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1. Node perturbation analysis of each articulation point interactome in the prenatal and postnatal networks

We performed single node and multiple node perturbation analyses (OE/KO) at four different simulations i.e. when TF activates gene and miRNA (Simulation 1), when TF represses both miRNA and gene (Simulation 2), when TF represses miRNA and activates gene expression (Simulation 3) and when TF represses gene and activates miRNA expression (Simulation 4). In single node perturbation analysis, we perturbed each miRNA and TF regulating the AP interactome (PC1). In multiple node perturbation analysis, we perturbed genes positively regulating each stage of neurodevelopment either along with all miRNAs and TFs regulating the articulation point interactome (PC2 and PC3) or along with each miRNA/TF regulating the articulation point interactome (PC4 and PC5). We have shown the perturbation results as activation frequency i.e. for every 1000 simulations, the number of times a given stage is upregulated at t =150. We have used the term regulatory state (RS), to show the neurodevelopmental stages which are shown to be regulated in more than one regulatory state (RS). For example, in a particular PC, if a specific stage shows all three regulatory states i.e. upregulation (100%), downregulation (0%) as well as regulation between 0%-100%, we represent such states as RS1. We have four such regulatory states (RS1, RS2, RS3 and RS4), explained in each table. We have presented the results of node perturbation analysis for each articulation point in the prenatal and postnatal network under two headings, single node perturbation analysis and multiple node perturbation analysis as shown below:

Single node perturbation analysis

- ***Perturbation condition 1:*** OE and KO of each miRNA and each TF regulating AP interactome

Multiple node perturbation analysis

- ***Perturbation condition 2:*** OE of genes positively regulating each stage of neurodevelopment (regulated by AP interactome) and OE of miRNAs and TFs regulating AP interactome
- ***Perturbation condition 3:*** KO of genes positively regulating each stage of neurodevelopment (regulated by AP interactome) and OE of miRNAs and TFs regulating AP interactome
- ***Perturbation condition 4:*** OE of genes positively regulating stage of neurodevelopment (regulated by AP interactome) along with OE of each factor (miRNA/TF) regulating AP interactome
- ***Perturbation condition 5:*** KO of genes positively regulating stage of neurodevelopment (regulated by AP interactome) along with OE of each factor (miRNA/ TF) regulating AP interactome

1.1 Interactomes involved in regulation of prenatal development

We analyzed the effect of each perturbation (PC1-PC5) on each stage of neurodevelopment and the overall neurodevelopment process (combined all the stages regulated by AP interactome as one stage). We could not perform node perturbation analysis for the following articulation points, DTNBP1, CNTNAP2, DLG2 and GRIN2A. There were no experimentally validated miRNAs shown to regulate DTNBP1, so no feedforward loops (FFLs) were identified for this articulation point. We could also note perform NP analysis for CNTNAP2, DLG2 and GRIN2A genes, as the FFLs regulating these APs did not regulate genes that interact with these APs

A. DISC1 interactome

During prenatal neurodevelopment, DISC1 interactome has been shown to regulate embryogenesis, neurulation, proliferation, migration, differentiation, neurite growth and synaptogenesis. We have specified rules for each stage of neurodevelopment regulated by DISC1 interactome as well as for the overall neurodevelopment process (all the stages regulated by DISC1 combined as one stage). As GSK3B gene is shown to regulate migration in two different gene expression states, we have given 2 Boolean rules for migration as well as for the overall neurodevelopment process, where DISC1 and GSK3B is expressed regulating neurodevelopment (when GSK3B is expressed) and where DISC1 is expressed and GSK3B is not expressed regulating neurodevelopment (when GSK3B is not expressed).

Single node perturbation

Perturbation condition 1: OE and KO of each miRNA and each TF regulating DISC1 interactome

Simulations 1-4: OE and KO of each miRNA and each TF downregulated (0%) each of the above-mentioned stages of development and the overall neurodevelopment process regulated by DISC1 interactome.

Multiple node perturbation

Perturbation condition 2: OE of genes positively regulating each stage of neurodevelopment (regulated by DISC1 interactome) and OE of miRNAs and TFs regulating DISC1 interactome

Simulations 1-4: OE of genes positively regulating each stage of neurodevelopment regulated by DISC1 interactome (embryogenesis/ neurulation/ proliferation/ migration (when GSK3B not expressed)/ migration (when GSK3B expressed)/ differentiation/ neurite growth/ synaptogenesis) along with miRNAs and TFs, upregulated (100%) each same stage of development (embryogenesis/ neurulation/ proliferation/ migration / differentiation/

neurite growth/ synaptogenesis). Differentiation stage was also shown to upregulated along with upregulation of each stage.

OE of genes positively regulating neurodevelopment process (when GSK3B is not expressed), upregulated (100%) all the stages of neurodevelopment including the overall neurodevelopment process (when GSK3B is not expressed) whereas OE of genes positively regulating neurodevelopment (when GSK3B is expressed), upregulated (100%) neurodevelopment (when GSK3B is expressed), differentiation, migration, neurulation and synaptogenesis.

Perturbation condition 3: KO of genes positively regulating each stage of development (regulated by DISC1 interactome) and KO of miRNAs and TFs regulating DISC1 interactome

Simulations 1-4: KO of genes positively regulating each stage of neurodevelopment (embryogenesis/ neurulation/ proliferation/ migration (when GSK3B expressed)/ migration (when GSK3B not expressed)/ differentiation/ neurite growth/ synaptogenesis/ neurodevelopment (when GSK3B not expressed)/ neurodevelopment (when GSK3B expressed) along with KO of miRNAs and TFs, downregulated (0%) each same stage of neurodevelopment.

Simulations 2 and 4: KO of genes positively regulating each stage of neurodevelopment (except genes positively regulating migration (when GSK3B is expressed) and genes positively regulating neurodevelopment (when GSK3B is expressed)), along with KO of miRNAs and TFs upregulated migration stage (when GSK3B is expressed) (100%).

Perturbation condition 4: OE of genes positively regulating each stage of neurodevelopment (regulated by DISC1 interactome) along with OE of each factor (miRNA/TF) regulating DISC1 interactome

a. Embryogenesis

Simulations 1-4: OE of genes positively regulating embryogenesis and OE of each miRNA/TF upregulated embryogenesis (100%). Similarly, OE of genes positively regulating neurodevelopment (when GSK3B is not expressed), upregulated embryogenesis (100%).

Simulation 3: OE of each miRNA/TF along with OE of genes positively regulating neurulation/ proliferation/ migration (when GSK3B is not expressed)/ differentiation/ neurite growth/ synaptogenesis showed overall regulation of embryogenesis process in all three regulatory states (RS1), upregulation (100%), regulation between 0%-100% and downregulation (0%). OE of either let7e, miR124, miR155, miR26a, miR877, miR190a, miR5011, EP300, TAL1, STAT3, HNF4A, GATA1, KDM2B, KDM5B or PPARG or TEAD4 along with OE of genes positively regulating neurulation/proliferation/migration (GSK3B is not expressed)/differentiation/neurite growth/synaptogenesis downregulated embryogenesis (0%). OE of either TP53 or miR320a or NUCKS1 along with OE of genes positively regulating neurulation/proliferation/migration (when GSK3B is not expressed)/differentiation/neurite growth/synaptogenesis upregulated embryogenesis (100%). OE of each miRNA/ TF (except OE of let7e/ miR124/ miR155/ miR26a/ miR877/ miR190a/ miR5011/ miR320a/ EP300/ TAL1/ STAT3/ HNF4A/ GATA1/ KDM2B/ KDM5B/ PPARG/TP53/NUCKS1) along with OE of genes positively regulating neurulation/proliferation/migration (when GSK3B is not expressed)/differentiation/neurite growth/synaptogenesis regulated embryogenesis (between 0%-100%).

b. Neurulation

Simulations 1-4: OE of genes positively regulating neurulation and OE of each miRNA/ TF upregulated neurulation (100%). Similarly, OE of genes positively regulating neurodevelopment (when GSK3B is not expressed) along with OE of each miRNA/TF, upregulated neurulation (100%).

c. Proliferation

Simulations 1-4: OE of genes positively regulating proliferation and OE of each miRNA/ TF upregulated proliferation (100%).

Simulations 1, 2 and 4: OE of genes positively regulating neurodevelopment (when GSK3B is not expressed), upregulated proliferation (100%).

Simulation 3: OE of each factor along with OE of genes positively regulating neurulation/ embryogenesis/ migration (GSK3B is not expressed)/ neurite growth/ differentiation/ synaptogenesis/ neurodevelopment (GSK3B is not expressed) showed regulation of overall proliferation process in all three regulatory states (RS1), upregulation (100%), regulation between 0%-100% and downregulation (0%). OE of either miR744 or HNF4A along with OE of genes positively regulating neurulation/ embryogenesis/ neurite growth/ differentiation/ synaptogenesis/ neurodevelopment (GSK3B is not expressed) downregulated proliferation (0%). OE of either miR320a, EP300, TRIM28, STAT3, NUCKS1, NFI, KDM2B, GATA1 or PPARG along with OE of genes positively regulating neurulation/ embryogenesis/ neurite growth/ migration (GSK3B is not expressed)/ differentiation/ synaptogenesis/ neurodevelopment (GSK3B is not expressed), upregulated proliferation (100%). OE of each factor (except miR744/ HNF4A/ miR320a/ EP300/ TRIM28/ STAT3/ NUCKS1/ NFI/ KDM2B/ PPARG) along with OE of genes positively regulating neurulation/ embryogenesis/ neurite growth/

differentiation/ synaptogenesis/ neurodevelopment (when GSK3B is not expressed) regulated proliferation between 0%-100%.

We also observed that OE of genes positively regulating migration (when GSK3B is not expressed) and OE of either miR124/miR155/miR744/HNF4A, downregulated proliferation (0%). OE of genes positively regulating migration (when GSK3B is not expressed) and OE of either miR190a/ miR5011, regulated proliferation (between 0%-100%). OE of each factor (except OE miR124 or miR155 or miR744 or HNF4A or miR190a or miR5011) along with OE of genes positively regulating migration (when GSK3B not expressed) upregulated proliferation (100%). Thus, OE of each factor along with OE of genes positively regulating migration (when GSK3B not expressed) showed regulation of overall proliferation process in all three regulatory states (RS1), upregulation (100%), regulation between 0%-100% and downregulation (0%).

d. Migration (when GSK3B is not expressed)

Simulations 1-4: OE of genes positively regulating migration (when GSK3B is not expressed) or OE of genes positively regulating neurodevelopment (when GSK3B is not expressed) along with OE of each miRNA/ TF, upregulated migration (100%).

e. Migration (GSK3B is expressed)

Simulations 1-4: OE of genes positively regulating migration (when GSK3B is expressed) or OE of genes positively regulating neurodevelopment (when GSK3B is expressed) along with OE of each miRNA/TF, upregulated migration (100%).

f. Differentiation

Simulations 1-4: OE of miRNA/TF along with OE of genes positively regulating embryogenesis/ migration (when GSK3B is not expressed)/ neurite growth/ neurodevelopment (when GSK3B is expressed)/ neurodevelopment (when GSK3B is not

expressed)/ neurulation/ proliferation/ synaptogenesis/ differentiation, upregulated differentiation (100%).

h. Neurite growth

Simulations 1-4: OE of each miRNA/TF along with OE of genes positively regulating neurite growth/ genes positively regulating neurodevelopment (when GSK3B is not expressed), upregulated neurite growth (100%).

i. Synaptogenesis

Simulations 1-4: OE of each miRNA/TF along with OE of genes positively regulating synaptogenesis/ genes positively regulating neurodevelopment (when GSK3B is not expressed)/ genes positively regulating neurodevelopment (when GSK3B is expressed), upregulated synaptogenesis (100%).

j. Neurodevelopment (GSK3B is expressed)

Simulations 1-4: OE of each miRNA/TF along with OE of genes positively regulating neurodevelopment (when GSK3B is expressed), upregulated neurodevelopment (100%).

k. Neurodevelopment (GSK3B is not expressed)

Simulations 1-4: OE of each miRNA/TF along with OE of genes positively regulating neurodevelopment (when GSK3B is not expressed), upregulated neurodevelopment (100%).

Perturbation condition 5: KO of genes positively regulating each stage of neurodevelopment (regulated by DISC1 interactome) along with KO of each factor (miRNA/TF) regulating DISC1 interactome

Simulations 1-4: KO of genes positively regulating each stage of neurodevelopment (embryogenesis, neurulation, proliferation, migration, differentiation, neurite growth and synaptogenesis/ neurodevelopment (when GSK3B is expressed)/ neurodevelopment (when GSK3B is not expressed)) along with KO of each miRNA/TF, downregulated each same stage of neurodevelopment (0%).

Table 1: Perturbation results of DISC1 interactome involved in prenatal development

Perturbed nodes	PC	Effect of perturbation on each stage at t =150 (Activation frequency for 1000 simulations at t = 150)																			
		Embryogenesis				Neurulation				Proliferation				Migration (when GSK3B is not expressed)				Migration (when GSK3B is expressed)			
		Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4
Factors	1	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating embryogenesis and factors	2	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%
	4	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	RS1	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurulation and factors	2	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%
	4	0%	0%	RS1	0%	100%	100%	100%	100%	0%	0%	RS1	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating proliferation and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%
	4	0%	0%	RS1	0%	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating migration (when GSK3B is not expressed) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%
	4	0%	0%	RS1	0%	0%	0%	0%	0%	0%	0%	RS1	0%	100%	100%	100%	100%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating migration (when GSK3B is expressed) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating differentiation and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%

	4	0%	0%	RS1	0%	0%	0%	0%	0%	0%	0%	RS1	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurite growth and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%
	4	0%	0%	RS1	0%	0%	0%	0%	0%	0%	0%	RS1	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating synaptogenesis and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%
	4	0%	0%	RS1	0%	0%	0%	0%	0%	0%	0%	RS1	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment (when GSK3B is expressed) and factors	2	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment (when GSK3B is not expressed) and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%
	4	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	RS1	100%	100%	100%	100%	100%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

PC denotes Perturbation condition; Sim1 – Simulation 1; Sim2 – Simulation 2; Sim3 – Simulation 3; Sim4 – Simulation 4; 0% - Downregulation; 100% - Upregulation; RS1 represents regulatory state 1, where PC leads to downregulation 0%, regulation between 0%-100% and upregulation 100%. RS2 represents regulatory state 2, where PC leads to upregulation 100% and downregulation 0%

Table 2: Perturbation results of DISC1 interactome involved in prenatal development (Contd)

Perturbed nodes	PC	Effect of perturbation on each stage at t =150 (Activation frequency for 1000 simulations at t = 150)																			
		Differentiation				Neurite growth				Synaptogenesis				Neurodevelopment (when GSK3B is expressed)				Neurodevelopment (when GSK3B is not expressed)			
		Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4
Factors	1	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating embryogenesis and factors	2	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurulation and factors	2	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating proliferation and factors	2	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating migration (when GSK3B is not expressed) and factors	2	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating migration (when GSK3B is expressed) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating	2	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

differentiation and factors	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurite growth and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating synaptogenesis and factors	2	100%	100%	100%	100%	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment (when GSK3B is expressed) and factors	2	100%	100%	100%	100%	0%	0%	0%	0%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	0%	0%	0%	0%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment (when GSK3B is not expressed) and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%	100%	100%	100%	100%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

PC denotes Perturbation condition; Sim1 – Simulation 1; Sim2 – Simulation 2; Sim3 – Simulation 3; Sim4 – Simulation 4; 0% - Downregulation; 100% - Upregulation

Summary of perturbation results for DISC1 interactome involved in prenatal regulation

PC1 (Simulations 1-4): Each stage of development regulated by DISC1 interactome was downregulated (0%), as none of the individual factor was shown to be involved in upregulation of stages of development.

PC2 (Simulations 1-4): When genes positively regulating each stage (except migration (when GSK3B is expressed)) regulated by DISC1 interactome was overexpressed along with factors, each same stage along with differentiation stage was upregulated (100%). As all these stages overexpress DISC1, DISC1 upregulates expression of genes involved in differentiation. When genes positively regulating migration (when GSK3B is expressed) along with factors were overexpressed, only migration stage was upregulated (100%). As DISC1 was not expressed in this migration stage, differentiation was not upregulated.

