiquitination and proteasome-mediated degradation. Binding of extracellular Wnt ligand to its co-receptors, Frizzled (Fzd) and low-density lipoprotein receptor-related protein 5 (LRP5) or LRP6, results in phosphorylation of the intracellular scaffold protein Dishevelled (Dvl) and its translocation to the receptor complex accompanied by axin, which is thereby removed from the destruc-

[1] In mammals, there are two GSK3 isoenzymes encoded by the GSK3α and GSK3β loci. As these isoforms are biochemically redundant in Wnt/β-catenin signaling and as there are no known pharmacological compounds that selectively block α vs. β, they will not be distinguished further in this review [14].

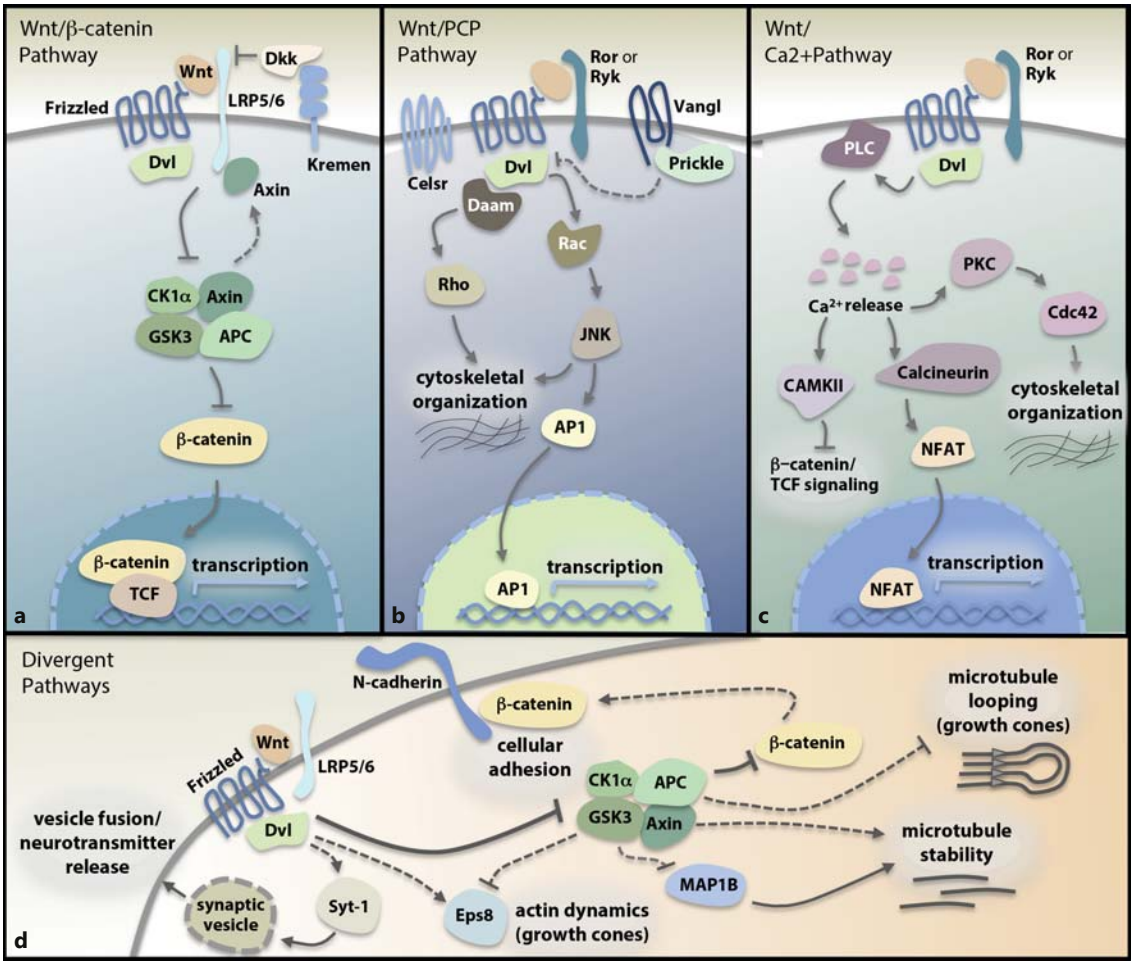

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Fig. 1. Schematic summary of Wnt pathways (see text).

tion complex. These translocation events contribute to Wnt-induced Fzd/LRP5/6 clustering, formation of signalosomes comprised of axin, Dvl and a number of other proteins [15, 16], and destabilization of the β-catenin destruction complex. Without the destruction complex to facilitate interactions between β-catenin and its 2 Wnt-pathway kinases, phosphorylation of β-catenin by CK1α and GSK3 is greatly reduced, and cytoplasmic β-catenin no longer efficiently degraded. β-Catenin that has not been phosphorylated by GSK3 accumulates and translocates to the nucleus where it interacts with members of the T-cell factor (TCF)/lymphoid enhancer factor family of transcription factors to regulate transcription of specific Wnt pathway target genes.

There are also divergent biochemical cascades that can be initiated simultaneously with canonical Wnt signaling by the same ligand-receptor interaction but that do not depend on β-catenin (Fig. 1d). An example is a pathway described in developing neurons in which dissociation of the destruction complex not only reduces phosphorylation of β-catenin but also phosphorylation of microtubule associated protein 1B (MAP1B), thereby leading to posttranslational changes in microtubule organization and stability important for growth cone guidance and presynapse formation [17, 18]. Other molecular changes facilitated by divergent Wnt pathways include: Dvl binding of synaptic vesicle proteins to facilitate neurotransmitter release [19]; Dvl modulation of the actin-binding protein Eps8 (epidermal growth factor receptor pathway substrate 8) to regulate actin dynamics critical for axon growth [20]; dissociation of APC from plus ends of microtubules to facilitate growth cone mobility [21]; and formation of β-catenin/cadherin complexes at the plasma membrane to promote cell-cell adhesion.

Table 1. Summary of Wnt pathway genes associated with neural plate specification and neural tube formation

Process	Wnt pathway	Gene	Ref.
Neural plate specification	Wnt/β-catenin	Wnt3A	[30, 31]
		β-catenin	[30, 31]
		Wnt8	[29]
		Tcf3	[32]
		Wnt8c	[33]
		Dkk1	[35–37]
		Sp1	[39]
Neural tube formation	Wnt/β-catenin	Axin	[53]
		Tcf3	[54]
		LRP6	[55–59]
	Wnt/PCP	Dact1	[52]
		Scribble	[41, 47, 50]
		Celsr1	[40, 47, 51]
		Dvl1/2/3	[44, 49]
		Vangl1/2	[43]

Separate Wnt ligand-receptor interactions lead to other pathways. In the noncanonical Wnt/planar cell polarity (PCP) pathway, Wnt-Fzd binding, at least in vertebrates, can lead to downstream activation of c-Jun N-terminal kinase (JNK), RhoA and Rac1, causing changes in both actin and microtubule-associated cytoskeletal dynamics (Fig. 1b). Core components of this pathway include several transmembrane proteins unique to it, particularly Van Gogh/strabismus (Vangl) and Flamingo (Celsr1–3) – plus a set of submembranously localized scaffold proteins that partially overlap with the Wnt/β-catenin pathway, including Dvl, Diego, and Prickle. These transmembrane and submembranous components engage in both cooperative and competitive interactions leading to their polarized distribution within the cell; one of the critical roles of the pathway, for which it is named, is the establishment of transverse (planar) polarity of epithelial cells and regulation of intercalating "convergent-extension" cell movements during certain developmental processes.

In the noncanonical Wnt/Calcium (Ca^{2+}) pathway, Wnt-Fzd binding regulates phospholipase C in a Dvl-dependent manner (Fig. 1c). This catalyzes an IP_3/DAG-dependent increase in intracellular Ca^{2+} levels with consequent activation of protein kinase C (PKC), calcineurin, and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII). Activated PKC phosphorylates the small GTPase Cdc42 regulating organization of the actin cytoskeleton. Calcineurin promotes nuclear import of nuclear factor of activated T-cells (NFAT), a transcription-activating protein. CAMKII activates a pathway that inhibits nuclear β-catenin, thereby inactivating Wnt/β-catenin transcriptional activity. The increase in cytosolic Ca^{2+} has also recently been linked to production of nitric oxide (NO) in neurons, which influences synaptic excitability through modulation of potassium (K^+) channels [22].

Finally, in the Frizzled-nuclear import (FNI) pathway which thus far has only been described at the *Drosophila melanogaster* (fruit fly) neuromuscular junction [23–25], Wnt-Fzd binding causes internalization and cleavage of Fzd. Subsequent nuclear trafficking of a transcriptionally active Fzd cleavage fragment depends on its interaction with 7-PDZ-domain glutamate-receptor interacting protein (GRIP) [24, 26].