When genes positively regulating neurodevelopment (when GSK3B is expressed) along with factors were overexpressed, neurulation, differentiation, migration (when GSK3B is expressed), synaptogenesis and neurodevelopment (when GSK3 is expressed) stages were upregulated (100%). In all these stages, GSK3B expression was not involved in negative regulation. When genes positively regulating neurodevelopment (when GSK3B is not expressed) was overexpressed along with factors, except migration (when GSK3B is expressed) and neurodevelopment (when GSK3B is expressed), all other stages regulated by DISC1 interactome were upregulated (100%).

PC3 (Simulations 1-4): When genes positively regulating each stage (regulated by DISC1 interactome) was KO along with factors regulating the DISC1 interactome, each same stage was downregulated (0%)

Simulations 2 and 4: At simulations 2 and 4, TF repress gene expression so KO of all factors as well as KO of genes in stages (which express DISC1), upregulated migration (when GSK3B is expressed). DISC1 negatively regulates GSK3B expression.

PC4 (Simulations 1-4): When genes positively regulating each stage (except migration (when GSK3B is expressed)) regulated by DISC1 interactome was overexpressed along with each factor, each same stage as well as the differentiation stage was upregulated (100%). As all these stages OE DISC1, DISC1 upregulates expression of genes involved in differentiation. When genes positively regulating migration (when GSK3B is expressed) along with each factor was overexpressed, only migration stage was upregulated (100%). As DISC1 was not expressed in this migration stage, differentiation was not upregulated.

When genes positively regulating neurodevelopment (when GSK3B is expressed) along with each factor were overexpressed, neurulation, differentiation, migration (when GSK3B is expressed), synaptogenesis and neurodevelopment (when GSK3 is expressed) stages were upregulated (100%). In all these stages, GSK3B expression was not involved in negative regulation. When genes positively regulating neurodevelopment (when GSK3B is not expressed) was overexpressed along with each factor, except migration (when GSK3B is expressed) and neurodevelopment (when GSK3B is expressed), all other stages regulated by DISC1 interactome were upregulated (100%).

Simulation 3: OE of genes positively regulating neurulation/ proliferation/ migration (when GSK3B is not expressed)/ differentiation/ neurite growth/ synaptogenesis along with OE of each factor showed overall regulation of embryogenesis process in more than one regulatory state (RS1). Similarly, OE of genes positively regulating neurulation/ proliferation/ migration (when GSK3B is not expressed)/ differentiation/ neurite growth/ synaptogenesis/ neurodevelopment (when GSK3B is not expressed) along with OE of each factor showed

overall regulation of proliferation process in more than one regulatory state (RS1). These perturbation results show the definite role of certain factors (along with genes in other stages) in regulation of embryogenesis and proliferation stages.

PC5 (Simulations 1-4): When genes positively regulating each stage (regulated by DISC1 interactome) was KO along with each factor regulating the DISC1 interactome, each same stage was downregulated (0%).

Summary of the NP results for DISC1 interactome is given in Table 1 and Table 2.

B. GSK3B interactome

During prenatal development, GSK3B interactome has been shown to regulate embryogenesis, neurulation, proliferation, migration, neurite growth and synaptogenesis. Boolean rules for each of these stages has been given. We have given two different Boolean rules for migration stage, to specify the condition where GSK3B upregulation regulates migration and where GSK3B downregulation regulates migration. So, we also have two different Boolean rules to represent the regulation of overall neurodevelopmental process.

Single node perturbation analysis

Perturbation condition 1: OE and KO of each miRNA and each TF regulating GSK3B interactome

Simulations 1, 2 and 4: OE and KO of each miRNA and each TF downregulated each stage of neurodevelopment (0%) regulated by GSK3B interactome.

Simulation 3: In PC1, the overall neurulation process was shown to be regulated in all three different regulatory states (RS1), upregulation (100%), regulation between 0%-100% and downregulation (0%). OE of each miRNA/TF (except miR744, miR877, miR15a, miR15b, miR16, miR195, miR182, EP300, CREB1, STAT3, FOXM1) regulated neurulation (between 0% and 100%). Similarly, KO of each miRNA (except KO of miR15b/ CREB1) regulated neurulation (between 0% and 100%). OE of miR744/ miR877 downregulated neurulation

(0%). OE of miR15a/ miR15b/ miR16/ miR195/ miR182/ EP300/ CREB1/ STAT3/ FOXM1, upregulated neurulation (100%).

Multiple node perturbation analysis

Perturbation condition 2: OE of genes positively regulating each stage of neurodevelopment (regulated by GSK3B interactome) and OE of miRNAs and TFs regulating GSK3B interactome

Simulations 1-4: OE of genes positively regulating each stage of neurodevelopment (embryogenesis/ neurulation/ proliferation/ migration (when GSK3B is not expressed) /migration (when GSK3B is expressed)/ neurite growth/ synaptogenesis) along with OE of miRNAs and TFs, upregulated each same stage of neurodevelopment (100%). OE of genes positively regulating neurodevelopment (when GSK3B is not expressed) and OE of miRNAs and TFs, upregulated embryogenesis, neurulation, proliferation, migration (when GSK3B is not expressed), neurite growth and neurodevelopment (when GSK3B is not expressed) (100%).

a. Synaptogenesis

Simulations 1-4: OE of genes positively regulating migration (when GSK3B is expressed)/ neurodevelopment (when GSK3B is expressed) along with OE of miRNAs and TFs, also upregulated synaptogenesis (100%).

b. Migration (when GSK3B is expressed)

Simulations 1-4: OE of genes positively regulating neurodevelopment (when GSK3B is expressed) along with OE of miRNAs and TFs, upregulated migration (when GSK3B is expressed) and neurodevelopment (when GSK3B is expressed) (100%).

Perturbation condition 3: KO of genes positively regulating each stage of neurodevelopment (regulated by GSK3B interactome) and KO of miRNAs and TFs regulating GSK3B interactome

Simulations 1-4: KO of genes positively regulating each stage of neurodevelopment (embryogenesis/ neurulation/ proliferation/ migration/ neurite growth/ synaptogenesis/ neurodevelopment (when GSK3B is expressed)/ neurodevelopment (when GSK3B is not expressed)) and KO of miRNAs and TFs did not upregulate each same stage of neurodevelopment (0%).

Perturbation condition 4: OE of genes positively regulating each stage of neurodevelopment (regulated by GSK3B interactome) along with OE of each factor (miRNA/ TF) regulating GSK3B interactome

a. Embryogenesis

Simulations 1-4: OE of genes positively regulating embryogenesis along with OE of each miRNA/ TF, upregulated embryogenesis (100%). Similarly, OE of genes positively regulating neurodevelopment (GSK3B not expressed) and OE of each miRNA/TF, upregulated embryogenesis (100%).

Simulation 3: We observed overall regulation of embryogenesis in two different regulatory states (RS3), downregulation (0%) and regulation between 0%-100%. OE of genes positively regulating migration (when GSK3B not expressed)/ proliferation/ neurite growth along with OE of miR320a/SMAD4/NUCKS1/TEAD4 regulated embryogenesis (between 0% and 100%). OE of genes positively regulating migration (when GSK3B not expressed)/ proliferation/ neurite growth along with OE of each miRNA/ TF (except OE of miR320a/SMAD4/NUCKS1/TEAD4) downregulated embryogenesis (0%).

b. Neurulation

Simulation 1: We observed overall regulation of neurulation in two different regulatory states (RS4), upregulation (100%) and regulation between 0%-100%. OE of genes positively

regulating neurulation and OE of miR190a/ miR5011/ miR124/ TP53/ HNF4A regulated neurulation (between 0%-100%). Similarly, OE of genes positively regulating neurodevelopment (when GSK3B is not expressed) and OE of miR190a/ miR5011/ miR124/ TP53 /HNF4A regulated neurulation (between 0%-100%). OE of genes positively regulating neurodevelopment (when GSK3B not expressed)/ neurulation and OE of each miRNA/TF (except OE of miR190a/ miR5011/ miR124/ TP53 /HNF4A) upregulated neurulation (100%).

Simulation 2: OE of genes positively regulating neurulation/ neurodevelopment (when GSK3B is not expressed) and OE of each miRNA/TF upregulated neurulation (100%).

Simulation 3: We observed overall regulation of neurulation in three different regulatory states (RS1), upregulation (100%), regulation between 0%-100% and downregulation (0%). OE of genes either positively regulating embryogenesis/ migration (when GSK3B is not expressed)/ neurite growth/ proliferation/ neurulation/ neurodevelopment (when GSK3B is not expressed) and OE of EP300/STAT3/CREB1/FOXM1 downregulated neurulation (0%). OE of miR744/ miR877 along with OE of genes either positively regulating embryogenesis/ migration (when GSK3B is not expressed)/ neurite growth/ proliferation downregulated neurulation (0%). We also observed that OE of miR15a/ miR15b/ miR16/ miR195/ miR182 along with OE of genes either positively regulating embryogenesis/ migration (when GSK3B is not expressed)/ neurite growth/ proliferation/ neurulation/ neurodevelopment (when GSK3B is not expressed) upregulated neurulation (100%).

OE of genes positively regulating embryogenesis/ migration (when GSK3B is not expressed)/ neurite growth/ proliferation/ neurulation/ neurodevelopment (when GSK3B is not expressed) along with OE of each miRNA/TF (except OE of EP300/STAT3/CREB1/FOXM1/ miR15a/ miR15b/ miR16/ miR195/ miR182) regulated neurulation (between 0%-100%). Similarly, OE of each miRNA (except OE of miR744/ miR877) along with OE of genes

positively regulating embryogenesis/ migration (GSK3B is not expressed)/ neurite growth/ proliferation regulated neurulation (between 0%-100%).

Simulation 4: We observed overall regulation of embryogenesis in two different regulatory states (RS4), upregulation (100%) and regulation between 0%-100%. OE of genes positively regulating neurodevelopment (when GSK3B not expressed)/ genes positively regulating neurulation and OE of miR190a/miR5011/miR124/TP53/HNF4A regulated neurulation (between 0% - 100%). OE of genes positively regulating neurodevelopment (when GSK3B is not expressed)/ genes positively regulating neurulation and OE of each miRNA/TF (except miR190a/miR5011/miR124/TP53/HNF4A), upregulated neurulation (100%).

c. Proliferation

Simulations 1-4: OE of genes positively regulating proliferation/genes positively regulating neurodevelopment (when GSK3B is not expressed) and OE of each miRNA/TF, upregulated proliferation (100%).

Simulation 3: We observed overall regulation of proliferation process in three different regulatory states (RS1), upregulation (100%), regulation between 0%-100% and downregulation (0%). OE of genes either positively regulating embryogenesis/ migration (when GSK3B is not expressed)/ neurite growth and OE of miR155/ miR124/ TP53/ HNF4A/miR744 downregulated proliferation (0%). OE of genes either positively regulating embryogenesis/ migration (when GSK3B is not expressed)/ neurite growth and OE of miR190a/ miR5011 regulated proliferation (between 0% - 100%). However, OE of each miRNA/TF (except OE of miR155/ miR124/ TP53/ HNF4A/miR744/ miR190a/ miR5011) along with OE of genes either positively regulating embryogenesis/ migration (when GSK3B is not expressed)/ neurite growth showed upregulation of proliferation (100%).

d. Migration (when GSK3B is not expressed)

Simulations 1-4: OE of genes positively regulating migration (when GSK3B is not expressed)/ neurodevelopment (when GSK3B is not expressed) along with OE of each miRNA/TF, upregulated migration (100%).

e. Migration (when GSK3B is expressed)

Simulations 1-4: OE of genes positively regulating migration (when GSK3B is expressed)/ neurodevelopment (when GSK3B is expressed) along with OE of each miRNA/TF, upregulated migration (100%).

f. Neurite growth

Simulations 1-4: OE of genes positively regulating neurite growth/ neurodevelopment (when GSK3B is not expressed) along with OE of each miRNA/TF, upregulated neurite growth (100%).

g. Synaptogenesis

Simulations 1-4: OE of genes positively regulating migration (when GSK3B is expressed)/ genes positively regulating synaptogenesis/ genes positively regulating neurodevelopment (when GSK3B is expressed) along with OE of each miRNA/TF, upregulated synaptogenesis (100%).

h. Neurodevelopment (when GSK3B is not expressed)

Simulation 1: We observed regulation of overall neurodevelopment in two different regulatory states (RS4), upregulation (100%) and regulation between 0%-100%. OE of miR190a/ miR5011/ miR124/ TP53/ HNF4A and OE of genes positively regulating neurodevelopment (when GSK3B is not expressed) regulated neurodevelopment (between 0% - 100%). However, OE of each miRNA/TF (except OE of miR190a/ miR5011/ miR124/ TP53/ HNF4A) and OE of genes positively regulating neurodevelopment (when GSK3B is not expressed), upregulated neurodevelopment (100%).

Simulation 2: OE of genes positively regulating neurodevelopment (when GSK3B is not expressed) and OE of each miRNA/TF upregulated neurodevelopment (100%).

Simulation 3: We observed overall regulation of neurodevelopment in two different regulatory states (RS4), upregulation (100%) and regulation between 0%-100%. OE of EP300/ STAT3/ CREB1/ FOXM1/ miR15a/ miR15b/ miR16/ miR195/ miR182 and OE of genes positively regulating neurodevelopment (when GSK3B is not expressed) upregulated neurodevelopment (100%). OE of each miRNA/TF (except OE of EP300/ STAT3/ CREB1/ FOXM1/ miR15a/ miR15b/ miR16/ miR195/ miR182) and OE of genes positively regulating neurodevelopment (when GSK3B is not expressed) regulated neurodevelopment (between 0%-100%).

Simulation 4: We observed overall regulation of neurodevelopment in two different regulatory states (RS4), upregulation (100%) and regulation between 0%-100%. OE of genes positively regulating neurodevelopment (when GSK3B is not expressed) and OE of miR190a/ miR5011/ miR124/ TP53/ HNF4A regulated neurodevelopment (between 0% - 100%). OE of genes positively regulating neurodevelopment (when GSK3B is not expressed) and OE of each miRNA/TF (except OE of miR190a/ miR5011/ miR124/ TP53/ HNF4A) upregulated neurodevelopment (100%).

i. Neurodevelopment (when GSK3B is expressed)

Simulations 1-4: OE of genes positively regulating migration (when GSK3B is expressed)/ OE of genes positively regulating neurodevelopment (when GSK3B is expressed) along with OE of each miRNA/TF, upregulated neurodevelopment (100%).

Perturbation condition 5: KO of all genes positively regulating each stage of neurodevelopment (regulated by GSK3B interactome) along with KO of each miRNA and each TF regulating GSK3B interactome

Simulations 1-4: KO of all genes positively regulating each stage of neurodevelopment (embryogenesis/ neurulation/ proliferation/ migration/ neurite growth/ synaptogenesis/ neurodevelopment (when GSK3B is expressed)/ neurodevelopment (when GSK3B is not expressed)) and KO of each miRNA/TF downregulated each same stage of neurodevelopment (0%)

a. Neurulation

Simulation 1: We observed overall regulation of neurulation in two different regulatory states (RS2), upregulation (100%) and downregulation (0%). KO of miR744 and KO of genes positively regulating embryogenesis/ migration (when GSK3B is not expressed)/ migration (when GSK3B is expressed)/ neurite growth/ neurodevelopment (when GSK3B is expressed)/ proliferation/ synaptogenesis upregulated neurulation (100%). KO of each factor (except miR744) and KO of genes positively regulating embryogenesis/ migration (when GSK3B is not expressed)/ migration (when GSK3B is expressed)/ neurite growth/ neurodevelopment (when GSK3B is expressed)/ proliferation/ synaptogenesis downregulated neurulation (0%).

Simulation 2: KO of all genes positively regulating neurulation and KO of each miRNA/TF, downregulated neurulation (0%).