Neural Plate Specification and Neural Tube Formation

Wnt signaling is required for proper patterning of the CNS in vertebrates beginning at the earliest stages of neural development [27, 28], involving specification of the ectodermally derived neural plate and its subsequent folding to form the neural tube (Table 1). Although signaling defects during these early stages are often associated with gross neurological defects, when considering behavioral disorders and their treatment (as well as potential side effects of treatment), it is important to have a firm grasp of Wnt signaling at all stages of neural development.

Some of the first experiments implicating Wnt/β-catenin signaling in neural plate specification illustrated its caudalizing (posteriorizing) effects. Experiments using *Xenopus laevis* (African clawed frog) animal caps demonstrated that ectopic expression of either Wnt3a or β-catenin induces posterior neural markers and suppresses rostral (anterior) neural markers, whereas expression of a dominant-negative form of Wnt8 inhibits posterior markers [29–31]. Subsequent genetic experiments showed the extent to which gross abnormalities can result from disrupted Wnt signaling at early developmental stages. This includes analysis of the *Danio rerio* (zebrafish) *null* mutation in Tcf3, called *headless* (*hdl*) because it leads to absence of anterior neural structures [32]. Similar posteriorizing effects are caused by transgenically overexpressing Wnt8c in *Mus musculus* (laboratory mice), leading to absence of the anterior forebrain [33]. During normal development, Wnt ligands secreted by the

underlying paraxial dorsolateral mesoderm establish a signaling gradient that helps specify the anterior-posterior axis of the neural plate [34]. Expression of the secreted Wnt antagonist, Dickkopf1 (Dkk1), ensures anterior inhibition of Wnt signaling: loss of Dkk1 expression yields a posteriorized phenotype reminiscent of Wnt overexpression [35–38]. Additional gain-of-function and loss-of-function (LOF) analyses in zebrafish suggest Wnt/β-catenin signaling establishes posterior neuroectoderm identities at least in part by promoting expression of the Sp1 family transcription factors Sp5 and Sp5-like [39].

After specification, cells within the neural plate undergo morphogenetic movements giving rise to lateral upwellings of the neural plate called neural folds. The folds from each side eventually merge and fuse at the dorsal midline, converting the initially flat neural plate into a neural tube which develops further to become spinal cord and brain. Disruptions in this process cause neural tube defects (NTDs), which range in severity and include conditions such as spina bifida, anencephaly, and craniorachischisis. Mice with genetic disruptions in critical modulators of Wnt/PCP signaling, including Dact1 (Dapper, Frodo), Scribble (Scrib), cadherin EGF LAG seven-pass G-type receptor 1 (Celsr1), Dvl2, Vangl1, and Vangl2, have highly penetrant NTD phenotypes [40–44]. Importantly, human genomic studies of patients with NTDs have also revealed mutations in several of these same Wnt/PCP pathway genes [45–51, 52]. A role for the Wnt/β-catenin pathway is indicated in this process as well. For example, mice with LOF mutations in either Axin1 or Tcf3 exhibit incomplete neural tube closure [53, 54], and various mutations in LRP6 cause NTDs in mice [55–57], and are present in human NTD patients [58, 59]. Recent evidence suggests defects in this case may be due in part to inappropriate fate specification of the laterally placed neural plate border cells governed by the Wnt/β-catenin pathway [60]. Furthermore, there may be a biochemical connection between the Wnt/β-catenin and Wnt/PCP pathways in facilitating neural tube closure. While the LRP6 receptor is generally thought to be dedicated to Wnt/β-catenin signaling, recent data show that NTD-associated LRP6 mutations decrease Wnt/β-catenin activity while simultaneously increasing Wnt/PCP activity [58]. This supports the notion that these seemingly separable Wnt pathways engage in reciprocal inhibition and other forms of cross talk to form integrated signaling networks involved in developmental decision-making [13, 61]. Similar observations have been made in other neurodevelopmental contexts (cf. Neural Precursor Migration, below).

Table 2. Summary of Wnt pathway genes associated with brain regionalization

Pathway/brain region	Gene	Ref.
Uncharacterized		
Forebrain	Wnt2b	[73, 74]
	Wnt3a	[73, 74]
	Wnt5a	[73]
	Wnt7b	[75]
	Wnt8b	[75]
Wnt/β-catenin		
Forebrain	Lef/Tcf	[79]
Forebrain, midbrain, hindbrain	LRP6	[57, 80, 89]
Midbrain, hindbrain	Wnt1	[82–84, 91]
Midbrain, hindbrain, spinal cord	β-catenin	[85, 86]
Midbrain	Fzd3	[87]
	Fzd6	[87]

Uncharacterized: genes characterized by expression data only.

Brain Regionalization

At the stage of the early germinal neuroepithelium, Wnt genes and Wnt pathway modulators are expressed in overlapping spatial and temporal patterns [62–64] and are critical for establishing signaling centers that inform regional identities along the rostral-caudal and dorsal-ventral axes of the developing CNS [65–67] (Table 2). Structural and functional impairments in the forebrain (derived from telencephalon and diencephalon), midbrain (derived from mesencephalon), and hindbrain (derived from metencephalon and myelencephalon) have all been associated with neuropsychiatric pathogenesis [68–70].

Rostrally, Wnt signaling is integrally involved in development of the forebrain [71], arguably the most physiologically complex structure in vertebrate anatomy. Wnt-mediated dorsal-ventral patterning in the telencephalon has been demonstrated by analysis of Foxg1-mediated transcriptional repression of Wnts in zebrafish, showing that loss of Wnt/β-catenin signaling prevents cortical specification [72]. Wnt expression (Wnt2b, Wnt3a, Wnt5a, Wnt7b, and Wnt8b) and β-catenin-dependent signaling activity is high in the cortical hem, a forebrain signaling center that instructs hippocampal development [73–76]. Consistent with a patterning role for Wnts secreted from this source, mutant mice with no functional Gli3, a transcription factor necessary for Wnt expression in the cortical hem, lack dorsomedial telencephalic Wnt/

β-catenin signaling activity and fail to develop hippocampi [73, 77, 78]. This phenotype has been reproduced through inhibition of lymphoid enhancer factor/TCF signaling, underscoring the requirement for Wnt/β-catenin signaling in hippocampal development [79]. Finally, characterization of LRP6 mutant mice has not only confirmed a requirement for Wnt/β-catenin signaling in cortical and hippocampal patterning [80], but has further suggested a role in development of the dorsal thalamus and thalamocortical neural circuitry: only a small, disorganized dorsal thalamus lacking most major thalamic nuclei and thalamocortical projections develops in mice lacking LRP6 [81].

Impairing the Wnt/β-catenin pathway also disrupts midbrain and hindbrain regionalization. In mice, LOF mutations in Wnt1 lead to complete lack of midbrain and cerebellum [82–84]. Conditional deletion of β-catenin mimics these defects [85, 86], LRP6 mutants partially mimic the Wnt1 mutant phenotype [57], and Fzd3/Fzd6 double mutants also display disruptions in midbrain development [87]. Moreover, several studies, including LRP6 mutant analysis, overexpression of β-catenin, and ablation of β-catenin support a requirement for Wnt/β-catenin signaling in neurogenesis of midbrain dopaminergic neurons in the mouse [88–91].

The Wnt/β-catenin pathway plays critical roles in patterning the most caudal component of the CNS, the developing spinal cord. For example, in the developing spinal cord of *Gallus gallus* (chick) embryos, ectopic expression of mutant-stabilized (dominant-active) β-catenin causes overexpression of neural patterning genes including Olig3 in neural precursor cells (NPCs) [92]. The presence of an Olig3 LOF mutation in the context of this dominant-active form of β-catenin leads to a decrease in a subset of dorsal interneurons, indicating that Wnt/β-catenin pathway-induced transcription of Olig3 is required for specification of these neuronal subtypes [92]. At the same time, Wnt/β-catenin signaling inhibits differentiation of oligodendrocytes in the developing ventral spinal cord, as evidenced by increased generation of these cells in response to ectopic expression of a Wnt antagonist [93].

Neural Stem and Precursor Cell Proliferation

Right from the discovery of the first Wnt gene in vertebrates, Wnt signaling has been associated with the regulation of cell division. The first vertebrate Wnt gene was identified because it acts as a mammary oncogene when pathogenically activated by a tumor virus in mice [94].

Table 3. Summary of Wnt pathway genes associated with neural precursor cell or neural stem cell proliferation

Process/Wnt pathway	Gene	Ref.
Neural precursor cell proliferation		
Wnt/β-catenin	Wnt1	[63, 82, 83, 97, 99, 104]
	Wnt3a	[63, 97–99]
	Dkk1	[100, 101]
	β-catenin	[100, 101, 108, 109]
	GSK3	[110]
	Tcf4	[97]
	DISC1	[111]
	DixDC1	[111]
Neural stem cell proliferation		
Wnt/β-catenin	Wnt7a	[126]

Since that time, a large number of Wnt genes and other core Wnt/β-catenin pathway components have been strongly implicated in oncogenesis – more specifically in mitogenesis – when improperly activated [95, 96]. So, it is not surprising that one of the physiological roles of Wnt signaling in the CNS is to regulate NPC proliferation (Table 3).