Simulation 3: We observed overall regulation of neurulation in two different regulatory states (RS3), downregulation (0%) and regulation between 0%-100%. KO of miR15b/ CREB1 and KO of genes positively regulating embryogenesis/ migration (when GSK3B is not expressed)/ neurite growth/ proliferation/ neurodevelopment (when GSK3B is not expressed)/ synaptogenesis, downregulated neurulation (0%). KO of each miRNA/TF (except

KO of miR15b and CREB1) and KO of genes embryogenesis/ migration (when GSK3B is not expressed)/ neurite growth/ proliferation/ neurodevelopment (when GSK3B is not expressed)/ synaptogenesis, regulated neurulation (between 0% - 100%).

Simulation 4: We observed overall regulation of neurulation in two different regulatory states (RS3), downregulation (0%) and regulation between 0%-100%. KO of AR and KO of genes positively regulating embryogenesis/ proliferation/ synaptogenesis regulated neurulation (between 0% - 100%). KO of each miRNA/TF (except AR) and KO of genes positively regulating embryogenesis/ proliferation/ synaptogenesis downregulated neurulation (0%).

Table 3: Perturbation results of GSK3B interactome involved in prenatal development

Perturbed nodes	PC	Effect of perturbation on each stage at t =150 (Activation frequency for 1000 simulations at t = 150)																			
		Embryogenesis				Neurulation				Proliferation				Migration (when GSK3B is not expressed)				Migration (when GSK3B is expressed)			
		Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4
Factors	1	0%	0%	0%	0%	0%	0%	RS1	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating embryogenesis and factors	2	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	0%	0%	RS1	0%	0%	0%	RS1	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	RS2	0%	RS3	RS3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurulation and factors	2	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	RS4	100%	RS1	RS4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating proliferation and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	RS3	0%	0%	0%	RS1	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	RS2	0%	RS3	RS3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating migration (when GSK3B is not expressed) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	RS3	0%	0%	0%	RS1	0%	0%	0%	RS1	0%	100%	100%	100%	100%	0%	0%	0%	0%
	5	0%	0%	0%	0%	RS2	0%	RS3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating migration (when GSK3B is expressed) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%
	5	0%	0%	0%	0%	RS2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurite growth and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

	4	0%	0%	0%	0%	0%	0%	RS1	0%	0%	0%	RS1	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	RS2	0%	RS3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating synaptogenesis and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	RS2	0%	RS3	RS3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment (when GSK3B is not expressed) and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	RS4	100%	RS1	RS4	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	RS3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment (when GSK3B is expressed) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%
	5	0%	0%	0%	0%	RS2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

PC: Perturbation condition; Sim1: Simulation 1; Sim2: Simulation 2; Sim3: Simulation 3; Sim4: Simulation 4; RS1 represents regulatory state 1, where PC leads to upregulation (100%), regulation between 0%-100% and downregulation (0%). RS2 represents regulatory state 2, where PC leads to upregulation (100%) and downregulation (0%); RS3 represents regulatory state 3, where PC leads to downregulation (0%) and regulation between 0%-100%; RS4 represents regulatory state RS4, where PC leads to upregulation (100%) and regulation between 0%-100%

Table 4: Perturbation results of GSK3B interactome involved in prenatal development (Contd)

Perturbed nodes	PC	Effect of perturbation on each stage at t =150 (Activation frequency for 1000 simulations at t = 150)															
		Neurite growth				Synaptogenesis				Neurodevelopment (when GSK3B is not expressed)				Neurodevelopment (when GSK3B is expressed)			
		Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4
Factors	1	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating embryogenesis and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

neurulation and factors	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating proliferation and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating migration (when GSK3B is not expressed) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating migration (when GSK3B is expressed) and factors	2	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	100%	100%	100%	100%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurite growth and factors	2	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating synaptogenesis and factors	2	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment (when GSK3B is not expressed) and factors	2	100%	100%	100%	100%	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	0%	0%	0%	0%	RS4	100%	RS4	RS4	0%	0%	0%	0%

	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment (when GSK3B is expressed) and factors	2	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	100%	100%	100%	100%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

PC: Perturbation condition; Sim1: Simulation 1; Sim2: Simulation 2; Sim3: Simulation 3; Sim4: Simulation 4; 100% - upregulation; 0% - downregulation

Summary of perturbation results of GSK3B interactome involved in prenatal regulation

PC1 (Simulations 1, 2 and 4): Perturbation of each factor regulating GSK3B interactome showed that none of the factor was individually involved in upregulation of stages of development.

Simulation 3: Perturbation of each factor showed neurulation to be regulated in all three different regulatory states (RS1). Overall regulation of neurulation was shown to be regulated in three different regulatory states (RS1), upregulation (100%), regulation between 0%-100% as well downregulation (0%).

PC2 (Simulations 1-4): OE of genes positively regulating each stage of development regulated by GSK3B interactome along with OE of all factors regulating GSK3B interactome, upregulated each same stage of development. OE of genes positively regulating migration (when GSK3B is expressed) along with OE of all factors, upregulated (100%) synaptogenesis and neurodevelopment (when GSK3B is expressed). OE of genes positively regulating neurodevelopment (when GSK3B is not expressed), upregulated (100%) all the stages except neurodevelopment (when GSK3B is expressed) and migration (when GSK3B is expressed). Similarly, OE of genes positively regulating neurodevelopment (when GSK3B is expressed) upregulated migration (when GSK3B is expressed) and neurodevelopment (when GSK3B is expressed) (100%).

PC3 (Simulations 1-4): KO of genes positively regulating each stage of development regulated by GSK3B interactome along with KO of factors regulating GSK3B interactome, downregulated each same stage of development (0%).

PC4 (Simulations 1-4): OE of genes positively regulating each stage of development regulated by GSK3B interactome (except neurulation, proliferation and embryogenesis) along with OE of each miRNA and each TF upregulated each same stage of development

(100%). OE of genes positively regulating migration (when GSK3B is expressed) along with OE of each factor, upregulated (100%) synaptogenesis and neurodevelopment (when GSK3B is expressed).

Simulations 1 and 4: OE of genes positively regulating neurulation along with OE of each factor, showed overall regulation of neurulation in two different regulatory states (RS4), upregulation (100%) and regulation b/w 0%-100%.

Simulation 3: OE of genes positively regulating neurulation/ proliferation along with OE of each factor, showed regulation of each same stage in three different regulatory states (RS1), upregulation (100%), regulation b/w 0%-100% as well as downregulation (0%). OE of genes positively regulating embryogenesis along with OE of each factor, showed overall regulation of embryogenesis in two different regulatory states (RS4), upregulation (100%) and regulation b/w 0%-100%.

At simulations 1,2 and 4, perturbation of genes involved in proliferation/ embryogenesis along with perturbation of each factor showed upregulation of embryogenesis and proliferation (100%). Similarly, at simulation 2, perturbation of genes involved in neurulation along with perturbation of each factor showed upregulation of neurulation (100%).

Simulations 1, 3 and 4: OE of genes positively regulating neurodevelopment (when GSK3B is not expressed) along with OE of each factor, showed overall regulation of neurodevelopment process in two different regulatory states (RS4), upregulation (100%) and regulation b/w 0%-100%.

PC5 (Simulations 1-4): KO of genes positively regulating each stage of development regulated by GSK3B interactome (except neurulation and neurodevelopment (when GSK3B is not expressed)) along with KO of each miRNA and each TF downregulated each same stage of development (0%).

Simulations 1, 3 and 4: KO of genes positively regulating neurulation/ neurodevelopment (when GSK3B is not expressed) regulated by GSK3B interactome along with KO of each miRNA and each TF showed overall regulation of neurulation process in more than one regulatory state, RS2 (downregulation (0%) and upregulation (100%)) at simulation 1, RS3 (regulation b/w 0%-100% and downregulation (0%)) at simulations 3 and 4. The overall neurodevelopment process was shown to affected by genes regulating neurulation.
At simulation 2, KO of genes positively regulating neurulation/ neurodevelopment (when GSK3B is not expressed) regulated by GSK3B interactome showed downregulation of both the stages (0%). Summary of the NP results for GSK3B interactome is given in Table 3 and Table 4.

C. BDNF interactome

During prenatal development, BDNF interactome regulates proliferation, migration, differentiation, neurite growth and synaptogenesis. Self-regulated NOS1 downregulates differentiation, whereas NOS1 expression which is regulated by BDNF, upregulates differentiation. So, two different Boolean rules have been given for differentiation and the overall neurodevelopment process (all the stages regulated by BDNF combined as one stage).

Single node perturbation

Perturbation condition 1: OE and KO of each miRNA and each TF regulating BDNF interactome

Simulations 1-4: OE and KO of each miRNA and each TF downregulated each of the above-mentioned stages of neurodevelopment and the overall neurodevelopment process regulated by BDNF interactome.

Multiple node perturbation

Perturbation condition 2: OE of genes positively regulating each stage of neurodevelopment (regulated by BDNF interactome) and OE of miRNAs and TFs regulating BDNF interactome

Simulations 1-4: OE of genes positively regulating each stage of neurodevelopment (proliferation/migration/ differentiation (when NOS1 is regulated by BDNF) / differentiation (when NOS1 is self-regulated)/ neurite growth/ synaptogenesis) along with OE of miRNAs and TFs, upregulated each same stage of neurodevelopment (100%). OE of genes positively regulating neurodevelopment (when NOS1 is self-regulated) along with OE of miRNAs and TFs, upregulated (100%) each stage of development. OE of genes positively regulating neurodevelopment (when NOS1 is regulated by BDNF) along with OE of miRNAs and TFs upregulated each stage of development (100%) but did not upregulate neurodevelopment process (when NOS1 is self-regulated).

a. Proliferation

Simulations 1-4: OE of genes positively regulating each stage of neurodevelopment migration/ (differentiation (when NOS1 is regulated by BDNF) / differentiation (when NOS1 is self-regulated)/ neurite growth/ synaptogenesis) as well as OE of genes positively regulating overall neurodevelopment process (neurodevelopment (when NOS1 is regulated by BDNF), neurodevelopment (when NOS1 is self-regulated) along with OE of miRNAs and TFs, upregulated proliferation (100%).

a. Migration

Simulations 1-4: OE of genes positively regulating each stage of neurodevelopment proliferation/ (differentiation (when NOS1 is regulated by BDNF) / differentiation (when NOS1 is self-regulated)/ neurite growth/ synaptogenesis) as well as OE of genes positively regulating overall neurodevelopment process (neurodevelopment (NOS1 is regulated by

BDNF)), neurodevelopment (when NOS1 is self-regulated) along with OE of miRNAs and TFs, upregulated proliferation (100%).

c. Differentiation (when NOS1 is regulated by BDNF)

Simulations 1-4: OE of genes positively regulating each stage of neurodevelopment (proliferation/ migration/ differentiation (when NOS1 is self-regulated)/ neurite growth/ synaptogenesis) as well as OE of genes positively regulating overall neurodevelopment process (neurodevelopment (when NOS1 is regulated by BDNF), neurodevelopment (when NOS1 is self-regulated) along with OE of miRNAs and TFs, upregulated differentiation (100%).

Perturbation condition 3: KO of genes positively regulating each stage of neurodevelopment (regulated by BDNF interactome) and KO of miRNAs and TFs regulating BDNF interactome

Simulations 1-4: KO of genes positively regulating each stage of neurodevelopment (proliferation/ migration/ differentiation (when NOS1 is regulated by BDNF)/ differentiation (when NOS1 is self-regulated)/ neurite growth/ synaptogenesis/ neurodevelopment (when NOS1 is regulated by BDNF)/ neurodevelopment (when NOS1 is self-regulated)) and KO of miRNAs and TFs, downregulated each same stage of neurodevelopment (0%).

Perturbation condition 4: OE of all genes positively regulating each stage of neurodevelopment (regulated by BDNF interactome) along with OE of each factor (miRNA/TF) regulating BDNF interactome

a. Proliferation

Simulations 1-4: OE of genes positively regulating proliferation/ migration/ differentiation (when NOS1 is regulated by BDNF)/ differentiation (when NOS1 is self-regulated)/ neurite growth/ synaptogenesis/ neurodevelopment (when NOS1 is self-regulated)/ neurodevelopment (when NOS1 is regulated by BDNF) along with OE of each miRNA/TF upregulated proliferation (100%).

b. Migration

Simulations 1-4: OE of genes positively regulating proliferation/ migration/ differentiation (when NOS1 is regulated by BDNF)/ differentiation (when NOS1 is self-regulated)/ neurite growth/ synaptogenesis/ neurodevelopment (when NOS1 is self-regulated)/ neurodevelopment (when NOS1 is regulated by BDNF) along with OE of each miRNA/TF upregulated proliferation (100%).

c. Differentiation (when NOS1 is regulated by BDNF)

Simulations 1-4: OE of genes positively regulating differentiation (when NOS1 is regulated by BDNF)/ differentiation (when NOS1 is self-regulated)/ neurite growth/ proliferation/ migration/ synaptogenesis/ neurodevelopment (when NOS1 is regulated by BDNF)/ neurodevelopment (when NOS1 is self-regulated) and OE of each miRNA/TF upregulated differentiation (100%).

d. Differentiation (when NOS1 is self-regulated)

Simulations 1-4: OE of genes positively regulating differentiation (when NOS1 is self-regulated) / neurodevelopment (when NOS1 is self-regulated) and OE of each miRNA/TF, upregulated differentiation (100%).

Simulation 3: We observed overall regulation of differentiation in all three regulatory states (RS1), upregulation (0%), regulation between 0%-100% and downregulation (0%). OE of genes positively regulating differentiation (when NOS1 is regulated by BDNF)/ neurite growth/ proliferation/ migration/ neurodevelopment (when NOS1 is regulated by BDNF)/ synaptogenesis along with OE of miR22/ SOX2 regulated differentiation (between 0%-100%). OE of genes positively regulating differentiation (when NOS1 is regulated by BDNF)/ neurite growth/ proliferation/ migration/ neurodevelopment (when NOS1 is regulated by BDNF)/ synaptogenesis and OE of miR149/ miR4728/ miR5698/ miR625/ miR6785/ miR6825/ miR6883, downregulated differentiation (0%). However, OE of genes positively

regulating differentiation (when NOS1 is regulated by BDNF)/ neurite growth/ proliferation/ migration/ neurodevelopment (when NOS1 is regulated by BDNF)/ synaptogenesis and OE of each miRNA/TF (except OE of miR149/ miR4728/ miR5698/ miR625/ miR6785/ miR6825/ miR6883/ miR22/ SOX2), upregulated differentiation (100%).

e. Neurite growth

Simulations 1-4: OE of genes positively regulating neurite growth/ neurodevelopment (when NOS1 is regulated by BDNF)/ neurodevelopment (when NOS1 is self-regulated) along with OE of each miRNA/each TF, upregulated neurite growth (100%).

f. Synaptogenesis

Simulations 1-4: OE of genes positively regulating synaptogenesis/ neurodevelopment (when NOS1 is regulated by BDNF)/ neurodevelopment (when NOS1 is self-regulated) along with OE of each miRNA/each TF, upregulated synaptogenesis (100%).

g. Neurodevelopment (when NOS1 is regulated by BDNF)

Simulations 1-4: OE of genes positively regulating neurodevelopment (when NOS1 is regulated by BDNF)/ genes positively regulating neurodevelopment (when NOS1 is self-regulated) and OE of each miRNA/TF, upregulated neurodevelopment (100%).

h. Neurodevelopment (when NOS1 is not expressed)

Simulations 1-4: OE of genes positively regulating genes positively regulating neurodevelopment (when NOS1 is self-regulated) and OE of each miRNA/ TF, upregulated neurodevelopment (100%).

Perturbation condition 5: KO of genes positively regulating each stage of neurodevelopment (regulated by BDNF interactome) along with KO of each miRNA and each TF regulating BDNF interactome

Simulations 1-4: KO of genes positively regulating each stage of neurodevelopment (proliferation/ migration/ differentiation/ neurite growth/ synaptogenesis/ neurodevelopment (when NOS1 is regulated by BDNF)/ neurodevelopment (when NOS1 is

self-regulated)) and KO of each miRNA/ TF, downregulated each same stage of neurodevelopment (0%).