In fact, the gradient of NPC mitotic activity in the developing neural tube directly corresponds to a gradient of Wnt/β-catenin signaling (dorsal-high to ventral-low) established by Wnt1 and Wnt3a secreted from the dorsal midline [63, 82, 97]. As discussed earlier, genetic studies in mice have established that loss of Wnt1 prevents midbrain development [82, 83], loss of Wnt3a prevents hippocampal development [98], and loss of both Wnt1 and Wnt3a together cause additional defects in the caudal diencephalon, rostral hindbrain, and cranial and spinal ganglia [99].

Experimental dissection of phenotypes resulting from loss of β-catenin or exposure to the Wnt antagonist Dkk1 in the developing telencephalon has demonstrated an interwoven role for Wnt/β-catenin signaling in both NPC proliferation and dorsal-ventral patterning [100, 101]. Similarly, in the metencephalon, Wnt/β-catenin signaling is thought to regulate both the growth and differentiation of NPCs [102, 103]. In toto, data support important roles for this pathway in both brain regionalization and cell division, revealing that many Wnt ligands are partially redundant in these processes.

The gross brain regionalization and proliferative defects caused by loss of Wnt1 and Wnt3a have led to experiments designed to dissect out functions of Wnt/β-catenin signaling specifically in NPC proliferation. Supporting a role in proliferation per se, studies in the chick

neural tube have revealed that ectopic expression of Wnt1 significantly increased numbers of NPCs [97, 104]. Similarly, NPC proliferation increased upon introduction of dominant-active β-catenin in the developing chick spinal cord, mouse neocortex or mouse cerebellum [97, 103, 105–107]. Conversely, expression of dominant-negative Tcf4 cell autonomously blocked entry of NPCs into the S phase in the developing chick spinal cord [97]. LOF analysis conducted through ablation of β-catenin in the mouse neocortical ventricular zone caused premature cell cycle exit and differentiation [108, 109], while deletion of GSK3 led to increased proliferation and decreased differentiation of neural progenitors along the mouse neuraxis [110]. Further support comes from in utero electroporation of inhibitory RNA (RNAi) for disrupted in schizophrenia-1 (DISC1) or Dix domain containing-1 (Dixdc1), positive regulators of Wnt/β-catenin signaling; their reduction by RNAi reduces NPC proliferation in the developing mouse cerebral cortex [111]. Finally, studies in culture strongly support the critical importance of Wnt/β-catenin signaling in promoting neural stem cell (NSC) proliferation [103, 112] and, coming full circle back to the proto-oncogenic effects of Wnt, hyperactivated Wnt/β-catenin signaling is a primary cause of the aggressive pediatric brain tumor, medulloblastoma [113]. In fact the cell-cycle regulator *N-myc*, itself a proto-oncogene, is a downstream effector of Wnt pathway-induced NPC proliferation: conditional deletion of *N-myc* prevents β-catenin-induced NPC proliferation in vitro [114]. In the concluding section of this review, we discuss the therapeutic implications of links between the Wnt/β-catenin pathway and cancer.

In the last decade, it has become increasingly clear that neural proliferation continues in some brain areas into adulthood; moreover, that disruptions in adult neurogenesis are linked to psychiatric disorders (as well as neurodegenerative diseases) [115, 116], whereas enhancing neurogenesis may be an important mechanism of action for antidepressant and antipsychotic drugs [117–120]. Wnt signaling is involved in adult neurogenesis of the 2 identified NSC populations in the adult brain (reviewed in [121, 122]), which reside within the subventricular zone (SVZ) of the lateral ventricles and subgranular zone (SGZ) of the hippocampal dentate gyrus (DG). Inhibition of Wnt/β-catenin signaling in cultured adult hippocampal progenitors depletes the number of multipotent progenitors, indicating a requirement of this pathway for NSC maintenance [123, 124]. Similarly, in vivo inhibition of Wnt/β-catenin in the DG of adult mice or rats causes reduced NSC proliferation in the SGZ [123, 125], and *Wnt7a* null mice exhibit decreased NSC proliferation in both the SVZ and SGZ [126]. Thus, Wnt signaling affects the proliferation of neural stem and progenitor cells throughout embryonic and adult life with potential relevance to both psychopathology and therapeutics.

Table 4. Summary of Wnt pathway genes associated with neural precursor migration

Process	Wnt pathway	Gene	Ref.
Neural precursor migration	Wnt/β-catenin	DISC1	[134, 135]
		TCF4	[136]
		β-catenin	[137]
	Wnt/PCP	Wnt5a	[129, 133]

Neural Precursor Migration

After their final mitotic division, most early NPCs undergo "radial" migration out of the ventricular zone in close apposition to the cytoneme-like projections of radial glia extending perpendicularly to the neural tube surface (Table 4). In doing so, migrating NPCs establish a basic layered architecture comprised of mantle (gray matter) and marginal (white matter) zones throughout the CNS. The spinal cord retains this basic 2-layer organization, whereas the brain's more complex neural architecture arises from far more complicated and highly derived patterns of NPC migration. For instance, in the developing neocortex, sequential waves of NPC migration give rise to 6 cortical layers populated by neurons with distinctive molecular signatures, functional properties, connectivity patterns, and synaptic targets. Moreover, some NPCs residing in circumscribed regions of the SVZ give rise to specialized neuronal subtypes that disperse more broadly in the cortex via additional migratory mechanisms (such as cortical GABAergic interneurons that arise from the ventrally located ganglionic eminences and travel to their final destinations via tangential migration followed by either inward or outward radial migration [127]). Changes in the temporal or spatial program of NPC migration affect the coordinated development of presynaptic and postsynaptic connections, thereby disrupting neural networks. On this basis, it can be expected to lead to both neurologic diseases (e.g., epilepsy) and psychiatric disorders (e.g., behavioral/cognitive/emotional dysregulation).

Table 5. Summary of Wnt pathway genes associated with axon pathfinding

Cell type	Pathway (regulatory target)	Gene	Ref.
Ventral midbrain DA neurons	Wnt/β-catenin	Wnt7a	[173]
Cerebellar granule cells	Divergent "canonical" (MAP1B)	Wnt7a	[169–171]
DRG neurons	Divergent "canonical" (Eps8)	Dvl	[20]
	Unknown (GSK3-dependent)	Wnt3	[172]
Spinal commissural neurons	Wnt/PCP	Wnt4	[158]
		Wnt5a	[158, 159]
		Wnt7b	[158]
		Fzd3	[158, 159]
		Celsr3	[159]
		Vangl2	[159]
		Dvl1	[159]
Brainstem monoaminergic neurons	Wnt/PCP	Fzd3	[157]
		Celsr3	[157]
		Vangl2	[157]
Prethalamic neurons	Wnt/PCP	Fzd3	[161]
		Celsr3	[161]
Cortical neurons (corticospinal and callosal axons)	Wnt/Ca^{2+}	Wnt5a	[155, 174–177]
		Ryk	[174–177]

Divergent "canonical": divergent Wnt pathway genes.

Wnt signaling has been linked to neural and glial cell migration in diverse systems. This includes the lateral line primordium, a group of cells giving rise to a sensory organ in zebrafish, and in which Wnt/β-catenin signaling influences the expression of chemokine receptors necessary for proper cell migration [128]. In cultured glioblastoma cells, Wnt5a signals through a noncanonical pathway to affect expression of matrix metalloproteinase 2 (MMP-2) [129], a protein that facilitates migration (tumor invasion) via degradation of extracellular matrix components. In both mice and humans, Wnt signaling participates in the migration of oligodendrocyte precursor cells that develop into the myelinating cells of the CNS, again by regulating expression of a chemokine receptor (Cxcr4) [130]. The Wnt/PCP pathway also plays a major role in the extensive migrations of neural crest cells [131, 132] that give rise to most of the peripheral nervous system (PNS) and also contribute critical cell types to many other tissues in all vertebrates.

Studies over the last 5 years have revealed that Wnt signaling participates in migration of NPCs in the developing cerebral cortex and cerebellum. Analyses of pyramidal neuron precursors in the ventricular zone of developing mouse neocortex have demonstrated critical interconnected roles of the Wnt/PCP and Wnt/β-catenin pathways in the regulation of NPC migration. Experiments using both constitutive and conditional genetic approaches to target Wnt5a-mediated PCP signaling and β-catenin/TCF-dependent Wnt signaling support a model in which the Wnt/PCP pathway inhibits the Wnt/β-catenin pathway to promote transcriptional activation of ephrin-B1, a transmembrane protein critical for pyramidal precursor migration [133]. In addition to its effects on NPC proliferation, reduction of DISC1, a positive regulator of Wnt signaling, disrupts the tangential migration of cortical interneurons [134, 135], at least in part by influencing filamentous F-actin assembly critical for filopodial and lamellopodial dynamics [134]. Similarly, knockdown of *Tcf4* in cortical progenitor cells impairs the formation of actin-rich leading processes, thereby inhibiting neuronal migration [136]. In vitro cell migration assays using mouse NSCs indicate that Wnt/β-catenin signaling also promotes cell migration via cross talk with prostaglandin E2 (PGE2) signaling. This pathway leads to transcriptional upregulation of *Ctnnb1*, *Ptgs2*, *Ccnd1*, *Mmp9* [137] – all of which, likely not coincidentally, have been linked to the etiopathology of ASD and Scz [138–145].