Table 5: Perturbation results of BDNF interactome involved in prenatal development

Perturbed stages	PC	Effect of perturbation on each stage at t =150 (Activation frequency for 1000 simulations at t = 150)															
		Proliferation				Migration				Differentiation (when NOS1 is regulated by BDNF)				Differentiation (when NOS1 self-regulated)			
		Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4
Factors	1	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating proliferation and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	RS1	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating migration and factors		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%
		0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
		100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	RS1	0%
		0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating differentiation (when NOS1 is regulated by BDNF) and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	RS1	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating differentiation (when NOS1 is self-regulated) and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurite growth and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	RS1	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating	2	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%

synaptogenesis and factors	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	RS1	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment (when NOS1 is regulated by BDNF) and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	RS1	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment (when NOS1 is self-regulated) and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

PC: Perturbation condition; Sim1: Simulation 1; Sim2: Simulation 2; Sim3: Simulation 3; Sim4: Simulation 4; RS1 represents regulatory state RS1, where PC leads to upregulation (100%), regulation between 0%-100% and downregulation (0%).

Table 6: Perturbation results of BDNF interactome involved in prenatal development (Contd)

Perturbed stages	PC	Effect of perturbation on each stage at t =150 (Activation frequency for 1000 simulations at t = 150)															
		Neurite growth				Synaptogenesis				Neurodevelopment (when NOS1 is regulated by BDNF)				Neurodevelopment (when NOS1 is self-regulated)			
		Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4
Factors	1	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating proliferation and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating migration and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

Genes positively regulating differentiation (when NOS1 is regulated by BDNF) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating differentiation (when NOS1 is self-regulated) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurite growth and factors	2	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating synaptogenesis and factors	2	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment (when NOS1 is regulated by BDNF) and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment (when NOS1 is self-regulated) and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

PC: Perturbation condition; Sim1: Simulation 1; Sim2: Simulation 2; Sim3: Simulation 3; Sim4: Simulation 4; Upregulation (100), downregulation (0%)

Summary of perturbation results of BDNF interactome involved in prenatal development

PC1 (Simulations 1-4): Each stage of neurodevelopment regulated by BDNF interactome was shown to be downregulated (0%), showing the individual regulatory effect of each factor on each stage of neurodevelopment. As each factor is involved in FFLs, perturbation of each factor, affects the expression of either miRNA or TF, which in turn affects gene expression. But no factor was shown to be involved in upregulation of the any one of the stages of neurodevelopment regulated by BDNF interactome.

PC2 (Simulations 1-4): OE of genes positively regulating each stage of neurodevelopment along with OE of miRNAs and TFs regulating BDNF interactome, upregulated each same stage of development. In addition, differentiation (when NOS1 is regulated by BDNF), proliferation and migration stages were also shown to be upregulated (100%), when genes positively regulating other stages were OE along with factors regulating BDNF interactome. OE of genes positively regulating neurodevelopment (when NOS1 is self-regulated) along with OE of all factors, upregulated each stage of development. But OE of genes positively regulating neurodevelopment (when NOS1 is regulated by BDNF) along with OE of factors upregulated each stage (100%) except differentiation (when NOS1 is self-regulated) and neurodevelopment (when NOS1 is self-regulated).

PC3 (Simulations 1-4): KO of genes positively regulating each stage of development along with KO of miRNAs and TFs regulating BDNF interactome, upregulated each same stage of development.

PC4 (Simulations 1-4): OE of genes positively regulating each stage of development along with OE of each factor regulating BDNF interactome, upregulated (100%) each same stage of development. In addition, differentiation (when NOS1 is regulated by BDNF), proliferation and migration stages were also shown to be upregulated (100%), when genes positively regulating other stages were OE along with each factor regulating BDNF interactome. OE of

BDNF in other stages, upregulated proliferation, migration and differentiation stages (when NOS1 is regulated by BDNF). OE of genes positively regulating neurodevelopment (when NOS1 is self-regulated) along with OE of each factor, upregulated each stage of development. But OE of genes positively regulating neurodevelopment (when NOS1 is regulated by BDNF) along with OE of each factor upregulated each stage (100%) except differentiation (when NOS1 is self-regulated) and neurodevelopment (when NOS1 is self-regulated).

Simulation 3: OE of genes positively regulating each stage (except differentiation (when NOS1 is self-regulated) and neurodevelopment (when NOS1 is self-regulated) along with OE of each factor, regulated overall differentiation (when NOS1 is self-regulated) process in all three different regulatory states (RS1), upregulation, downregulation and regulation between 0%-100%. As TF downregulates miRNA expression in simulation 3, NGFR expression is either regulated between 0%-100% or upregulated, which in turn either regulates (b/w 0%-100%) or upregulates (100%) differentiation (when NOS1 is self-regulated). NGFR expression is also downregulated as miRNA repress NGFR expression, downregulating (0%) differentiation (when NOS1 is self-regulated).

At simulations 1, 2 and 4, OE of genes positively regulating each stage (except differentiation (when NOS1 is self-regulated) and neurodevelopment (when NOS1 is self-regulated)) along with OE of each factor, downregulated differentiation (when NOS1 is self-regulated) (0%).

PC5 (Simulations 1-4): OE of genes positively regulating each stage of development along with OE of each factor regulating BDNF interactome, downregulated (0%) each same stage

of development. Summary of the NP results for BDNF interactome is given in Table 5 and Table 6.

D. GRM5 interactome

GRM5 interactome regulates proliferation, differentiation and synaptogenesis during prenatal development.

Single node perturbation

Perturbation condition 1: OE and KO of each miRNA and each TF regulating GRM5 interactome

Simulations 1-4: OE and KO of each miRNA and each TF regulating GRM5 interactome downregulated (0%) each stage of neurodevelopment and the overall neurodevelopment process (all the stages regulated by GRM5 are combined as one stage).

Multiple node perturbation

Perturbation condition 2: OE of genes positively regulating each stage of neurodevelopment (regulated by GRM5 interactome) and OE of miRNAs and TFs regulating GRM5 interactome

Simulations 1-4: OE of genes positively regulating each stage of neurodevelopment (proliferation/ differentiation/ synaptogenesis) and OE of miRNAs and TFs, upregulated each same stage of neurodevelopment (100%). OE of genes positively regulating neurodevelopment and OE of miRNAs and TFs, upregulated all the stages of neurodevelopment (100%).

a. Proliferation

Simulations 1-4: OE of genes positively regulating differentiation/ neurodevelopment and OE of miRNAs and TFs, upregulated proliferation (100%).

b. Differentiation

Simulations 1-4: OE of genes positively regulating proliferation/ neurodevelopment and OE of miRNAs and TFs, upregulated differentiation (100%).

Perturbation condition 3: KO of genes positively regulating each stage of neurodevelopment (regulated by GRM5 interactome) and KO of miRNAs and TFs regulating GRM5 interactome)

Simulations 1-4: KO of genes positively regulating each stage of neurodevelopment (proliferation/ differentiation/ synaptogenesis) and KO of miRNAs and TFs, downregulated each stage of neurodevelopment (0%).

Perturbation condition 4: OE of genes positively regulating each stage of neurodevelopment (regulated by GRM5 interactome) along with OE of each factor (miRNA/TF) regulating GRM5 interactome

a. Proliferation

Simulations 1-4: OE of genes positively regulating proliferation/ differentiation/ neurodevelopment and OE of each miRNA and each TF, upregulated proliferation (100%).

Simulations 1, 3 and 4: Synaptogenesis was shown to be regulated in two different regulatory states (RS3), downregulation (0%) and regulation between 0%-100%. OE of genes positively regulating synaptogenesis and OE of miR4719 regulated proliferation (between 0%-100%). OE of genes positively regulating synaptogenesis and OE of each factor (except OE of miR4719) downregulated proliferation (0%).

b. Differentiation

Simulations 1-4: OE of genes positively regulating proliferation/ differentiation/ neurodevelopment and OE of each miRNA and each TF, upregulated differentiation (100%).

Simulations 1, 3 and 4: Overall differentiation was shown to be regulated in two different regulatory states (RS3), downregulation (0%) and regulation between 0%-100%. OE of genes positively regulating synaptogenesis and OE of miR4719 regulated differentiation (between 0%-100%). OE of genes positively regulating differentiation and OE of each factor (except OE of miR4719) downregulated differentiation (0%).

c. Synaptogenesis

Simulations 1-4: OE of genes positively regulating synaptogenesis/ neurodevelopment and OE of each miRNA and each TF, upregulated synaptogenesis (100%).

d. Neurodevelopment

Simulations 1-4: OE of genes positively regulating neurodevelopment and OE of each miRNA and each TF, upregulated all the stages of neurodevelopment (100%).

Simulations 1, 3 and 4: Neurodevelopment was shown to be regulated in two different regulatory states (RS3), downregulation (0%) and regulation between 0%-100%. OE of genes positively regulating neurodevelopment and OE of miR4719 regulated neurodevelopment (between 0%-100%). OE of genes positively regulating neurodevelopment and OE of each factor (except OE of miR4719) downregulated differentiation (0%).

Perturbation condition 5: KO of genes positively regulating each stage of neurodevelopment (regulated by GRM5 interactome) along with KO of each factor (miRNA/ TF) regulating GRM5 interactome

Simulations 1-4: KO of genes positively regulating each stage of neurodevelopment (proliferation/ neurite growth/ synaptogenesis/ neurodevelopment) and KO of each miRNA/ TF, downregulated each stage of neurodevelopment (0%).

Table 7: Perturbation results of GRM5 interactome involved in prenatal neurodevelopment

Perturbed nodes	PC	Effect of perturbation on each stage at t =150 (Activation frequency for 1000 simulations at t = 150)															
		Proliferation				Differentiation				Synaptogenesis				Neurodevelopment			
		Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4
Factors	1	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating proliferation and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating differentiation and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating synaptogenesis and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	RS3	0%	RS3	RS3	RS3	0%	RS3	RS3	100%	100%	100%	100%	RS3	0%	RS3	RS3
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

PC: Perturbation condition; Sim1: Simulation 1; Sim2: Simulation 2; Sim3: Simulation 3; Sim4: Simulation 4; RS3 represents regulatory state 3, where PC leads to downregulation (0%) and regulation between 0%-100%.

Summary of node perturbation results of GRM5 interactome involved in prenatal development

PC1 (Simulations 1-4): Perturbation of each factor showed downregulation (0%) of each stage of development, regulated by GRM5 interactome.

PC2 (Simulations 1-4): OE of genes positively regulating each stage of development along with OE of miRNAs and TFs regulating GRM5 interactome, upregulated each same stage of development (100%). OE of genes positively regulating differentiation along with OE of all factors upregulated proliferation (100%). OE of genes positively regulating proliferation along with OE of all factors upregulated differentiation (100%). Genes GRM5, ERK1, ERK2 are involved in positive regulation of both proliferation and differentiation stages, so OE of genes positively regulating either proliferation/ differentiation along with OE of all factors, upregulates both stages.

PC3 (Simulations 1-4): KO of genes positively regulating each stage of development along with KO of all factors, downregulated each same stage of development (0%).

PC4 (Simulations 1-4): OE of genes positively regulating each stage of development along with OE of each factor, upregulated each same stage of development (100%).

Simulations 1, 3 and 4: OE of genes positively regulating synaptogenesis along with OE of each factor, regulated each stage of development (except synaptogenesis) in more than one regulatory state (RS3), regulation between 0%-100% and downregulation (0%). OE of miR4719 along with OE of genes positively regulating synaptogenesis regulates GRM5 expression, in turn regulating each stage between 0%-100% (except synaptogenesis). OE of each factor (except OE of miR4719) along with OE of genes positively regulating synaptogenesis, downregulated each stage (0%).

At simulation 2, OE of genes positively regulating synaptogenesis along with OE of each factor, downregulated (0%) each stage of development (except synaptogenesis).

PC5 (Simulations 1-4): KO of genes positively regulating each stage of development along with KO of each factor, downregulated each same stage of development (0%). Summary of the NP results for GRM5 interactome is given in Table 7.

E. NRG1 interactome

NRG1 interactome regulates proliferation, migration, neurite growth and synaptogenesis during prenatal development. NRG1 gene was shown to be regulated by miR124, in turn miR124 has been shown to be regulated by TFs, STAT3, REST, EGR1 and TP53 (TF-miRNA FFLs). The direction of regulation of miRNA by these four TFs is known from experimental evidence, where STAT3 and REST represses miR124 expression and EGR1 and TP53activates miR124 expression. So, rule for miR124 is same across all four simulations. Furthermore, the Boolean rules for simulation 1 and 3 also remains same, as TF upregulates gene expression in both simulations and the TF regulation of miRNA expression remains same in both the simulations. Similarly, Boolean rules for simulations 2 and 4 are same, as TF downregulates gene expression in both the simulations and the TF regulation of miRNA expression remains same in both the simulations.

Single node perturbation

Perturbation condition 1: OE and KO of each miRNA and each TF regulating NRG1 interactome

Simulations 1-4: OE and KO of each miRNA and each TF regulating NRG1 interactome, downregulated (0%) each stage of neurodevelopment and the overall neurodevelopment process (all the stages regulated by NRG1 interactome were combined into one stage).

Multiple node perturbation

Perturbation condition 2: OE of genes positively regulating each stage of neurodevelopment (regulated by NRG1 interactome) and OE of miRNAs and TFs regulating NRG1 interactome

Simulations 1-4: OE of genes positively regulating each stage of neurodevelopment (proliferation/ migration/ neurite growth/ synaptogenesis) and OE of miRNAs and TFs, upregulated each stage of neurodevelopment (100%). OE of genes positively regulating overall neurodevelopment and OE of miRNAs and TFs, upregulated the above-mentioned stages of neurodevelopment (100%).

a. Proliferation

Simulations 1-4: OE of genes positively regulating migration/ neurite growth/ synaptogenesis/ neurodevelopment and OE of miRNAs and TFs, upregulated proliferation (100%).

Perturbation condition 3: KO of genes positively regulating each stage of neurodevelopment (regulated by NRG1 interactome) and KO of miRNAs and TFs regulating NRG1 interactome

Simulations 1-4: KO of genes positively regulating each stage of neurodevelopment (proliferation/ migration/ neurite growth/ synaptogenesis) and KO of miRNAs and TFs, downregulated each stage of neurodevelopment (0%).

Perturbation condition 4: OE of genes positively regulating each stage of neurodevelopment (regulated by NRG1 interactome) along with OE of each miRNA and each TF regulating NRG1 interactome

a. Proliferation

Simulations 1-4: OE of genes positively regulating proliferation/ migration/ neurite growth/ synaptogenesis/ overall neurodevelopment process and OE of each miRNA/TF, upregulated proliferation (100%).

b. Migration

Simulations 1-4: OE of genes positively regulating migration/neurodevelopment and OE of each miRNA/TF, upregulated migration (100%).

Simulations 1 and 3: We observed overall regulation of migration process in all three different regulatory states (RS1), upregulation (100%), regulation between 0%-100% and downregulation (0%). OE of miR124 and OE of genes positively regulating proliferation/ neurite growth/ synaptogenesis, downregulated migration (0%). Similarly, OE of TP53 and OE of genes positively regulating proliferation/ neurite growth/ synaptogenesis regulated migration (between 0%-100%). OE of each factor (except miR124/TP53) and OE of genes positively regulating proliferation/ neurite growth/ synaptogenesis upregulated migration (100%).

c. Neurite growth

Simulations 1-4: OE of genes positively regulating neurite growth/neurodevelopment and OE of each miRNA and each TF, upregulated neurite growth (100%).

d. Synaptogenesis

Simulations 1-4: OE of genes positively regulating synaptogenesis/neurodevelopment and OE of each miRNA/TF, upregulated synaptogenesis (100%).

e. Neurodevelopment

Simulations 1-4: OE of genes positively regulating neurodevelopment and OE of each miRNA/TF, upregulated neurodevelopment (100%).

Perturbation condition 5: KO of genes positively regulating each stage of neurodevelopment (regulated by NRG1 interactome) along with KO of each miRNA and each TF regulating NRG1 interactome

Simulations 1-4: KO of genes positively regulating each stage of neurodevelopment (proliferation/ migration/ neurite growth/ synaptogenesis/ neurodevelopment) and KO of each miRNA/TF, downregulated each same stage of neurodevelopment (0%).

Table 8: Perturbation results of NRG1 interactome involved in prenatal development

Perturbed nodes	PC	Effect of perturbation on each stage at t =150 (Activation frequency for 1000 simulations at t = 150)											
		Proliferation				Migration				Neurite growth			
		Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4
Factors	1	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating proliferation and factors	2	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	RS1	0%	RS1	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating migration and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurite growth and factors	2	100%	100%	100%	100%	0%	0%	0%	0%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	RS1	0%	RS1	0%	100%	100%	100%	100%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating synaptogenesis and factors	2	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	RS1	0%	RS1	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

PC: Perturbation condition; Sim1: Simulation 1; Sim2: Simulation 2; Sim3: Simulation 3; Sim4: Simulation 4; RS1 represents regulatory state RS1, where PC1 leads to upregulation (100%), downregulation (0%) and regulation between 0%-100%

Table 9: ***Perturbation results of NRG1 interactome involved in prenatal development (contd)***

Perturbed nodes	PC	Effect of perturbation on each stage at t =150 (Activation frequency for 1000 simulations at t = 150)							
		Synaptogenesis				Neurodevelopment			
		Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4
Factors	1	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating proliferation and factors	2	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating migration and factors	2	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurite growth and factors	2	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%

	4	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating synaptogenesis and factors	2	100%	100%	100%	100%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment and factors	2	100%	100%	100%	100%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%
	5	0%	0%	0%	0%	0%	0%	0%	0%

Summary of node perturbation results of NRG1 interactome involved in prenatal development

PC1 (Simulations 1-4): Perturbation of each factor downregulated each stage of development (0%).

PC2 (simulations 1-4): OE of each gene positively regulating each stage of development along with OE of all factors, upregulated each same stage of development (100%) as well as proliferation stage (100%).

PC3 (Simulations 1-4): KO of each gene positively regulating each stage of development along with KO of all factors, downregulated each stage of development (0%).

PC4 (Simulations 1-4): OE of genes positively regulating each stage of development along with OE of each factor, upregulated (100%) each same stage of development.

Simulations 1 and 3: OE of genes positively regulating each stage, overall regulated migration in three regulatory states (RS1), upregulation (100%) regulation between 0%-100% and downregulation (0%). NRG1 OE in other stages upregulated migration and when miRNA downregulates TF expression, ERBB2 expression is regulated, in turn regulating migration between 0%-100%. When miRNA repress gene expression, migration is downregulated (0%).

Simulations 2 and 4: OE of genes positively regulating each stage, downregulated migration (0%), as TF downregulates gene expression at simulations 2 and 4.

PC5 (Simulations 1-4): KO of genes positively regulating each stage of development along with KO of each factor, downregulated (0%) each same stage of development. Summary of the NP results for NRG1 interactome is given in Table 8 and Table 9.

F. YWHAE interactome

During prenatal development, YWHAE interactome regulates migration and neurite growth. YWHAE regulates migration at 2 different conditions, when GSK3B is expressed as well as when GSK3B is not expressed. So, two different Boolean rules have been given for migration as well as the overall neurodevelopment process.

Single node perturbation

Perturbation condition 1: OE and KO of each miRNA and each TF regulating YWHAE interactome

Simulations 1-4: OE and KO of each miRNA and each TF downregulated (0%) the above-mentioned stages of neurodevelopment and the overall neurodevelopment process (all the stages regulated by YWHAE interactome were combined as one stage)

Multiple node perturbation

Perturbation condition 2: OE of genes regulating each stage of neurodevelopment regulated by YWHAE interactome and OE of miRNAs and TFs regulating YWHAE interactome

Simulations 1-4: OE of genes positively regulating each stage of neurodevelopment (migration and neurite growth) and OE of miRNAs and TFs, upregulated (100%) each same stage of neurodevelopment. OE of genes positively regulating neurodevelopment (when GSK3B is not expressed) and OE of miRNAs and TFs upregulated (100%) migration (when GSK3B is not expressed) and neurodevelopment (when GSK3B is not expressed). OE of genes positively regulating neurodevelopment (when GSK3B is expressed) upregulated

(100%) migration (when GSK3B is expressed), neurite growth and neurodevelopment (when GSK3B is expressed)

Perturbation condition 3: KO of genes positively regulating each stage of neurodevelopment regulated by YWHAE interactome and KO of miRNAs and TFs regulating YWHAE interactome)

Simulations 1-4: KO of genes positively regulating each stage of neurodevelopment (migration/ neurite growth/ neurodevelopment) and KO of miRNAs and TFs, downregulated each same stage of neurodevelopment (0%).

Perturbation condition 4: OE of genes positively regulating each stage of neurodevelopment (regulated by YWHAE interactome) along with OE of each miRNA and each TF regulating YWHAE interactome

a. Migration (when GSK3B is expressed)

Simulations 1-4: OE of genes positively regulating migration (when GSK3B is expressed)/ neurodevelopment (when GSK3B is expressed) and OE of each miRNA/ TF, upregulated migration (100%).

b. Migration (when GSK3B is not expressed)

Simulations 1-4: OE of genes positively regulating migration (when GSK3B is not expressed)/ neurodevelopment (when GSK3B is not expressed) and OE of each miRNA/TF, upregulated migration (100%).

c. Neurite growth

Simulations 1-4: OE of genes positively regulating neurite growth/ neurodevelopment (when GSK3B is expressed) and OE of each miRNA/TF, upregulated neurite growth (100%).

d. Neurodevelopment (when GSK3B is expressed)

Simulations 1-4: OE of genes positively regulating neurodevelopment (when GSK3B is expressed) and OE of each miRNA/TF, upregulated neurodevelopment (100%).

e. Neurodevelopment (when GSK3B is not expressed)

Simulations 1-4: OE of genes positively regulating neurodevelopment (when GSK3B is not expressed)/ migration (when GSK3B is not expressed) and OE of each miRNA/TF, upregulated neurodevelopment (100%).

Perturbation condition 5: KO of genes positively regulating each stage of neurodevelopment (regulated by YWHAE interactome) along with KO of each miRNA and each TF regulating YWHAE interactome

Simulations 1-4: KO of all genes positively regulating each stage of neurodevelopment (migration and neurite growth) along with KO of each miRNA/TF, downregulated each same stage of neurodevelopment (0%).

Table 10: Perturbation results of YWHAE interactome involved in prenatal development

Perturbed nodes	PC	Effect of perturbation on each stage at t =150 (Activation frequency for 1000 simulations at t = 150)																			
		Migration (when GSK3B is expressed)				Migration (when GSK3B is not expressed)				Neurite growth				Neurodevelopment (when GSK3B is expressed)				Neurodevelopment (when GSK3B is not expressed)			
		Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4
Factors	1	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating migration (when GSK3B is expressed) and factors	2	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating migration (when GSK3B is not expressed) and factors	2	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurite growth and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment (when GSK3B is expressed) and factors	2	100%	100%	100%	100%	0%	0%	0%	0%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	0%	0%	0%	0%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment (when GSK3B is not expressed) and factors	2	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

PC: Perturbation condition; Sim1: Simulation 1; Sim2: Simulation 2; Sim3: Simulation 3; Sim4: Simulation 4; Upregulation (100%); Downregulation (0%)

Summary of node perturbation results of YWHAE interactome regulating prenatal development

PC1 (Simulations 1-4): Perturbation of each factor downregulated each stage of neurodevelopment (0%).

PC2 (Simulations 1-4): OE of genes positively regulating each stage of development and OE of all factors, upregulated each same stage of development (100%). OE of genes positively regulating neurodevelopment (when GSK3B is expressed) along with OE of factors upregulated (100%) neurite growth, migration (when GSK3B is expressed) and neurodevelopment (when GSK3B is expressed). OE of genes positively regulating neurodevelopment (when GSK3B is not expressed) along with OE of factors upregulated migration (when GSK3B is not expressed) and neurodevelopment (when GSK3B is not expressed) (100%).

PC3 (Simulations 1-4): KO of genes positively regulating each stage of development along with KO of all factors downregulated each same stage of development (0%).

PC4 (Simulations 1-4): OE of genes positively regulating each stage of development and OE of each factor, upregulated each same stage of development (100%). OE of genes positively regulating neurodevelopment (when GSK3B is expressed) along with OE of each factor upregulated (100%) neurite growth, migration (when GSK3B is expressed) and neurodevelopment (when GSK3B is expressed). OE of genes positively regulating neurodevelopment (when GSK3B is not expressed) along with OE of each factor upregulated migration (when GSK3B is not expressed) and neurodevelopment (when GSK3B is not expressed) (100%).

PC5 (Simulations 1-4): KO of genes positively regulating each stage of development along with KO of each factor downregulated each same stage of development (0%).

Summary of the NP results for YWHAE interactome is given in Table 10.

1.2 Interactomes involved in regulation of postnatal development

We performed single node and multiple node perturbation analyses in the postnatal network. We could not perform node perturbation analysis for APs: CNTNAP2 and DTNBP1. As no miRNAs were shown to regulate DTNBP1, we could not curate miRNA-TF regulatory loops for DTNBP1 gene. The FFLs regulating CNTNAP2 were not shown to regulate the genes interacting with CNTNAP2 gene.

A. DISC1 interactome

During postnatal development, DISC1 interactome regulates proliferation, migration, differentiation, neurite growth and synaptogenesis. We have more than 1 Boolean rule for the following stages of development: neurite growth, synaptogenesis and the overall neurodevelopment process (all the stages are combined as one stage). Neurite growth is upregulated, when DISC1 is expressed (rule 1) and also when DISC1 is not expressed (rule 2). In synaptogenesis, PDE4B gene plays a major role along with DISC1 in upregulation of synaptogenesis. Synaptogenesis is upregulated, when DISC1 downregulates PDE4B expression (rule 1) and when DISC1 upregulates PDE4B gene expression (rule 2). We have given another separate rule for synaptogenesis, where NRG1 and ERBB4 interacts and upregulates synaptogenesis (rule 3). DISC1 is not included in this rule, as DISC1 inhibits ERBB4 expression. So, we also have given 2 Boolean rules for neurodevelopment, when DISC1 is expressed and downregulates PDE4B expression (rule 1) and when DISC1 is expressed and upregulates PDE4B expression (rule 2). We have not combined the regulation of synaptogenesis by NRG1 and ERBB4 with other stages of development, as ERBB4 is inhibited by DISC1.

Single node perturbation

Perturbation condition 1: OE and KO of each miRNA and each TF regulating DISC1 interactome

Simulations 1-4: OE and KO of each miRNA and each TF regulating DISC1 interactome downregulated (0%) proliferation, migration, differentiation, neurite growth (when DISC1 is expressed), synaptogenesis (when PDE4B is downregulated), synaptogenesis (when PDE4B is upregulated), neurodevelopment (when PDE4B is upregulated) and neurodevelopment (when PDE4B is downregulated).

a. Neurite growth (when DISC1 is not expressed)

Simulations 1 and 3: OE and KO of each miRNA and each TF (except OE of HNF4A or miR124), upregulated (100%) neurite growth (when DISC1 is not expressed). OE of HNF4A or miR124 downregulated (0%) neurite growth (when DISC1 is not expressed).

Simulation 1: OE of HNF4A downregulated (0%) neurite growth (when DISC1 is not expressed).

Simulation 3: OE of HNF4A regulated neurite growth (when DISC1 is not expressed) b/w 0%-100%.

At simulation 1, we observed overall regulation of neurite growth in two different regulatory states (RS2), upregulation (100%) and downregulation (0%).

At simulation 3, we observed overall regulation of neurite growth in three different regulatory states (RS1), upregulation (100%), regulation between 0%-100% and downregulation (0%).

Simulations 2 and 4: OE and KO of each miRNA and each TF, downregulated (0%) neurite growth (when DISC1 is not expressed).

b. Synaptogenesis (when NRG1 is expressed)

Simulations 1 and 3: We observed overall regulation of synaptogenesis in two different regulatory states (RS1), upregulation (100%), downregulation (0%) and regulation between 0%-100%. OE and KO of each miRNA and each TF (except OE of HNF4A or miR124 and KO of AR), upregulated (100%) synaptogenesis (when NRG1 is expressed). OE of HNF4A or miR124 downregulated (0%) synaptogenesis (when NRG1 is expressed). KO of AR regulated synaptogenesis (when NRG1 is expressed) between 0%-100%.

Simulations 2 and 4: We observed overall regulation of synaptogenesis in two different regulatory states (RS4), downregulation (0%) and regulation between 0%-100%. OE and KO of each miRNA and each TF (except AR KO), downregulated (0%) synaptogenesis (when NRG1 is expressed). KO of AR showed regulation of synaptogenesis (when NRG1 is expressed) between 0%-100%.

Multiple node perturbation analysis

Perturbation condition 2: OE of genes positively regulating each stage of neurodevelopment (regulated by DISC1 interactome) and OE of miRNAs and TFs regulating DISC1 interactome

Simulations 1-4: OE of genes positively regulating each stage of neurodevelopment (proliferation/ migration/differentiation/ neurite growth (when DISC1 is expressed)/ neurite growth (when DISC1 is not expressed)/ synaptogenesis (when PDE4B is downregulated)/ synaptogenesis (when PDE4B is upregulated)/ synaptogenesis (when NRG1 is expressed)/ neurodevelopment (when PDE4B is upregulated)/ neurodevelopment (when PDE4B is downregulated)) and OE of miRNAs and TFs, upregulated each same stage of neurodevelopment (100%). OE of genes positively regulating neurodevelopment (when PDE4B is upregulated)/ genes positively regulating neurodevelopment (when PDE4B is downregulated) and OE of miRNAs and TFs, upregulated (100%) all the stages of

development regulated by DISC1 interactome, except neurite growth (when DISC1 is not expressed) and synaptogenesis (when NRG1 is expressed) stages.

OE of synaptogenesis (when PDE4B is upregulated) along with OE of miRNAs and TFs upregulated (100%) synaptogenesis (when PDE4B is downregulated) and similarly OE of genes positively regulating synaptogenesis (when PDE4B is downregulated) along with OE of miRNAs and TFs upregulated (100%) synaptogenesis (when PDE4B is upregulated).

Perturbation condition 3: KO of genes positively regulating each stage of neurodevelopment (regulated by DISC1 interactome) and KO of miRNAs and TFs regulating DISC1 interactome

Simulations 1-4: KO of genes positively regulating each stage of neurodevelopment (proliferation/ migration/ differentiation/ neurite growth (when DISC1 is expressed)/ synaptogenesis (when PDE4B is downregulated)/ synaptogenesis (when PDE4B is upregulated)/ neurodevelopment (when PDE4B is upregulated)/ neurodevelopment (when PDE4B is downregulated)) and KO of miRNAs and TFs, downregulated each same stage of neurodevelopment (0%).

a. Neurite growth (when DISC1 is not expressed)

Simulations 1 and 3: KO of genes positively regulating proliferation, migration, differentiation, synaptogenesis (when PDE4B is upregulated), synaptogenesis (when PDE4B is downregulated), synaptogenesis (when NRG1 is expressed) and KO of miRNAs and TFs, downregulated (0%) neurite growth (when DISC1 is not expressed).

Simulations 2 and 4: KO of genes positively regulating proliferation, migration, differentiation, synaptogenesis (when PDE4B is upregulated), synaptogenesis (when PDE4B is downregulated), synaptogenesis (when NRG1 is expressed) and KO of miRNAs and TFs, upregulated (100%) neurite growth (when DISC1 is not expressed).

b. Synaptogenesis (when NRG1 is expressed)

Simulations 1 and 3: KO of genes positively regulating proliferation, migration, differentiation, synaptogenesis (when PDE4B is upregulated), synaptogenesis (when PDE4B is downregulated), neurite growth (when DISC1 is not expressed), neurite growth (when DISC1 is expressed) and KO of miRNAs and TFs, downregulated (0%) synaptogenesis (when NRG1 is expressed).

Simulations 2 and 4: KO of genes positively regulating proliferation, migration, differentiation, synaptogenesis (when PDE4B is upregulated), synaptogenesis (when PDE4B is downregulated), neurite growth (when DISC1 is not expressed), neurite growth (when DISC1 is expressed) and KO of miRNAs and TFs, upregulated (100%) synaptogenesis (NRG1 is expressed).