Axon Pathfinding

As neurons migrate to their final destination, a next critical phase of their maturation is the formation, elongation, and targeting of a (typically single) axon (Table 5).

Depending on the neuronal subtype and its function, this highly specialized presynaptic neurite may extend over extremely long anatomical distances to connect with cellular targets locally, in another region of the CNS, in the PNS, or even outside the nervous system proper. The development of functional neural circuits governing thought and behavior relies in large measure on precisely guided outgrowth and pathfinding of axons to reach specific target cells. On this basis, dysregulated axon guidance is a candidate neurodevelopmental mechanism that could conceptually contribute to a wide range of behavioral disorders [146–151].

The developing axons of many neurons receive positional information in the form of extracellular Wnt gradients [152, 153]. The growing axon is tipped with a highly motile lamellopodial and filopodial structure called the growth cone responsible for detecting and responding to extracellular guidance cues that direct axon outgrowth. As receptors on the surface interact with extracellular cues, the growth cone rapidly translates extracellular gradients into intracellular signals driving changes in cytoskeletal organization to directionally guide axon extension [154]. Wnt receptors expressed on growth cones couple extracellular Wnt gradients to downstream pathways mediating directed axon outgrowth [155–157].

Wnt/PCP pathway-mediated axon guidance was initially observed in spinal cord commissural neurons [158]. In the vertebrate spinal cord, commissural neurons first project axons ventrally toward the floor plate, where they turn and move rostrally or caudally after crossing the midline ("postcrossing"). Analyses using open book explants of developing *Rattus norvegicus* (rat) spinal cords showed that postcrossing commissural axons are directed by gradients of Wnt4, Wnt5a, and Wnt7b along the rostral-caudal axis [158]. This effect was at least partially dependent on Fzd3-mediated Wnt/PCP signaling; loss of Fzd3 caused postcrossing commissural neurons to project randomly, while loss of LRP6 had no effect on guidance of commissural neurons [158]. Genetic studies demonstrated that other core Wnt/PCP pathway components are also required for commissural axon guidance, including Celsr3, Vangl2, and Dvl1 [159]. Further experiments using rat spinal cord open book explants as well as dissociated cultures of commissural neurons have revealed a unique molecular mechanism governing Wnt/PCP pathway-related growth cone guidance [159]. Dvl1, a protein usually associated with Fzd activation, inhibits Fzd3-mediated PCP signaling by promoting Fzd3 phosphorylation, preventing its internalization and concomitant intracellular signal transduction [159]. However, in response to Fzd3-Wnt5a binding, Vangl2 antagonizes the inhibitory effect of Dvl1, preventing Fzd3 phosphorylation and promoting transduction of the Wnt5a signal via JNK activation [159]. This mechanism allows for a localized gradient-sensitive response of the growth cone to extracellular Wnt5a.

In addition to spinal cord commissural neurons, the Wnt/PCP pathway facilitates axon guidance in many other neuronal subtypes [156]. In mice, genetic deletion of Fzd3 caused aberrant axon guidance in subpopulations of cranial and spinal motor neurons [160], and deletion of Celsr3, Vangl2, or Fzd3 each caused axon pathfinding defects in monoaminergic neurons of the developing brainstem [157]. Furthermore, conditional deletion of either Fzd3 or Celsr3 in subpopulations of neurons in the early ventral telencephalon and prethalamus led to disrupted thalamocortical axon guidance [161, 162]. Interestingly, malfunctions in brainstem monoaminergic neurons and thalamocortical interactions have been associated with Scz, BD, and ASD [163–168].

Instead of the Wnt/PCP pathway, Wnt7a is thought to regulate axon guidance through activation of both Wnt/β-catenin and distinctly divergent Wnt pathways in different neuronal subtypes. In cerebellar granule cells, recombinant Wnt7a expression induced axonal spreading, axonal branching, and increased growth cone size and complexity in vitro [169–171]. Deletion of *Wnt7a* in mice caused simpler, less mature glomerular rosettes [170], a structural hallmark of the cerebellar mossy fiber-granule cell synapse. Investigation of the Wnt7a signaling mechanism indicated that, rather than phosphorylation of β-catenin, axon growth mediated by Wnt7a depends on regulation of GSK3-mediated phosphorylation of microtubule-associated proteins including MAP1B to affect cytoskeletal changes [17]. This is an example of a divergent Wnt signaling pathway using upstream components of the Wnt/β-catenin pathway but not transcriptional regulation via β-catenin to achieve its effects [18]. Another instance of pathway divergence was identified using cultured dorsal root ganglion (DRG) neurons; Dvl directly binds the actin-binding protein Eps8, which increases F-actin abundance in DRG growth cones and enables lamellar protrusion [20]. In this study, GSK3 inhibition blocked Wnt-mediated Eps8 activity, indicating involvement of upstream components of the Wnt/β-catenin pathway [20] although stabilized β-catenin does not appear to play a role. Perhaps this is the mechanism by which Wnt3, produced by motor neurons, increases axon branching and growth cone size in neurotrophin-3-responsive DRG sensory neurons – there is evidence these

Table 6. Summary of Wnt pathway genes associated with dendritogenesis

Cell type	Pathway (regulatory target)	Gene	Ref.
Cortical pyramidal neurons	Wnt/β-catenin	TCF4[a]	[189]
		Wnt2	[191]
Hippocampal pyramidal neurons	Wnt/β-catenin	Wnt2	[190]
	Divergent "canonical" (catenin/cadherin)	β-catenin	[187]
	Wnt/PCP	Vangl2	[197–199]
		Wnt7b	[194]
		Dvl	[194]
		Rho	[194]
		JNK	[194]
		Dact1	[195]
Cortical GABAergic interneurons	Wnt/PCP	Dact1	[196, 197]
Hippocampal pyramidal neurons	Wnt/Ca^{2+}	Wnt7a	[206]

Divergent "canonical": divergent Wnt pathway genes. [a] Also affects glutamatergic synapse density – unclear if a primary effect or secondary to dendrite phenotype.

phenotypes are GSK3-dependent [172], though the downstream events remain unclear. In contrast, dopaminergic neurons within the developing ventral midbrain *do* require Wnt7a-mediated activation of β-catenin transcriptional activity to ensure their axons reach appropriate forebrain targets [173].

Wnt5a is thought to signal through the Wnt/Ca^{2+} pathway to exert its effect as a repulsive cue for postcrossing corticospinal axons descending from the cerebral cortex along the dorsal spinal cord [174] as well as for cortical axons projecting across the corpus callosum [155]. Corticospinal axons only become sensitive to Wnt-facilitated repulsion after midline crossing, coincident with expression of the Ryk receptor [174]. In vitro studies using mouse cortical explants indicated that Wnt5a repels Ryk-expressing axons [155]. Moreover, when the interaction between Ryk and Wnt5a was blocked by injection of a Ryk antibody [174] or by RNAi-mediated knockdown of Ryk in developing *Mesocricetus auratus* (hamster) cortical slices [175], postcrossing axons projected randomly, indicating that Ryk is required for their guidance. In vitro analysis of cortical neurons and in vivo analysis of cortical slices showed that the Wnt5a-Ryk interaction causes fluctuations in intracellular calcium [175–177]. Moreover, knockdown of Ryk [175] or exposure to CaMKII inhibitors [175, 177] caused defects in axon outgrowth and guidance. Taken together, these data suggest that the Wnt5a/Ryk interaction initiates a Wnt/Ca^{2+} signaling pathway to regulate axon growth and guidance of corticospinal and callosal axons.

Dendritogenesis

Dendritogenesis involves a process called arborization (or ramification) by which dendrites extend from neuronal cell bodies and elaborate to form intricate branching patterns (Table 6). Time-lapse imaging has revealed dendritic arborization to be a highly dynamic process involving extension and retraction of fine filopodial branches, only a fraction of which persist to become enduring components of the dendritic arbor [178–180]. The complex networks of dendritic arbors greatly expand the surface area and reach of each neuron allowing reception of electrical inputs from a correspondingly greatly expanded set of axon terminals. Moreover, while inhibitory synapses primarily form along dendritic shafts or directly on the neuronal soma, a large proportion of excitatory axon terminals synapse at dendritic spines – small protrusions decorating the length of dendrites on "spiny" neurons – most of which are themselves excitatory (glutamatergic) pyramidal projection neurons. Dendritic spines are highly dynamic and exhibit a striking degree of experience-dependent structural and functional plasticity [181], as do synapses in general (discussed in the following section). Unsurprisingly, impaired dendrite arborization, spine morphogenesis and dendritic plasticity have been implicated in the pathology of neurodevelopmental and neuropsychiatric disorders through both postmortem neuropathological analyses of affected individuals and studies in animal models [182–186]. In this section, we review Wnt-based studies

relating to dendrite development, while the subsequent section focuses on how synapses form between the elaborated (postsynaptic) dendrites and (presynaptic) axon terminals.