Perturbation condition 4: OE of all genes positively regulating each stage of neurodevelopment (regulated by DISC1 interactome) along with OE of each factor (miRNA/TF) regulating DISC1 interactome

a. Proliferation

Simulations 1-4: OE of genes positively regulating proliferation/ neurodevelopment (when PDE4B is upregulated)/ neurodevelopment (when PDE4B is upregulated) along with OE of each miRNA/ TF, upregulated proliferation (100%).

Simulation 3: Proliferation was shown to be regulated in three different regulation states (RS1), upregulation (100%), regulation between 0%-100% and downregulation (0%). OE of genes positively regulating differentiation/ migration/ neurite growth (when DISC1 is expressed)/ synaptogenesis (when PDE4B is upregulated)/ synaptogenesis (when PDE4B is downregulated) and OE of HNF4A regulates proliferation (between 0%-100%).

OE of genes positively regulating differentiation/ migration/ neurite growth (when DISC1 is expressed)/ synaptogenesis (when PDE4B is upregulated)/ synaptogenesis (when PDE4B is downregulated) and OE of miR744/ miR155/ miR124 downregulated proliferation (0%).
OE of genes positively regulating differentiation/ migration/ neurite growth (when DISC1 is expressed)/ synaptogenesis (when PDE4B is upregulated)/ synaptogenesis (when PDE4B is downregulated) and OE of each miRNA /TF (except OE of HNF4A/ miR124/ miR155/ miR744), upregulated proliferation (100%).

b. Migration

Simulations 1-4: OE of genes positively regulating proliferation/ migration/ differentiation/ neurite growth (when DISC1 is expressed)/ synaptogenesis (when PDE4B is upregulated)/ synaptogenesis (when PDE4B is downregulated)/ neurodevelopment (when PDE4B is upregulated)/ neurodevelopment (when PDE4B is downregulated) along with OE of each miRNA/ TF, upregulated migration (100%).

c. Differentiation

Simulations 1-4: OE of genes positively regulating proliferation/ migration/ differentiation/ neurite growth (when DISC1 is expressed)/ synaptogenesis (when DISC1 is expressed)/ synaptogenesis (when DISC1 is not expressed)/ neurodevelopment (when PDE4B is upregulated)/ neurodevelopment (when PDE4B is downregulated) along with OE of each miRNA/ TF, upregulated differentiation (100%).

d. Neurite growth (when DISC1 is expressed)

Simulations 1-4: OE of genes positively regulating neurite growth (when DISC1 is expressed)/ neurodevelopment (when PDE4B is upregulated)/ neurodevelopment (when PDE4B is downregulated) along with OE of each miRNA/TF, upregulated neurite growth (100%).

e. Neurite growth (when DISC1 is not expressed)

Simulations 1-4: OE of genes positively regulating neurite growth (when DISC1 is not expressed) along with OE of each miRNA/ TF regulating DISC1 interactome, upregulated neurite growth (100%).

Simulation 1: OE of genes positively regulating synaptogenesis (when NRG1 is expressed) along with OE of HNF4A downregulated neurite growth (0%).

Simulation 3: OE of genes positively regulating synaptogenesis (when NRG1 is expressed) along with OE of HNF4A regulated neurite growth (between 0%-100%).

Simulations 1 and 3: OE of genes positively regulating synaptogenesis (when NRG1 is expressed) along with OE of miR124 downregulated neurite growth (0%).

At simulation 1, we observed overall regulation of neurite growth in two different regulatory states (RS2), upregulation (100%) and downregulation (0%). OE of genes positively regulating synaptogenesis (when NRG1 is expressed) along with OE of each factor (except miR124/ HNF4A) upregulated neurite growth (100%).

At simulation 3, we observed overall regulation of neurite growth in three different regulatory states (RS1), upregulation (100%), regulation between 0%-100% and downregulation (0%). OE of genes positively regulating synaptogenesis (when NRG1 is expressed) along with OE of each factor (except miR124/ HNF4A) upregulated neurite growth (100%).

f. Synaptogenesis (when PDE4B is upregulated)

Simulations 1-4: OE of genes positively regulating synaptogenesis (when PDE4B is upregulated)/ synaptogenesis (when PDE4B is downregulated)/ neurodevelopment (when PDE4B is upregulated)/ neurodevelopment (when PDE4B is downregulated) along with OE of each miRNA/TF, upregulated synaptogenesis (100%).

g. Synaptogenesis (when PDE4B is downregulated)

Simulations 1-4: OE of genes positively regulating synaptogenesis (PDE4B is downregulated)/ synaptogenesis (when PDE4B is downregulated)/ neurodevelopment (when PDE4B is upregulated)/ neurodevelopment (when PDE4B is downregulated) along with OE of each miRNA/TF, upregulated synaptogenesis (100%).

h. Synaptogenesis (when NRG1 is expressed)

Simulations 1-4: OE of genes positively regulating synaptogenesis (when NRG1 is expressed) along with OE of each miRNA/TF, regulated synaptogenesis (100%).

Simulation 1: OE of genes positively regulating neurite growth (when DISC1 is not expressed) along with OE of HNF4A downregulated synaptogenesis (0%).

Simulation 3: OE of genes positively regulating neurite growth (when DISC1 is not expressed) along with OE of HNF4A regulated synaptogenesis (between 0%-100%).

Simulations 1 and 3: OE of genes positively regulating neurite growth (when DISC1 is not expressed) along with OE of miR124 downregulated synaptogenesis (0%).

At simulation 1, we observed overall regulation of synaptogenesis in two different regulatory states (RS2), upregulation (100%) and downregulation (0%). OE of genes positively regulating neurite growth (when DISC1 is not expressed) along with OE of each factor (except miR124/ HNF4A) upregulated synaptogenesis (100%).

At simulation 3, we observed overall regulation of synaptogenesis in three different regulatory states (RS1), upregulation (100%), regulation between 0%-100% and downregulation (0%). OE of genes positively regulating neurite growth (when DISC1 is not expressed) along with OE of each factor (except miR124/ HNF4A) upregulated synaptogenesis (100%).

i. Neurodevelopment (when PDE4B is upregulated)

Simulations 1-4: OE of genes positively regulating neurodevelopment (when PDE4B is upregulated)/ neurodevelopment (when PDE4B is downregulated) along with OE of each miRNA/TF upregulated neurodevelopment (100%).

j. Neurodevelopment (when PDE4B is downregulated)

Simulations 1-4: OE of genes positively regulating neurodevelopment (when PDE4B is upregulated)/ neurodevelopment (when PDE4B is downregulated) along with OE of each miRNA/TF upregulated neurodevelopment (100%).

Perturbation condition 5: KO of genes positively regulating each stage of neurodevelopment (regulated by DISC1 interactome) along with KO of each factor (miRNA/ TF) regulating DISC1 interactome

Simulations 1-4: KO of genes positively regulating each stage of neurodevelopment (proliferation/ migration/ differentiation/ neurite growth (when DISC1 is expressed)/ synaptogenesis (when PDE4B is downregulated)/ synaptogenesis (when PDE4B upregulated)/ neurodevelopment (when PDE4B is upregulated)/ neurodevelopment (when PDE4B is downregulated)) and KO of each miRNA/TF, downregulated each same stage of neurodevelopment (0%).

a. Neurite growth (when DISC1 is not expressed)

Simulations 1 and 3: KO of genes positively regulating proliferation/ migration/ differentiation/ synaptogenesis (when PDE4B is upregulated)/ synaptogenesis (when PDE4B is downregulated)/ synaptogenesis (when NRG1 is expressed) and KO of each miRNA/TF, upregulated (100%) neurite growth (when DISC1 is not expressed).

Simulations 2 and 4: KO of genes positively regulating proliferation/ migration/ differentiation/ synaptogenesis (when PDE4B is upregulated)/ synaptogenesis (when PDE4B is downregulated)/ synaptogenesis (when NRG1 is expressed) and KO of each miRNA/TF, downregulated (0%) neurite growth (when DISC1 is not expressed).

b. Synaptogenesis (when NRG1 is expressed)

Simulations 1 and 3: KO of genes positively regulating proliferation/ migration/ differentiation/ synaptogenesis (when PDE4B is upregulated)/ synaptogenesis (when PDE4B is downregulated)/ neurite growth (when DISC1 is expressed)/ neurite growth (when DISC1 is not expressed)/ neurodevelopment (when PDE4B is upregulated)/ neurodevelopment (when PDE4B is downregulated) and KO of each miRNA/TF (except AR KO), upregulated (100%) synaptogenesis (when NRG1 is expressed). KO of genes positively regulating proliferation/ migration/ differentiation/ synaptogenesis (when PDE4B is upregulated)/ synaptogenesis (when PDE4B is downregulated)/ neurite growth (when DISC1 is expressed)/ neurite growth (when DISC1 is not expressed)/ neurodevelopment (when PDE4B is upregulated)/ neurodevelopment (when PDE4B is downregulated) and KO of AR showed regulation of synaptogenesis (when NRG1 is expressed) between 0%-100%.

Simulations 2 and 4: KO of genes positively regulating proliferation/ migration/ differentiation/ synaptogenesis (when PDE4B is upregulated)/ synaptogenesis (when PDE4B is downregulated)/ neurite growth (when DISC1 is expressed)/ neurodevelopment (when PDE4B is upregulated)/ neurodevelopment (when PDE4B is downregulated) and KO of each miRNA/TF (except AR KO), downregulated (0%) synaptogenesis (when NRG1 is expressed). KO of genes positively regulating proliferation/ migration/ differentiation/ synaptogenesis (when PDE4B is upregulated)/ synaptogenesis (when PDE4B is downregulated)/ neurite growth (when DISC1 is expressed)/ neurodevelopment (when PDE4B is upregulated)/ neurodevelopment (when PDE4B is downregulated) and KO of AR showed regulation of synaptogenesis (when NRG1 is expressed) between 0%-100%.

Table 11: Perturbation results of DISC1 interactome involved in postnatal development

Perturbed nodes	PC	Effect of perturbation on each stage at t =150 (Activation frequency for 1000 simulations at t = 150)																			
		Proliferation				Migration				Differentiation				Neurite growth (when DISC1 is expressed)				Neurite growth (when is DISC1 not expressed)			
		Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4
Factors	1	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	RS2	0%	RS1	0%
Genes positively regulating proliferation and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%
	4	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%	0%
Genes positively regulating migration and factors	2	0%	0%	0%	0%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%
	4	0%	0%	RS1	0%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%	0%
Genes positively regulating differentiation and factors	2	0%	0%	0%	0%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%
	4	0%	0%	RS1	0%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%	0%
Genes positively regulating neurite growth (when DISC1 is expressed) and factors	2	0%	0%	0%	0%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	RS1	0%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurite growth (when DISC1 is not expressed) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating synaptogenesis (when PDE4B is	2	0%	0%	0%	0%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%

expressed) and factors	4	0%	0%	RS1	0%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%	0%
Genes positively regulating synaptogenesis (when PDE4B is not expressed) and factors	2	0%	0%	0%	0%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%
	4	0%	0%	RS1	0%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%	0%
Genes positively regulating synaptogenesis (when NRG1 is expressed) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	RS2	0%	RS1	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%	0%
Genes positively regulating neurodevelopment (when PDE4B is expressed) and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment (when PDE4B is not expressed) and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

PC: Perturbation condition; Sim1: Simulation 1; Sim2: Simulation 2; Sim3: Simulation 3; Sim4: Simulation 4; RS1 represents regulatory state 1, where PC leads to upregulation (0%), regulation between 0%-100% and downregulation (0%). RS2 represents regulatory state 2, where PC leads to regulation between 0%-100% and downregulation (0%)

Table 12: Perturbation results of DISC1 interactome involved in postnatal development (contd)

Perturbed nodes	PC	Effect of perturbation on each stage at t =150 (Activation frequency for 1000 simulations at t = 150)																			
		Synaptogenesis (when PDE4B is expressed)				Synaptogenesis (when PDE4B is not expressed)				Synaptogenesis (when NRG1 is expressed)				Neurodevelopment (when PDE4B is expressed)				Neurodevelopment (when PDE4B is not expressed)			
		Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4
Factors	1	0%	0%	0%	0%	0%	0%	0%	0%	RS1	RS4	RS1	RS4	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

proliferation and factors	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	RS4	RS3	RS4	RS3	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating migration and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	RS4	RS3	RS4	RS3	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating differentiation and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	RS4	RS3	RS4	RS3	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurite growth (DISC1 expressed) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	RS4	RS3	RS4	RS3	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurite growth (DISC1 not expressed) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	RS2	0%	RS1	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	RS4	RS3	RS4	RS3	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating synaptogenesis (PDE4B expressed) and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	RS4	RS3	RS4	RS3	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating synaptogenesis (PDE4B not expressed) and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

	5	0%	0%	0%	0%	0%	0%	0%	0%	RS4	RS3	RS4	RS3	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating synaptogenesis (when NRG1 is expressed) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment (when PDE4B is expressed) and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%	100%	100%	100%	100%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%	100%	100%	100%	100%	100%	100%	100%	100%
	5	0%	0%	0%	0%	0%	0%	0%	0%	RS4	RS3	RS4	RS3	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment (when PDE4B is not expressed) and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%	100%	100%	100%	100%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%	100%	100%	100%	100%	100%	100%	100%	100%
	5	0%	0%	0%	0%	0%	0%	0%	0%	RS4	RS3	RS4	RS3	0%	0%	0%	0%	0%	0%	0%	0%

PC: Perturbation condition; Sim1: Simulation 1; Sim2: Simulation 2; Sim3: Simulation 3; Sim4: Simulation 4

Summary of node perturbation results for DISC1 interactome regulating postnatal development

PC1 (Simulations 1-4): Perturbation of each factor downregulated each stage (except neurite growth (when DISC1 is not expressed), synaptogenesis (when NRG1 is expressed)) of development (0%).

Simulation 1: Perturbation of each factor regulated neurite growth (when DISC1 is not expressed) in two different regulatory states (RS2), downregulation (0%) as well as upregulation (100%).

Simulation 3: Perturbation of each factor regulated neurite growth (when DISC1 is not expressed) in three different regulatory states (RS1), regulation between 0%-100%, downregulation (0%) as well as upregulation (100%).

At simulations 2 and 4, perturbation of each factor, downregulated (0%) neurite growth (when DISC1 is not expressed) and synaptogenesis (NRG1 is expressed).

Simulations 1 and 3: Perturbation of each factor regulated synaptogenesis (when NRG1 is expressed) in three different regulatory states (RS1), regulation between 0%-100%, downregulation (0%) as well as upregulation (100%).

Simulations 2 and 4: Perturbation of each factor regulated synaptogenesis (when NRG1 is expressed) in two different regulatory states (RS1), regulation between 0%-100%, and upregulation (100%).

PC2 (Simulations1-4): OE of genes positively regulating each stage along with OE of factors upregulated each same stage of development (100%). OE of genes positively regulating each stage (except neurite growth (when DISC1 is not expressed)) and synaptogenesis (when NRG1 is expressed) along with OE of factors, upregulated migration and differentiation (100%). OE of genes positively regulating synaptogenesis (when PDE4B is upregulated) along with OE of factors, upregulated synaptogenesis (when PDE4B is downregulated) (100%). OE

of genes positively regulating synaptogenesis (when PDE4B is downregulated) along with OE of factors, downregulated synaptogenesis (when PDE4B is upregulated) (100%).
OE of genes positively regulating neurodevelopment (when PDE4B is upregulated) along with OE of factors, upregulated (100%) each stage of development (except neurite growth (when DISC1 is not expressed) and synaptogenesis (when NRG1 is expressed)). Similarly, OE of genes positively regulating neurodevelopment (when PDE4B is downregulated) along with OE of factors, upregulated (100%) each stage of development (except neurite growth (when DISC1 is not expressed) and synaptogenesis (when NRG1 is expressed)).

PC3 (Simulations 1-4): KO of genes positively regulating each stage of development along with KO of factors, downregulated each stage of development (0%).

Simulations 2 and 4: KO of genes positively regulating each stage of development (except neurite growth (when DISC1 not expressed), neurite growth (DISC1 expressed), neurodevelopment (when PDE4B is upregulated) and neurodevelopment (when PDE4B is downregulated)) along with KO of all factors, upregulated neurite growth (when DISC1 is not expressed) (100%). Similarly, KO of genes positively regulating each stage of development (except synaptogenesis (when NRG1 is expressed)) and KO of all factors, upregulated synaptogenesis (when NRG1 is expressed) (100%).