Dendritogenesis in the hippocampus is promoted by Wnt/β-catenin signaling, although not via transcriptional regulation of target genes. Instead, Wnt-mediated stabilization of β-catenin leads to increases in functional β-catenin/cadherin complexes at the membrane [187], facilitating adhesive interactions between presynaptic and postsynaptic elements required for dendrite growth, synapse formation, and maintenance of dendritic arbors [188]. This mechanism was uncovered through analysis of primary rat hippocampal neurons that display increased dendritic branching in direct proportion to the amount of stabilized β-catenin expressed, an effect potentiated by addition of other catenin/cadherin complex members and inhibited by addition of the secreted Wnt antagonist Dkk-1. In this study, expression of dominant-negative forms of Tcf that uncouple Wnt signaling from transcriptional activity had no bearing on dendritic branching [187]. In sum, the effector mechanism implicated by these experiments is that Wnt-dependent β-catenin stabilization facilitates dendritogenesis by directly enabling growing dendrites to make connections with other neurons through enhancement of catenin/cadherin complexes, as opposed to transcriptional changes. In contrast, a recent study has shown that in differentiating mouse cortical neurons, TCF4 restricts dendritic branching by directly regulating the expression of *Neurexin* loci [189]. Given the general mechanism of Wnt/β-catenin signaling, in which stabilized β-catenin binds to TCFs in the nucleus to switch their transcriptional activity, this finding suggests the possibility that a strictly canonical Wnt signaling pathway may promote dendritogenesis in postmitotic neurons by regulating transcription of *Neurexin* genes.

In several neuron subtypes, Wnt2 activates the Wnt/β-catenin pathway to mediate dendrite growth in response to upstream triggering events or molecules. For example, an activity-dependent N-methyl-D-aspartate receptor (NMDAR)-mediated Ca^{2+} signaling pathway leads to transcriptional upregulation of *Wnt2* in cultured hippocampal neurons, which then stimulates increased dendritic arborization [190]. Very similarly, brain-derived neurotrophic factor (BDNF), a signaling molecule that promotes dendrite growth and spine formation in most (if not all) differentiating neurons, exerts effects in primary mouse cortical neurons through transcriptional upregulation of *Wnt2* [191]; exposure to secreted or cytoplasmic Wnt inhibitors reduced the size of dendritic arbors and prevented BDNF-induced increases in spine density [191]. Wnt2-induced dendrite development is also implicated as a molecular mechanism in neurodevelopmental toxicity caused by the environmental pollutant polychlorinated biphenyl-95 (PCB-95) [183]. Experiments using primary rat hippocampal neurons showed that PCB-95 acts on ryanodine receptors (Ryr) in the endoplasmic reticulum to cause inappropriately high Ca^{2+} release into the cytosol, leading to cAMP response element binding (CREB)-dependent transcription of *Wnt2*, which then stimulates the growth of more elaborate dendritic arbors with decreased activity-dependent plasticity [183]. This example is especially noteworthy given the well-accepted but poorly understood interwoven effects of genetics and environment (and indeed other factors – e.g. "nature vs. nurture") in the pathology of mental illness [192, 193]. Specifically, this work empirically demonstrates mechanistic interplay between an environmental factor (i.e., exposure to PCB-95) and a signaling molecule encoded in the genome (*WNT2*) – with neurodevelopmental consequences (increased but less plastic dendritic arborization) that could plausibly contribute to behavioral symptoms manifesting as a psychiatric condition.

There is also evidence that Wnt/PCP signaling regulates dendrite formation. Hippocampal cultures derived from mice lacking *Dvl1* have reduced dendritic arbors, whereas exposure to Wnt7b or overexpression of Dvl1, both normally expressed in the hippocampus, cause increased dendritic branching [194]. Inhibition of downstream modulators of the PCP pathway (Rho and JNK) prevented Dvl1-facilitated outgrowth, whereas manipulation of GSK3 activity had no effect [194]. Further support for the role of Wnt/PCP signaling has come from analysis of *Dact1* mutant mice, in which both hippocampal pyramidal neurons [195] and cortical interneurons have simpler dendritic arbors [196, 197]. This same phenotype has been observed in hippocampal neurons derived from *Vangl2* mutant mice [197], as well as in cultured hippocampal neurons subjected to transient knockdown of *Vangl2* [198, 199]. Dact1 and Vangl2 are both modulators of Wnt/PCP signaling that function upstream of small GTPases [195, 200, 201] to influence cytoskeletal changes necessary for dendrite arborization and spine development [202–205]. Vangl2 also affects dendritogenesis through direct interactions with N-cadherin [198, 199], indicating a potential bidirectional mechanism downstream of Wnt/PCP signaling during dendrite development, as

Table 7. Summary of Wnt pathway genes associated with synapse formation and function

Cell type	Synaptic process	Pathway (regulatory target)	Gene	Ref.
DRG neurons	Synapse formation	Divergent "canonical" (APC to MT +ends)	Wnt3a, APC	[21]
Granule cell mossy fiber synapse	Synaptic protein clustering Excitatory function	Divergent "canonical" (TCF-independent) Unknown	Wnt7a Wnt7a, Dvl	[169, 170, 207, 213] [207]
Hippocampal pyramidal neurons	Synaptic plasticity (LTP) Synaptic protein clustering	Wnt/β-catenin Wnt/PCP	Wnt3a Wnt5a,	[209] [211, 222, 223]
			Ror1, Ror2	[223]
	Excitatory function	Wnt/Ca^{2+} and possibly Wnt/PCP	Wnt5a, Ror2	[22, 208, 212, 216, 217]
	Inhibitory function	Wnt/CA^{2+}	Wnt5a	[210]
	Excitatory function	Dvl-dependent synaptic vesicle release and possibly Wnt/Ca^{2+}	Wnt7a, Dvl	[19, 206]
	Synapse formation	Wnt/PCP (N-cadherin)	Vangl2	[198, 199]
	Postsynaptic assembly	Wnt/PCP (PSD-95)	Vangl2	[198, 228]
			Prickle2	[227]
	Synapse formation and function (synaptic vesicle release)	Wnt/PCP (Syn1)	Prickle1	[229]
Hippocampal and cortical pyramidal neurons	Synapse formation	Wnt/PCP	Dact1	[226]
Forebrain pyramidal neurons	Synapse formation	Wnt/PCP	Vangl2	[197]

Divergent "canonical": divergent Wnt pathway genes.

well as potential cross talk with the aforementioned promotion of catenin/cadherin complexes contributing to dendritogenesis downstream of the Wnt/β-catenin pathway.

Finally, the Wnt/Ca^{2+} pathway facilitates dendrite development in the hippocampus. Similar to Wnt7b, Wnt7a is required for hippocampal dendrite development in vivo; however, in this case available data suggest signaling through the Wnt/Ca^{2+} pathway modulator CaMKII [206]. Wnt7a exposure leads to rapid activation of a postsynaptic CAMKII-reporter in dendritic spines. Moreover, CaMKII inhibitors or Ca^{2+} chelators prevent Wnt7a-mediated dendrite growth [206]. It is worth noting that while this study provides compelling evidence that Wnt7a activates the Wnt/Ca^{2+} pathway in dendritic spine formation, this does not preclude that other Wnt pathways may be involved as well. The same caveat applies to most of the foregoing evidence about Wnt signaling across neurodevelopmental events. In many cases, although a single "pathway" may have been experimentally explored by a specific study, other pathways have not been excluded from the process, and more than one Wnt-dependent mechanism or indeed a network of molecularly interconnected biochemical cascades may in fact be involved.

Synapse Formation and Function

As dendrites undergo arborization, they form connections with axon terminals to create synapses, specialized connections that permit rapid electrochemical communication between neurons (Table 7). For a dendritic filopodia to establish a synapse with an axon terminal, the 2 elements must form an initial adhesive interaction that is then replaced by critical synaptic components through a developmentally coordinated process. The elements of this process include presynaptic protein clustering in axonal terminal boutons, postsynaptic protein accumulation in apposing dendritic spines, and transsynaptic dialogue (i.e., intercellular signaling) to coordinate development of the 2 sides of the synapse belonging to different neurons. Considering the significant roles that Wnt signaling plays in axon and dendrite development, it comes as no surprise that Wnts are also important for synapse formation and function. In fact, Wnt7a, Wnt5a, Wnt3, Wnt3a, and Wnt2 all have established roles in synapse development and plasticity [21, 169, 170, 172, 206–212].

Accumulating data suggest that Wnt7a signals bidirectionally through divergent pathways to influence both presynaptic and postsynaptic assembly, as well as to promote excitatory synapse function. In fact, Wnt7a was the first Wnt protein to be associated with synaptogenesis when it was found to be expressed in granule cells of the

developing mouse cerebellum at the time when these cells form synapses with mossy fiber axons [169, 170]. Further examination led to the discovery that soluble Wnt7a is sufficient to induce axon remodeling and synapsin-1 clustering (requisite for presynaptic function) in cultured mossy fibers, and that these effects are mimicked by GSK3 inhibition [170]. Moreover, granule cell-conditioned medium phenocopies the effect of Wnt7a on cultured mossy fibers, and this effect is inhibited by addition of a Wnt antagonist [170]. These data support that Wnt7a secreted from granule cells is required to induce presynaptic formation in mossy fibers, and that the pathway downstream involves GSK3-dependent activity. Ablation of *Wnt7a* in mice led to disruption of glomerular rosettes and delay of synapsin-1 clustering [170]. *Dvl1* null mice exhibit the same phenotype, while *Wnt7a/Dvl1* double mutant mice show even simpler glomerular rosettes [207]. Postsynaptically, exposure to Wnt7a increased clustering of PSD95, the major scaffold protein of the excitatory postsynaptic density [206, 213].

Electrophysiological recordings of cerebellar slices have further indicated that *Wnt7a/Dvl1* double mutant mice have a diminished frequency of miniature excitatory postsynaptic currents (mEPSCs) [207]. In studies using cultured hippocampal neurons, Wnt7a was found to increase the frequency of mEPSCs without affecting miniature inhibitory postsynaptic currents [206]. The mechanisms involved are not restricted to neurodevelopment: a pathway downstream of Wnt7a modulates EPSCs through effects on the synaptic vesicle fusion process [19]. Specifically, Wnt7a at the synapse promotes interaction of Dvl1 with synaptotagmin-1 (Syt-1), SNAP25, and syntaxin – facilitating Ca^{2+}-induced vesicle-presynaptic membrane fusion and neurotransmitter release in an activity-dependent manner [19].

Given the preceding sections, it will come as no surprise that Wnt7a signals through multiple pathways to fulfill its synapse-promoting functions. While Dvl1 and GSK3 are required for the Wnt7a-mediated promotion of synaptogenesis, a mutant form of β-catenin lacking the Tcf binding domain does not phenocopy loss of Wnt7a in hippocampal neurons [214]. This indicates that Tcf-dependent transcription is not required for Wnt7a-mediated effects on synapse formation. Additionally, an apparent absence of JNK and CaMKII activation in the presence of Wnt7a in hippocampal neurons initially suggested that neither the Wnt/PCP nor Wnt/Ca^{2+} pathways were utilized [215]. However, a more recent study found significant activation of CaMKII activity in hippocampal neurons upon treatment with Wnt7a, and moreover that inhibition of CaMKII prevents Wnt7a-mediated increases of mEPSCs [206]. This finding does not exclude the model of facilitated neurotransmitter release mediated by Wnt7a-dependent interactions of Dvl1 with synaptic vesicle proteins, but it does suggest participation of additional mechanisms downstream of Dvl1. Wnt7a-mediated axonal remodeling in cerebellar mossy fibers is associated with changes in microtubule organization [170], reminiscent of earlier findings involving the inhibition of GSK3-mediated phosphorylation of MAP1B in axon remodeling. A reasonable synthesis of these data is that Wnt7a promotes synapse formation and function by influencing cytoskeletal changes downstream of the Wnt/Ca^{2+} pathway and also by modulating excitatory neurotransmitter release in a Dvl-dependent manner, perhaps via multiple downstream cascades.

Wnt5a similarly acts through at least 2 pathways to facilitate processes required for synapse formation and function, including excitatory and inhibitory synaptic transmission and presynaptic and postsynaptic protein clustering. The Wnt/Ca^{2+} pathway was first implicated when Wnt5a was shown to trigger increased calcium concentrations in dendritic processes of cultured hippocampal neurons and increased amplitude of field excitatory postsynaptic potentials in rat hippocampal slices; both effects can be inhibited by calcium channel blockers [212]. It was later found that Wnt5a facilitates fast excitatory glutamatergic synaptic transmission by potentiating NMDAR currents [208]. Wnt5a-evoked Ca^{2+} release from Ryr channels is required for NO production, which directly increases NMDAR assembly at the postsynaptic membrane [216]. Wnt-mediated NMDAR potentiation is impeded by addition of calcium chelators, PKC inhibitors and JNK inhibitors [208], reaffirming a requirement for the Wnt/Ca^{2+} pathway while also suggesting a role for the Wnt/PCP pathway. To modulate NMDAR synaptic transmission in hippocampal neurons, Wnt5a signals through receptor tyrosine-kinase-like orphan receptor 2 (Ror2) [217], a well-characterized Wnt receptor implicated in both Wnt/Ca^{2+} and Wnt/PCP pathways [218, 219]. This Wnt5a-Ror2-Ca^{2+}-NO pathway also regulates hippocampal excitability by inhibiting voltage-gated K^+ currents (Kv currents) [22]. Kv channels play key roles in the spiking patterns of hippocampal neurons [220], and are thus important regulators of synaptic plasticity [221]. In addition to excitatory transmission, Wnt5a is implicated in inhibitory synaptic transmission through the Wnt/Ca^{2+}, but not the Wnt/PCP, pathway. Experiments using cultured rat hippocampal neurons showed that Wnt5a facilitates fast inhibitory γ-aminobutyric acid

(GABA)-ergic synaptic transmission through induction of surface expression and clustering of $GABA_A$ receptors in a CaMKII-, but not JNK-dependent manner [210]. Finally, Wnt5a induces postsynaptic clustering of PSD95 in cultured rat hippocampal neurons [211, 222] by binding Ror1-Ror2 receptor complexes [223] to activate the JNK-dependent Wnt/PCP pathway [211]. Interestingly, while Wnt5a increases *post*synaptic clustering in short-term experiments, long exposures (over 12 h) also increase *pre*synaptic clustering and synaptic contacts [222].

Wnt3a can signal through a divergent Wnt/β-catenin pathway to mediate synapse formation by decreasing the amount of APC associated with microtubule plus ends, thereby promoting formation of microtubule loops in axon growth cones [21]. Microtubule looping contributes to the architecture of axonal boutons and is important for their formation [224, 225]. There is also provocative evidence for Wnt/β-catenin pathway involvement in synaptic plasticity: tetanic stimulation of mouse hippocampal slices sufficient to cause long-term potentiation (LTP) led to NMDAR-dependent presynaptic release of Wnt3a, which in turn caused β-catenin accumulation and target gene regulation in postsynaptic neurons [209]. Additional evidence that Wnt/β-catenin signaling is involved in LTP was provided by experiments in which LTP was impaired in the presence of a secreted Wnt antagonist; conversely, LTP was enhanced by application of a specific GSK3 inhibitor, mimicking activation of the Wnt/β-catenin pathway [209].

We have framed the aforementioned studies in the context of specific Wnt ligands, but there have been numerous studies illustrating the roles that downstream Wnt pathway components play in synapse formation and function. For example, a role for the Wnt/PCP pathway in synaptogenesis, mechanistically separate from roles in dendritogenesis and spine formation, has been supported by analyses of differential genetic and rescue effects of neurodevelopmental phenotypes in forebrain neurons from *Dact1* and *Vangl2* knockout mice [197, 226]. Biochemical and molecular analyses revealed that Vangl2 binds directly to N-cadherin [198, 199], the transmembrane protein that facilitates the initial critical adhesive event between presynaptic and postsynaptic elements, to mediate its endocytic removal from the membrane [199]. Vangl2 and Prickle2 also bind and promote postsynaptic clustering of PSD95, critical for maintenance of synaptic integrity [199, 227, 228]. Prickle1 was found to regulate synaptogenesis and synaptic vesicle trafficking through a direct interaction with synapsin1 (Syn1) [229]; the synapsin protein family have important roles in synapse formation and neurotransmitter release and have previously been implicated in the pathogenesis of psychiatric disorders [230–236]. Indeed, *Prickle1*$^{+/-}$ mice exhibit ASD-like behaviors, and expression of a mutant form of Prickle in cultured cells phenocopies the vesicle trafficking defect observed with aberrant Syn1 function [229]. While upstream Wnt ligands involved in these events remain to be identified, these studies provide additional evidence that components of the Wnt/PCP pathway are critical contributors to synapse formation and function.

Human Genomic Studies

There are numerous studies, primarily in gene-targeted mouse lines, demonstrating that genetic disruption in Wnt pathway genes can affect complex behavior, including in assays of sociability, repetitive behaviors and vocalizations that could be relevant to the cardinal symptoms of ASD [237–242], sensory processing and prepulse inhibition that could be relevant to symptoms of Scz [243–245], and motivation, impulsivity, anxiety and activity patterns that could be relevant to symptoms of BD and other affective and anxiety disorders [246–248] (Table 8). These data clearly demonstrate behavioral phenotypes in these animal models, but controversy remains over the relevance of such findings to the genetic etiology of psychiatric disorders – that is, it remains unclear whether such data have predictive relevance for involvement of the corresponding genes in clinically defined behavioral disorders in the human population. On this basis we do not emphasize these types of animal behavioral data in this review except where the corresponding gene is separately linked to psychiatric disease by strong human genetic data.