PC4 (Simulations1-4): OE of genes positively regulating each stage along with OE of each factor upregulated each same stage of development (100%). OE of genes positively regulating each stage (except neurite growth (when DISC1 is not expressed) and synaptogenesis (when NRG1 is expressed) along with OE of each factor, upregulated migration and differentiation (100%). OE of genes positively regulating synaptogenesis (PDE4B is upregulated) along with OE of each factor, upregulated synaptogenesis (when PDE4B is downregulated) (100%). OE of genes positively regulating synaptogenesis (when

PDE4B is downregulated) along with OE of each factor, downregulated synaptogenesis (when PDE4B is upregulated) (100%).

OE of genes positively regulating neurodevelopment (when PDE4B is upregulated) along with OE of each factor, upregulated (100%) each stage of development (except neurite growth (when DISC1 is not expressed) and synaptogenesis (when NRG1 is expressed)).

Similarly, OE of genes positively regulating neurodevelopment (when PDE4B is downregulated) along with OE of each factor, upregulated (100%) each stage of development (except neurite growth (when DISC1 is not expressed) and synaptogenesis (when NRG1 is expressed)).

Simulation 1: OE of genes positively regulating neurite growth (when DISC1 is not expressed) and OE of each factor showed overall regulation of synaptogenesis (when NRG1 is expressed) in two different regulatory states (RS2), downregulation (0%) and upregulation (100%). OE of genes positively regulating synaptogenesis (when NRG1 is expressed) and OE of each factor regulated neurite growth (when DISC1 is not expressed) in two different regulatory states (RS2), downregulation (0%) and upregulation (100%).

Simulation 3: OE of genes positively regulating neurite growth (when DISC1 is not expressed) and OE of each factor showed overall regulation of synaptogenesis (when NRG1 is expressed) in three different regulatory states (RS1), upregulation (100%), regulation between 0%-100% and downregulation (0%). OE of genes positively regulating synaptogenesis (when NRG1 is expressed) and OE of each factor regulated neurite growth (when DISC1 is not expressed) in three different regulatory states (RS1), upregulation (100%), regulation between 0%-100% and downregulation (0%).

PC5 (Simulations 1-4): KO of genes positively regulating each stage of development along with KO of each factor, downregulated each stage of development (0%).

Simulations 1 and 3: We observed regulation of synaptogenesis (when NRG1 is expressed) in two different regulatory states (RS4), upregulation (100%) and regulation between 0%-100%. KO of genes positively regulating each stage of development (except neurite growth (when DISC1 not expressed) along with KO of each factor (except AR KO), upregulated synaptogenesis (when NRG1 is expressed) (100%). KO of genes positively regulating each stage of development (except neurite growth (when DISC1 not expressed) and KO of each factor, showed upregulation of neurite growth (100%).

Summary of the NP results for DISC1 interactome is given in Table 11Table 11 and Table 12.

B. GSK3B interactome

GSK3B interactome regulates proliferation, neurite growth and synaptogenesis. Synaptogenesis is upregulated, when GSK3B is expressed as well when GSK3B is not expressed, so two Boolean rules were given for the stage, synaptogenesis. All the stages of development regulated by GSK3B interactome were also combined as single stage, neurodevelopment.

Single gene perturbation

Perturbation condition 1: OE and KO of each miRNA and each TF regulating GSK3B interactome

Simulations 1-4: OE and KO of each miRNA and each TF regulating GSK3B interactome, downregulated (0%) neurite growth and the overall neurodevelopment process.

Simulation 2: OE and KO of each miRNA and each TF regulating GSK3B interactome, downregulated (0%) proliferation, neurite growth, synaptogenesis (when GSK3B is expressed), synaptogenesis (when GSK3B is not expressed) and the overall neurodevelopment process.

a. Proliferation

Simulation 1: Proliferation was shown to be regulated in two regulatory states (RS3), regulation between 0%-100% and downregulation (0%). AR KO regulates proliferation (between 0%-100%). OE of each miRNA/TF and KO of each miRNA/TF (except AR KO), downregulated proliferation (0%).

Simulation 3: Proliferation was shown to be regulated in two regulatory states (RS2), upregulation (100%) and downregulation (0%). OE of miR124/ miR744/miR155/ HNF4A downregulates proliferation (0%). OE of each miRNA/TF (except OE of miR124/ miR744/ miR155/ HNF4A) upregulates proliferation (100%). KO of each miRNA/TF upregulates proliferation (100%).

b. Synaptogenesis (when GSK3B is not expressed)

Simulation 1: Synaptogenesis was shown to be regulated in two regulatory states (RS3), regulation between 0%-100% and downregulation (0%). OE of miR124 and KO of AR or miR155 regulated synaptogenesis (between 0%-100%). OE of each miRNA/TF (except miR124 OE) and KO of each miRNA/TF (except KO of AR or miR155), downregulated synaptogenesis (0%).

Simulation 3: Synaptogenesis was shown to be regulated in three regulatory states (RS1), upregulation (100%), regulation between 0%-100% and downregulation (0%). KO of TCF3 regulated synaptogenesis (between 0%-100%). KO of each factor (except TCF3 KO), upregulated synaptogenesis (100%). OE of miR124 or KLF4/ miR15a/ miR16/ miR182/ miR744/ miR96/ STAT3 also regulated synaptogenesis (between 0%-100%). OE of miR155/ miR26b downregulates synaptogenesis (0%). OE of each miRNA/TF (except OE of miR124/ KLF4/ miR15a/ miR16/ miR182/ miR744/ miR96/ STAT3/ miR155/ miR26b), upregulated synaptogenesis (100%).

Simulation 4: Synaptogenesis was shown to be regulated in two regulatory states (RS3), regulation between 0%-100% and downregulation (0%). KO of AR or miR155 regulates synaptogenesis (between 0%-100%). OE of miR124 regulates synaptogenesis (between 0%-100%). OE of each miRNA/TF (except miR124 OE) and KO of each miRNA/TF (except KO of AR / miR155), downregulated synaptogenesis (0%).

c. Synaptogenesis (when GSK3B is expressed)

Simulation 1: Synaptogenesis was shown to be regulated in two regulatory states (RS3), regulation between 0%-100% and downregulation (0%). KO of AR and OE of miR124 regulated synaptogenesis (between 0%-100%). OE of each miRNA/TF (except miR124 OE) and KO of each miRNA/TF (except KO of AR), downregulated synaptogenesis (0%).

<u>Multiple node perturbation</u>

Perturbation condition 2: OE of genes positively regulating each stage of neurodevelopment (regulated by GSK3B interactome) and OE of miRNAs and TFs regulating GSK3B interactome

Simulations 1-4: OE of genes positively regulating each stage of neurodevelopment (proliferation/ neurite growth / synaptogenesis (when GSK3B is expressed)/ synaptogenesis (when GSK3B is not expressed)) and OE of miRNAs and TFs, upregulated each same stage of neurodevelopment (100%). OE of genes positively regulating overall neurodevelopment along with OE of miRNAs and TFs, upregulated neurite growth, proliferation, synaptogenesis (when GSK3B is not expressed) and neurodevelopment (100%).

Perturbation condition 3: KO of genes positively regulating each stage of neurodevelopment (regulated by GSK3B interactome) and KO of miRNAs and TFs regulating GSK3B interactome

Simulations 1-4: KO of genes positively regulating each stage of neurodevelopment (proliferation/ neurite growth / synaptogenesis (when GSK3B is expressed)/ synaptogenesis

(when GSK3B is not expressed)) and KO of miRNAs and TFs, downregulated each same stage of neurodevelopment (0%).

a. Proliferation

Simulations 2 and 4: KO of genes positively regulating neurite growth/ synaptogenesis (when GSK3B is expressed) along with KO of miRNAs and TFs, upregulated proliferation (100%).

b. Synaptogenesis (when GSK3B is not expressed)

Simulations 2 and 4: KO of genes positively regulating neurite growth/ synaptogenesis (when GSK3B is expressed)/ proliferation along with KO of miRNAs and TFs, upregulated synaptogenesis (when GSK3B is not expressed) (100%).

c. Synaptogenesis (when GSK3B is expressed)

Simulations 2 and 4: KO of genes positively regulating neurodevelopment (when GSK3B is not expressed) and KO of miRNAs and TFs upregulated synaptogenesis (when GSK3B is expressed) (100%).

Perturbation condition 4: OE of genes positively regulating each stage of neurodevelopment (regulated by GSK3B interactome) along with OE of each factor (miRNA/ TF) regulating GSK3B interactome

a. Proliferation

Simulations 1-4: OE of genes positively regulating proliferation/ neurodevelopment (when GSK3B is not expressed) and OE of each miRNA/TF regulating GSK3B interactome, upregulated proliferation (100%).

Simulation 3: Genes regulating other stages regulated proliferation in two regulatory states (RS2), upregulation (100%) and downregulation (0%). OE of genes positively regulating neurite growth/ synaptogenesis (when GSK3B is not expressed) and OE of miR124/ miR155/ HNF4A/ miR744, downregulated proliferation (0%). OE of genes positively regulating neurite growth/ synaptogenesis (when GSK3B is not expressed) and OE of each miRNA/ TF (except

OE of miR124/ miR155/ HNF4A/ miR744) regulating GSK3B interactome, upregulated proliferation (100%).

b. Neurite growth

Simulations 1-4: OE of genes positively regulating neurite growth/ neurodevelopment (when GSK3B is not expressed) and OE of each miRNA/TF, upregulated neurite growth (100%).

c. Synaptogenesis (when GSK3B is not expressed)

Simulations 1-4: OE of genes positively regulating synaptogenesis (GSK3B is not expressed)/ neurodevelopment (when GSK3B is not expressed) and OE of each miRNA/TF, upregulated synaptogenesis (100%).

Simulations 1 and 4: Genes positively regulating neurite growth/ proliferation regulated synaptogenesis in two different regulatory states (RS3), downregulation (0%) and regulation between 0%-100%. OE of genes positively regulating neurite growth/ proliferation and OE of miR124, regulated synaptogenesis (between 0%-100%). OE of genes positively regulating neurite growth/ proliferation and OE of each factor (except OE of miR124), regulated synaptogenesis (between 0%-100%).

Simulation 3: Genes positively regulating neurite growth/ proliferation regulated synaptogenesis in three different regulatory states (RS1), upregulation (0%), downregulation (0%) and regulation between 0%-100%. OE of genes positively regulating neurite growth/ proliferation and OE of miR124/ KLF4/ miR15a/ miR16/ miR182/ miR744/ miR96/ STAT3, regulated synaptogenesis (between 0%-100%). OE of genes positively regulating neurite growth/ proliferation and OE of miR155/ miR26b, downregulated synaptogenesis (0%). OE of genes positively regulating neurite growth/ proliferation and OE of each factor (except OE

of miR155/ miR26b/ miR124/ KLF4/ miR15a/ miR16/ miR182/ miR744/ miR96/ STAT3) showed upregulation of synaptogenesis (100%).

d. Synaptogenesis (when GSK3B is expressed)

Simulations 1-4: OE of genes positively regulating synaptogenesis (when GSK3B is expressed) and OE of each miRNA/ TF, upregulated synaptogenesis (100%).

e. Neurodevelopment (when GSK3B is not expressed)

Simulations 1-4: OE of genes positively regulating neurodevelopment (when GSK3B is not expressed) and OE of each miRNA/TF regulating GSK3B interactome upregulated neurodevelopment (100%).

Simulation 3: Neurodevelopment was shown to be regulated in three different regulatory states (RS1), upregulation (0%), regulation between 0%-100% and downregulation (0%). OE of genes positively regulating neurite growth and OE of KLF4/ miR15a/ miR16/ miR182/ miR744/ miR96/ STAT3, regulated neurodevelopment (0%-100%). OE of genes positively regulating neurite growth and OE of miR124/ miR155/ miR26b, downregulated neurodevelopment (0%). OE of genes positively regulating neurite growth and OE of each miRNA/TF (except OE of KLF4/ miR15a/ miR16/ miR182/ miR744/ miR96/ STAT3/ miR124/ miR155/ miR26b), upregulated neurodevelopment (100%).

Perturbation condition 5: KO of genes positively regulating each stage of neurodevelopment (regulated by GSK3B interactome) along with KO of each factor (miRNA/ TF) regulating GSK3B interactome

Simulations 1-4: KO of genes positively regulating each stage of neurodevelopment (proliferation/ neurite growth / synaptogenesis (when GSK3B is expressed)/ synaptogenesis (when GSK3B is not expressed)) and KO of each miRNA/ TF regulating GSK3B interactome, downregulated each same stage of neurodevelopment (0%).

a. Proliferation

Simulation 1: Proliferation was shown to be regulated in two different regulatory states (RS3), downregulation (0%) and regulation between 0%-100%. KO of genes positively regulating neurite growth/ synaptogenesis (when GSK3B is expressed)/ synaptogenesis (when GSK3B is not expressed) and KO of AR regulated proliferation (0%-100%). KO of genes positively regulating neurite growth/ synaptogenesis (when GSK3B is expressed)/ synaptogenesis (when GSK3B is not expressed) and KO of each miRNA/ TF (except AR KO) downregulated proliferation (0%).

b. Synaptogenesis (when GSK3B is not expressed)

Simulation 1: Synaptogenesis was shown to be regulated in two different regulatory states (RS3), downregulation (0%) and regulation between 0%-100%. KO of genes positively regulating neurite growth/ proliferation/ synaptogenesis (when GSK3B is expressed) and KO of AR/ miR155 regulated synaptogenesis (0%-100%). KO of genes positively regulating neurite growth/ proliferation/ synaptogenesis (when GSK3B is expressed) and KO of each miRNA/TF (except KO of AR/ miR155) downregulated synaptogenesis (0%).

Simulation 3: Synaptogenesis was shown to be regulated in two different regulatory states (RS4), upregulation (100%) and regulation between 0%-100%. KO of genes positively regulating neurite growth/ proliferation and KO of TCF3 regulated synaptogenesis between 0%-100%. KO of genes positively regulating neurite growth/ proliferation and KO of each miRNA/TF (except KO of TCF3) upregulated synaptogenesis (100%). KO of genes positively regulating synaptogenesis (when GSK3B is expressed) and KO of each miRNA/TF, upregulated synaptogenesis (100%).

Simulation 4: Synaptogenesis was shown to be regulated in two different regulatory states (RS3), downregulation (0%) and regulation between 0%-100%. KO of genes positively

regulating neurite growth/ proliferation and KO of AR/ miR155 regulated synaptogenesis (0%-100%). KO of genes positively regulating neurite growth/ proliferation and KO of each miRNA/TF (except AR/ miR155), downregulated synaptogenesis (0%).

c. Synaptogenesis (when GSK3B is expressed)

Simulation 1: Synaptogenesis was shown to be regulated in two different regulatory states (RS3), downregulation (0%) and regulation between 0%-100%. KO of genes positively regulating neurite growth/ proliferation/ neurodevelopment (when GSK3B is not expressed)/ synaptogenesis (when GSK3B is not expressed) and KO of AR regulated synaptogenesis (0%-100%). KO of genes positively regulating neurite growth/ proliferation/ neurodevelopment (when GSK3B is not expressed)/ synaptogenesis (when GSK3B is not expressed) and KO of each miRNA/TF (except AR KO) downregulated synaptogenesis (0%).

Simulations 2 and 4: KO of genes positively regulating neurodevelopment (when GSK3B is not expressed) and KO of each miRNA/TF, upregulated synaptogenesis (100%).

Simulation 3: KO of genes positively regulating neurodevelopment (when GSK3B is not expressed) and KO of each miRNA and each TF (except KO of TCF3), upregulated synaptogenesis (100%). KO of genes positively regulating neurodevelopment (when GSK3B is not expressed) and KO of TCF3 regulated synaptogenesis (between 0%-100%).