Through human genomic studies of psychiatric disorders, a picture is emerging of overlapping genetic etiologies: many genetic variants and loci are implicated across several psychiatric disorders [249–253]. Wnt pathway-associated genes are among hundreds of loci that have been identified in this effort. In this section, we discuss these genes in the context of individual disorders, focusing on ASD, Scz, and BD, for which the most reliable genetic data exist because of their relatively high heritability. However, before summarizing the Wnt pathway loci implicated in each of these 3 psychiatric disorders, it is important to establish context by providing an introduction to the genetics of complex disorders and describing the different classes of genetic studies and the type of evidence they offer.

Table 8. Summary of Wnt pathway genes associated with ASD, SCZ, and BD and corresponding human genomic analyses

Pathway/gene	Disorder	Type of genetic evidence	Ref.
Canonical Wnt/β-catenin			
CHD8	ASD	WES, CGA, sequencing of balanced chromosomal abnormalities	[261–264]
	SCZ	WES	[262]
CTNNB1 (β-catenin)	ASD	WES	[263, 271]
	SCZ	CGA	[145]
TCF7	ASD	WES	[261]
WNT7A	ASD	WGS	[268]
	BD	CGA	[296]
DISC1	ASD	WGS	[260]
	SCZ	LA	[274]
	BD	LA	[297–300]
TCF4	ASD	GWAS, sequencing of balanced chromosomal abnormalities	[272, 273]
	BD	GWAS, CGA	[301, 302]
	SCZ	GWAS	[253]
WNT2	ASD	GWAS, LA	[266]
WNT3	ASD	"NETBAG" analysis of de novo CNV data	[267]
APC	ASD	LA, CGA	[241, 269, 270]
FZD3	SCZ	LA	[291–293]
HMG2L1	BD	LA	[303]
SFRP1	SCZ	LA	[291–293]
DKK4	SCZ	LA, CGA	[290–293]
PTEN	ASD	CGA	[278–280]
WNT1	ASD	CGA	[240]
WNT2B	BD	CGA	[296]
DKK1	SCZ	CGA	[289]
KREMEN1	SCZ	CGA	[289]
PPARD	BD	CGA	[296]
Noncanonical Wnt			
PRICKLE1	ASD	WES	[282]
SESTD1	BD	GWAS	[305]
PRICKLE2	ASD	CGA	[237]

Noncanonical Wnt: Wnt/PCP pathway genes; WGS, whole genome sequencing; WES, whole exome sequencing; LA, linkage analysis; GWAS, genome-wide association study; CGA, candidate gene approach.

As with every multifactorial medical disorder with a heritable component, the genetic contribution to psychiatric disorders is complex and can be subdivided into several categories. One of the simplest classification schemes is to separate "common" genetic variation from "rare" (and de novo) genetic variation. Common variants arose in the human genome many generations ago and have since expanded such that they are now present in ≥1% of the total population or a well-defined subpopulation (e.g., ethnic group). Being common, these variants are likely to be either nondeleterious or to have small incremental effects on disease pathogenesis. By contrast, rare variants may have large effects on pathogenesis but have either arisen de novo in an individual still alive today or recently enough in the expansion of the human population that they have not yet been eliminated despite being deleterious. Most current models for complex diseases in psychiatry assume that common variants *in aggregate* are the major contributor to disease susceptibility in the general population. For example, a 2014 analysis of a large Swedish epidemiological sample estimated that narrow-sense heritability (the ratio of additive genetic variation to total phenotypic variation) in ASD is 52.4%, with common variation accounting for almost 50% and rare/de novo

mutations accounting for only 2.6% of total disease burden [254]. Models influenced by recent large-scale genome-wide sequencing studies estimate a larger proportion of disease burden arising from rare or de novo variants [255, 256] – but even so, they continue to posit that common variation accounts for the lion's share of overall genetic susceptibility in ASD. At this time, there is little reason to expect that the relative proportion of burden arising from rare versus common variation will be substantially different in other psychiatric disorders.

The different types of human genetic studies used to identify variants linked to disease susceptibility have varying degrees of statistical rigor. In general, the strongest current evidence is provided by large-scale genome-wide sequencing analysis in which every locus of the genome is sequenced in large numbers (i.e., thousands) of patients and controls. High statistical standards are used to ferret out recurrent LOF mutations that are strongly overrepresented in affected versus unaffected individuals and to correct for multiple comparisons (i.e., finding significance at a single locus while simultaneously examining every locus in the genome). While these studies reveal loci that are definitively causal, so far they have only identified rare causes that account for a small percentage of disease burden in the overall population. Another powerful type of genetic study, linkage analysis, relies on pedigrees to identify strong associations between disease and specific genetic variations within a family of related individuals. Similar to genome-wide sequencing, these studies have so far most successfully identified rare causes and are limited by the availability and discovery of informative pedigrees. The genome-wide association study (GWAS) is a method with the potential to provide data for contributions from common variants with high statistical rigor. GWAS takes advantage of common single-nucleotide polymorphisms (SNPs) used for genotyping to identify variants associated with disease by assuming linkage disequilibrium between SNPs and proximal loci. GWAS should ultimately identify the loci harboring the common sequence variation that in aggregate contributes to the majority of genetic disease burden in psychiatry. Although to date most GWAS findings in psychiatry have been modest due to a need for much larger sample sizes given small effect sizes and large numbers of contributory loci, an example of a recent high-impact study that used GWAS information combined with creative and targeted follow-up has linked common variation at the *C4* gene in the major histocompatibility complex to Scz, pointing to changes in immune molecule-driven synaptic pruning as a specific pathogenic mechanism [257]. It is to be expected that ever-expanding human genetic sample sizes and increasingly sophisticated statistical algorithms will lead to many more GWAS-guided advances of this kind in the coming decade. Finally, candidate gene sequencing approaches traditionally have tried to identify susceptibility loci by investigating a single or small number of loci in relatively limited sample and control datasets (i.e., $n < 10^3$) buttressing this by functional considerations derived from pharmacology, animal models, or other basic research findings. Given the low statistical power of this genetic approach, combined with the recent realization that there is a much higher-than-expected rate of rare and de novo nucleotide variation in the human exome, the significance of such findings is increasingly called into question pending stronger evidence derived from one of the other types of genetic study described above.

Autism Spectrum Disorder

The genomic analysis of ASD, a behaviorally defined neurodevelopmental disorder with a genetic contribution estimated to be upwards of 50% (in some studies as high as 95%) [254, 258–260], has led to the identification of a number of Wnt/β-catenin and Wnt/PCP pathway loci. Significantly, the single locus with the highest frequency of de novo LOF mutations in genome-wide sequencing studies of ASD is chromodomain helicase DNA-binding protein 8 (CHD8), encoding a DNA helicase that co-regulates many Wnt/β-catenin transcriptional targets [261–265]. Other genetic evidence supports roles for several core Wnt/β-catenin pathway loci in the genetics of ASD including *WNT1* [240], *WNT2* [266], *WNT3* [267], *WNT7A* [268], *APC* [241, 269, 270], *CTNNB1* (β-catenin) [263, 271], *TCF4* [272, 273], and *TCF7* [261]. This review has highlighted the critical roles these genes play during neural development. Outside the "core" of the pathway, other molecules implicated in pathway modulation with compelling genetic evidence for involvement in ASD include *DISC1* [268], *PTEN*, and the *Prickle* genes. Our neurodevelopmental discussion of *DISC1*, a Wnt pathway scaffold protein first identified in affected members of a large Scottish pedigree with high incidence of various psychiatric disorders [274], emphasized its roles in neural precursor proliferation and migration. However, there is also evidence that *DISC1* is required for development of glutamatergic synapses [275, 276], although it is not yet clear if this function is Wnt-dependent. The gene encoding PTEN, a cytoplasmic protein that suppresses Wnt/β-catenin signaling in the developing mouse cortex [277], has been repeatedly identified as a high-risk ASD susceptibility gene in human genomic studies [278–281]. Finally, single nu-

cleotide variants of the Wnt/PCP pathway genes *PRICKLE1* and *PRICKLE2* were identified in whole exome sequencing of affected families [237, 282]. Mutations in *PRICKLE1* and *PRICKLE2* have previously been associated with epilepsy [283, 284], a condition highly comorbid with ASD [285]. Both genes encode proteins with roles in synaptogenesis; PRICKLE1 is important for Syn1 function in the presynapse [229], while PRICKLE2 interacts with PSD95 and NMDA receptors in the postsynapse [227].

Schizophrenia

Wnt/β-catenin loci have also been prominent in large-scale genomic analyses of Scz, a disorder with an estimated heritability of ~65–80% [286–288]. In fact, some Wnt/β-catenin pathway loci have emerged as shared risk factors for Scz and ASD, including *DISC1* [274], *TCF4* [253, 273], *CTNNB1* [145], and *CHD8* [262]. Other Wnt genes implicated in Scz include the secreted Wnt antagonists *DKK1* [289] and *DKK4* [290], as well as the receptor required for DKK-mediated Wnt antagonism *KREMEN1* [289]. Moreover, *DKK4,* along with *FZD3* and *Secreted Frizzled-Related Protein 1* (*SFRP1*), reside on chromosome 8p, a genomic region repeatedly implicated in psychiatric genetic studies over the past 2 decades [291–293].

Bipolar Disorder

Genomic analysis of BD, with an estimated heritability of ~60–85% [286, 294, 295], has also uncovered disruptions in Wnt/β-catenin pathway loci, including *WNT7A* and *WNT2B* [296], *DISC1* [297–300], and *TCF7L2* (*TCF4*) [301, 302]. Other genes that help regulate the Wnt/β-catenin signaling have also been identified. For example, a family-based study of SNPs found a prominent Wnt/β-catenin target gene, *Peroxisome Proliferator-Activated Receptor-Delta* (*PPARD*), to be the most significantly associated SNP [296]. Another family-based SNP mapping study found a high mobility group (HMG) box family member, *HMG2L1*, to be significantly associated with BD [303], and there is emerging evidence that HMG2L1 functions as a negative regulator of Wnt/β-catenin signaling [304].

With regard to noncanonical Wnt signaling in BD, a recent large GWAS study identified a single locus containing a noncoding SNP with strong linkage to lithium-responsive BD: SEC14 and spectrin domain containing 1 (SESTD1) [305]. Sestd1, expressed both during neurodevelopment and in the mature CNS [306], has recently been shown to directly interact with Dvl2, Dact1, and Vangl2 in a PCP-related signaling cascade during embryonic development [307].

Concluding Remarks: Therapeutic Considerations

Lithium, which came into systematic use as a mood stabilizer shortly after World War II [308], is the oldest psychiatric drug in Western medicine with folk roots that may stretch back to antiquity [309]. It remains one of the staples of treatment in BD, with a significant subclass of patients exquisitely responsive to it. Lithium also remains in a class by itself as the only drug with a highly selective therapeutic utility in the treatment of mood swings; other drugs used for this indication were designed and are used for other indications – i.e. as anticonvulsants, antipsychotics, etc. – with side effect profiles and neurotransmitter impacts in line with these other drug classes. No medications have been devised based on an understanding of the molecular action of lithium with the intent to duplicate or improve upon it. This is despite the fact that in some otherwise responsive BD patients, the use of lithium is limited by its side effect profile, particularly a progressive nephrotoxicity that occurs with chronic treatment. So, there is certainly an unmet clinical need and a substantial potential market for such a pharmaceutical – yet no such drug has been intentionally developed or marketed.

The deficit of new drugs based on lithium is partly due to a complex mechanism of action; lithium affects several enzymes and cellular pathways simultaneously, making its most relevant molecular mechanism in the treatment of BD difficult to disentangle [310]. Nonetheless, it has become increasingly clear over the last 2 decades that one of the relevant (though by no means exclusive) mechanisms of action of lithium within the CNS is inhibition of GSK3, which mimics activation of Wnt/β-catenin signaling [311]. Lithium, a monovalent cation, directly inhibits GSK3, a metalloenzyme, by replacing divalent Mg in its structure. Lithium can similarly substitute for Mg in other metalloproteins; its relative specificity for GSK3 and a few other enzymes (such as inositol monophosphatase and inositol polyphosphate 1-phosphatase in the phosphoinositide pathway) stems from biophysical idiosyncrasies – the distribution of positive charges, bulky coordinating residues, and solvent accessibility – of the metal-binding pocket in lithium-sensitive metalloproteins [312]. But lithium is far from the only psychiatric drug to impact GSK3: the mood stabilizer/anticonvulsant valproic acid (VPA) [313–315], diverse antipsychotics [316–320], antidepressants including tricyclics and selective serotonin reuptake inhibitors [321–324], as well as the novel acute antidepressant ketamine [325], all modulate GSK3 as one of their many downstream effects. Many

orally administrable molecules with specific and selective inhibitory activity on GSK3 are commercially available and have been widely used in basic scientific studies including in live animal models, with little evidence of toxicity [326–330]. So, the absence of psychiatric drugs intentionally designed to impact this pathway does not reflect an absence of evidence for efficacy or a difficulty in chemically creating such a drug – more likely it reflects another major consideration: reluctance to develop and market a novel psychiatric drug deliberately designed to act on a pathway with links to cancer.

In fact, the extensive clinical experience with lithium itself provides evidence that such concerns regarding cancer risk are likely overblown. In over 60 years of systematic use in patients across the globe, no links between lithium therapy and oncogenesis have emerged; if anything, there is evidence that chronic administration of lithium has an oncoprotective effect in humans [331, 332]. Over a similar period, extensive basic science investigations in animal models and cell lines have provided little evidence that pharmaceutical activation of the Wnt pathway at the level of the plasma membrane or cytoplasm – i.e. at or above biochemical GSK3 regulation – leads to cancer [333, 334]. That said, as expected for a pathway with such diverse developmental functions there is reason to proceed with caution based on potentially adverse developmental consequences of manipulating Wnt signaling, particularly in utero. Indeed, extensive clinical experience has demonstrated that maternal use of either lithium or VPA is associated with the increased incidence of some birth defects. In the case of VPA, this includes an increased risk to the newborn for cognitive defects and ASD [335, 336]. In the case of lithium exposure, the data suggesting adverse neurodevelopmental consequences in the newborn is complicated: although in some studies children who experienced prenatal lithium exposure had normal neurological, cognitive, and behavioral outcomes [337, 338], at least 1 study found that prenatal exposure led to transient neurodevelopmental differences that resolved by 1 year of age [339]. Prenatal lithium exposure is however clearly associated with an increased risk for cardiovascular defects, particularly Ebstein's anomaly, a malformation of the tricuspid valve (in one recent study 0.6% of unexposed children experienced cardiovascular anomalies compared to 4.1% of lithium-exposed children, although ~60% of the lithium exposure cases resolved spontaneously) [340]. For both VPA and lithium, it is not clear if associated birth defects are caused by the drugs' activity on GSK3 and Wnt/β-catenin signaling, or if they may be a consequence of the drugs' effects on other molecular targets during development. Regardless, these clinical data do suggest caution is warranted before new drugs intentionally targeting GSK3 or the Wnt/β-catenin pathway are administered to pregnant women.

On the other hand, several recent studies in mouse models and hiPSCs support that modulation of the Wnt/β-catenin pathway has therapeutic potential in psychiatry. Mice with combined mutations in 2 *Dvl* genes (Dvl1 and Dvl3) have adult behavioral abnormalities reminiscent of ASD (increased repetitive behaviors and decreased social behavior), along with accelerated early brain growth similar to a subgroup of ASD patients. During prenatal development, these animals have hypoactivity of a β-catenin-dependent transcriptional cascade in cortical NPCs, with a resultant hyperproliferation phenotype. Prenatal administration of a specific GSK3 inhibitor to these animals corrected developmental brain growth abnormalities as well as adult ASD-like behavioral phenotypes [341]. A parallel study examined cellular and molecular defects in hiPSC lines derived from ASD patients with accelerated early brain growth, and similarly found a hyperproliferative NPC phenotype responsive to lithium [342]. Finally, cortical pyramidal neurons from a mouse line mutant for the neuronally expressed Wnt/β-catenin pathway activator and DISC1 partner *Dixdc1* have reduced dendritic spine and excitatory synapse density correlating with phenotypes in the affective domain (behavioral despair) and social domain (reciprocal social interaction); administration of either lithium or a selective GKS3 inhibitor corrects both the neurodevelopmental and behavioral phenotypes in these animals [343]. This supports that a major neurodevelopmental/neuroplastic target of lithium – and of other psychiatric drugs that either directly or indirectly modulate GSK3 – is the formation, stability, and/or turnover of dendritic spines and glutamatergic synapses [325, 344, 345]. The same study also provided evidence supporting a "goldilocks principle" for Wnt signaling in these processes at the dendritic spine and synapse, showing that either too much or too little signal pathway activation is similarly deleterious [343]. This is consistent with the established importance of Wnt pathway dosage and the role of Wnts as morphogens in other developmental contexts [75, 121, 197, 346–349]. Together, the recent work in animals and hIPSCs underscores how experimental model systems in which genetic, signaling, neurodevelopmental, circuit, and behavioral phenotypes are simultaneously characterized and correlated can be used to test hypotheses and potentially to develop and test novel psychopharmaceuticals that modulate Wnt/β-catenin signaling.

With regard to GSK3-independent (i.e., noncanonical) Wnt pathways, there is also reason to be optimistic. Naturally occurring and manufactured compounds that specifically inhibit the Wnt/PCP pathway have been identified [350], opening the door for development of new agents that can selectively inhibit or activate this pathway via similar molecular mechanisms [351]. In closing, as each of the Wnt pathways – even the most divergent pathways discussed in the preceding sections – is biochemically characterized, they provide promising targets for rational drug exploration and development in psychiatry with a clear path forward through the use of animal and hiPSC models as prescribed above.

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Disclosure Statement

The authors have no conflicts of interest to report.

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