Table 13: Perturbation results of GSK3B interactome involved in postnatal development

Perturbed nodes	PC	Effect of perturbation on each stage at t =150 (Activation frequency for 1000 simulations at t = 150)																			
		Proliferation				Neurite growth				Synaptogenesis (when GSK3B is not expressed)				Synaptogenesis (when GSK3B is expressed)				Neurodevelopment (when GSK3B is not expressed)			
		Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4
Factors	1	RS3	0%	RS2	0%	0%	0%	0%	0%	RS3	0%	RS1	RS3	RS3	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating proliferation and factors	2	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	0%	0%	0%	0%	RS3	0%	RS1	RS3	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	RS3	0%	RS4	RS3	RS3	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurite growth and factors	2	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	100%	0%	100%	0%	0%	0%	0%	0%	100%	0%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	RS2	0%	100%	100%	100%	100%	RS3	0%	RS1	RS3	0%	0%	0%	0%	0%	0%	RS1	0%
	5	RS3	0%	0%	0%	0%	0%	0%	0%	RS3	0%	RS4	RS3	RS3	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating synaptogenesis (when GSK3B is not expressed) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	RS2	0%	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	5	RS3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	RS3	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating synaptogenesis (when GSK3B is expressed) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%
	3	0%	100%	0%	100%	0%	0%	0%	0%	0%	100%	0%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%
	5	RS3	0%	0%	0%	0%	0%	0%	0%	RS3	0%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment (when GSK3B is not expressed) and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	100%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%	100%	100%	100%	100%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	RS3	100%	RS4	100%	0%	0%	0%	0%

PC: Perturbation condition; Sim1: Simulation 1; Sim2: Simulation 2; Sim3: Simulation 3; Sim4: Simulation 4; RS2 represents regulatory state, where PC leads to upregulation (100%) and downregulation (0%). RS3 represents regulatory state 3, where PC leads to upregulation (0%), regulation between 0%-100% and downregulation (0%). RS4 represents regulatory state 4, where PC leads to regulation between 0%-100% and upregulation (100%)

Summary of node perturbation results of GSK3B interactome involved in regulation of postnatal development

PC1 (Simulations 1-4): Perturbation of each factor regulating GSK3B interactome downregulated each stage of development (except proliferation, synaptogenesis (when GSK3 is not expressed) and synaptogenesis (when GSK3B is expressed) (0%).

Simulation 1: Perturbation of each factor resulted in overall regulation of proliferation and synaptogenesis (when GSK3B is not expressed) in two different regulatory states (RS3), regulation between 0%-100% and downregulation (0%). Synaptogenesis (when GSK3B is expressed) was shown to be regulated in two different regulatory states (RS3), downregulation (0%) and regulation between 0%-100%.

Simulation 2: Perturbation of each factor showed downregulation (0%) of proliferation, synaptogenesis (when GSK3B is not expressed) and synaptogenesis (when GSK3B is expressed).

Simulation 3: Perturbation of each factor resulted in overall regulation of proliferation in two different regulatory states (RS2), upregulation (100%) and downregulation (0%). Synaptogenesis (when GSK3B is not expressed) was shown to be regulated in three different regulatory states (RS1), upregulation (100%), downregulation (0%) and regulation between 0%-100%.

Simulation 4: Synaptogenesis (when GSK3B is not expressed) was shown to be regulated in two different regulatory states (RS3), downregulation (0%) and regulation between 0%-100%.

PC2 (Simulations 1-4): OE of genes positively regulating each stage of development along with OE of factors regulating GSK3B interactome, upregulated each same stage of development (100%). OE of genes positively regulating neurodevelopment (when GSK3B is

not expressed) along with OE of factors, upregulated each stage of development (except synaptogenesis (when GSK3B is expressed)).

PC3 (Simulations 1-4): KO of genes positively regulating each stage of development along with KO of factors regulating GSK3B interactome, downregulated each same stage of development (0%).

Simulations 2 and 4: KO of genes positively regulating neurite growth/ synaptogenesis (when GSK3B is expressed) along with KO of factors, upregulated proliferation (100%). Similarly, KO of each stage (except synaptogenesis (when GSK3B is not expressed) and neurodevelopment (when GSK3B is not expressed), upregulated (100%) synaptogenesis (when GSK3B is not expressed). We also observed that KO of genes positively regulating neurodevelopment (when GSK3B is not expressed) along with KO of factors, upregulated (100%) synaptogenesis (when GSK3B is expressed).

PC4 (Simulations 1-4): OE of each factor along with OE of genes positively regulating each stage of development, upregulated each same stage of development (100%).

Simulations 1 and 4: OE of genes positively regulating neurite growth/ proliferation showed overall regulation of synaptogenesis (when GSK3B is not expressed) in two different regulatory states (RS3), regulation between 0%-100% as well as downregulation (0%).

Simulation 3: OE of genes positively regulating neurite growth/ synaptogenesis (when GSK3B is not expressed) showed overall regulation of proliferation in two different regulatory states (RS2), upregulation (100%) as well as downregulation (0%). Similarly, OE of genes positively regulating neurite growth/ proliferation showed regulation of synaptogenesis (when GSK3B is not expressed) in two different regulatory states (RS2), upregulation (100%) as well as downregulation (0%). OE of genes positively regulating neurodevelopment (when GSK3B is not expressed) showed regulation of neurodevelopment

in three different regulatory states (RS1), upregulation (100%), regulation between 0%-100% as well as downregulation (0%).

PC5 (Simulations 1-4): KO of each factor along with KO of genes positively regulating each stage of development, downregulated each same stage of development (0%).

Simulation 1: KO of genes positively regulating neurite growth/ synaptogenesis (when GSK3B is expressed)/ synaptogenesis (when GSK3B is not expressed) along with KO of each factor, showed overall regulation of proliferation in two different regulatory states (RS3), downregulation (0%) and regulation between 0%-100%. Similarly, KO of genes positively regulating neurite growth/ proliferation/ synaptogenesis (when GSK3B is expressed) along with KO of each factor showed overall regulation of synaptogenesis (when GSK3B is not expressed) in two different regulatory states (RS3), downregulation (0%) and regulation between 0%-100%.

KO of genes positively regulating neurite growth/ proliferation/ synaptogenesis (when GSK3B is not expressed)/ neurodevelopment (when GSK3B is not expressed) and KO of each factor showed overall regulation of synaptogenesis (when GSK3B is expressed) in two different regulatory states, RS3, downregulation (0%) and regulation between 0%-100%.

Simulation 3: KO of genes positively regulating neurite growth/ proliferation along with KO of each factor showed overall regulation of synaptogenesis (when GSK3B is not expressed) in two different regulatory states (RS4), upregulation (100%) and regulation between 0%-100%. KO of genes positively regulating synaptogenesis (when GSK3B is expressed) with KO of each factor, upregulated synaptogenesis (when GSK3B is not expressed) (100%). Similarly, KO of genes positively regulating neurodevelopment (when GSK3B is not expressed) and KO of each factor, showed overall regulation of synaptogenesis (when GSK3B is expressed) in

two different regulatory states (RS4), upregulation (100%) and regulation between 0%-100%.

Simulations 2 and 4: KO of genes positively regulating neurodevelopment (when GSK3B is not expressed) along with KO of each factor, upregulated synaptogenesis (when GSK3B is expressed).

Simulation 4: KO of genes positively regulating neurite growth/ proliferation and KO of each factor showed overall regulation of synaptogenesis (when GSK3B is not expressed) in three different regulatory states (RS3), regulation between 0%-100% and upregulation (100%). Summary of the NP results for GSK3B interactome is given in Table 13Table 13.

C. BDNF interactome

During postnatal period, BDNF interactome regulates differentiation, neurite growth and synaptogenesis. We have specified two different Boolean rules for neurite growth and synaptogenesis. BDNF activates miR134 expression and upregulates neurite growth (rule 1) as well as BDNF represses miR134 expression and upregulates neurite growth (rule 2). Similarly, when BDNF is expressed, synaptogenesis is upregulated (rule 1) as well as when BDNF is not expressed synaptogenesis is upregulated (rule 2). So, for the overall neurodevelopment process (all stages combined into one stage), we also have given two different Boolean rules, neurodevelopment (when miR134 is expressed) and neurodevelopment (when miR134 is repressed).

Single node perturbation

Perturbation condition 1: OE and KO of each miRNA and each TF regulating BDNF interactome

Simulations 1-4: OE and KO of each miRNA and each TF regulating BDNF interactome, downregulated (0%) each stage of neurodevelopment and the overall neurodevelopment process (all the stages regulated by BDNF combined into one stage).

Perturbation condition 2: OE of genes positively regulating each stage of neurodevelopment (regulated by BDNF interactome) and OE of miRNAs and TFs regulating BDNF interactome

Simulations 1-4: OE of genes positively regulating each stage of neurodevelopment (differentiation, neurite growth (when miR134 is activated), neurite growth (when miR134 is repressed), synaptogenesis (BDNF is expressed), synaptogenesis (BDNF is not expressed), neurodevelopment (when miR134 is expressed) and neurodevelopment (when miR134 is repressed)) along with OE of miRNAs and TFs regulating BDNF interactome, upregulated each same stage of neurodevelopment (100%). OE of genes positively regulating neurodevelopment (when miR134 is expressed) and OE of miRNAs and TFs, upregulated (100%) differentiation, neurite growth (when miR134 is activated), neurite growth (when miR134 is repressed), synaptogenesis (when BDNF is expressed), neurodevelopment (when miR134 is activated) and neurodevelopment (when miR134 is repressed). OE of genes positively regulating neurodevelopment (when miR134 is repressed) along with OE of miRNAs and TFs, upregulated (100%) neurodevelopment (when miR134 is repressed), differentiation, synaptogenesis (when BDNF is expressed) and neurite growth (when miR134 is repressed).

a. Differentiation

Simulations 1-4: OE of genes positively regulating neurite growth (when miR134 is expressed)/ neurite growth (when miR134 is not expressed)/ synaptogenesis (when BDNF is expressed) along with OE of miRNAs and TFs, upregulated differentiation (100%).

b. Neurite growth (miR134 is not expressed)

Simulations 1-4: OE of genes positively regulating neurite growth (when miR134 is expressed)/ neurite growth (when miR134 is not expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed)/ synaptogenesis

(when BDNF is expressed) along with OE of miRNAs and TFs, upregulated neurite growth (100%).

Perturbation condition 3: KO of genes positively regulating each stage of neurodevelopment (regulated by BDNF interactome) and KO of miRNAs and TFs regulating BDNF interactome

Simulations 1-4: KO of genes positively regulating each stage of neurodevelopment (differentiation, neurite growth (when miR134 is activated), neurite growth (when miR134 is repressed), synaptogenesis (when BDNF is expressed), synaptogenesis (when BDNF is not expressed), neurodevelopment (when miR134 is expressed) and neurodevelopment (when miR134 is repressed)) along with KO of miRNAs and TFs, downregulated each same stage of neurodevelopment (0%).

Perturbation condition 4: OE of genes positively regulating each stage of neurodevelopment (regulated by BDNF interactome) along with OE of each factor (miRNA/ TF) regulating BDNF interactome

a. Differentiation

Simulation 1: Genes positively regulating each stage of development (except synaptogenesis (when BDNF is not expressed) showed overall regulation of differentiation in all three regulatory states (RS1), upregulation (100%), regulation between 0%-100% and downregulation (0%). OE of genes positively regulating differentiation/ neurite growth (when miR134 is expressed)/ neurite growth (when miR134 is not expressed)/ synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) along with OE of STAT3, downregulated differentiation (0%). OE of genes positively regulating differentiation/ neurite growth (when miR134 is expressed)/ neurite growth (when miR134 is not expressed)/ synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) along with OE of miR-1-3p/ miR15a/

KLF4/ TCF3 upregulated differentiation (100%). OE of genes positively regulating differentiation/ neurite growth (when miR134 is expressed)/ neurite growth (when miR134 is not expressed)/ synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) along with OE of each miRNA/TF (except miR-1-3p/ miR15a/ KLF4/ TCF3/ STAT3) regulated differentiation (between 0%-100%).

Simulation 2: Genes positively regulating each stage of development (except synaptogenesis (when BDNF is not expressed) showed overall regulation of differentiation in two regulatory states (RS4), upregulation (100%) and regulation between 0%-100%. OE of genes positively regulating differentiation/neurite growth (when miR134 is expressed)/ neurite growth (when miR134 is not expressed)/ synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) along with OE of miR16, regulated differentiation (between 0%-100%). OE of genes positively regulating differentiation/neurite growth (when miR134 is expressed)/ neurite growth (when miR134 is not expressed)/ synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) along with OE of each miRNA/TF (except miR16), upregulated differentiation (100%).

Simulation 3: Genes positively regulating each stage of development (except synaptogenesis (when BDNF is not expressed) showed overall regulation of differentiation in three regulatory states (RS1), upregulation (100%), regulation between 0%-100% and downregulation (0%). OE of genes positively regulating differentiation/ neurite growth (when miR134 is expressed)/ neurite growth (when miR134 is not expressed)/ neurodevelopment (when miR134 is not expressed)/ neurodevelopment (when miR134 is

expressed)/ synaptogenesis (when BDNF is expressed) and OE of miR-1-3p/ miR15a upregulated differentiation (100%). OE of genes positively regulating differentiation/ neurite growth (when miR134 is expressed)/ neurite growth (when miR134 is not expressed)/ neurodevelopment (when miR134 is not expressed)/ neurodevelopment (when miR134 is expressed)/ synaptogenesis (when BDNF is expressed) and OE of miR16 or KLF4, regulated differentiation (between 0%-100%). OE of genes positively regulating differentiation/neurite growth (when miR134 is expressed)/ neurite growth (when miR134 is not expressed)/ synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) along with OE of each miRNA/TF (except OE of miR16/ KLF4/ miR-1-3p/ miR15a), downregulated differentiation (0%).

Simulation 4: Genes positively regulating each stage of development (except synaptogenesis (when BDNF is not expressed) showed overall regulation of differentiation in two regulatory states (RS4), upregulation (100%) and regulation between 0%-100%. OE of genes positively regulating differentiation/ neurite growth (when miR134 is expressed)/ neurite growth (when miR134 is not expressed)/ synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) along with OE of miR-1-3p / miR15a/ KLF4/ TCF3/ STAT3 upregulated differentiation (100%). OE of genes positively regulating differentiation/ neurite growth (when miR134 is expressed)/ neurite growth (when miR134 is not expressed)/ synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) along with OE of each miRNA/TF (except OE of miR-1-3p / miR15a/ KLF4/ TCF3/ STAT3) regulated differentiation (between 0%-100%).

b. Neurite growth (when miR134 is expressed)

Simulations 1-4: Genes positively regulating neurite growth (when miR134 is expressed)/ neurodevelopment (when miR134 is expressed) and OE of each miRNA/TF regulating BDNF interactome, upregulated neurite growth (100%).

c. Neurite growth (when miR134 is not expressed)

Simulations 1-4: Genes positively regulating differentiation/ neurite growth (when miR134 is expressed)/ neurite growth (when miR134 is not expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed)/ synaptogenesis (when BDNF is expressed) and OE of each miRNA/TF regulating BDNF interactome, upregulated neurite growth (100%).

d. Synaptogenesis (when BDNF is expressed)

Simulation 1: Synaptogenesis was shown to be regulated in three different regulatory states (RS1), upregulation (100%), regulation between 0%-100% and downregulation (0%). OE of genes positively regulating synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) along with TCF3 OE, upregulated synaptogenesis (100%). However, OE of genes positively regulating synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) along with STAT3 OE, downregulated synaptogenesis (0%). OE of genes positively regulating synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) along with OE of each TF (except TCF3/STAT3 OE), regulated synaptogenesis (between 0%-100%). OE of genes positively regulating synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) along with OE of each miRNA regulated synaptogenesis (between 0%-100%).

Simulation 2: Synaptogenesis was shown to be regulated in two different regulatory states (RS4), upregulation (100%) and regulation between 0%-100%. OE of genes positively regulating synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) along with OE of miR16 regulated synaptogenesis (between 0%-100%). OE of genes positively regulating synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) along with OE of each miRNA (except miR16 OE) upregulated synaptogenesis (100%). OE of genes positively regulating synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) along with OE of each TF upregulated synaptogenesis (100%).

Simulation 3: OE of genes positively regulating synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) along with OE of each miRNA and each TF, downregulated synaptogenesis (0%).

Simulation 4: Synaptogenesis was shown to be regulated in two different regulatory states (RS3) regulation between 0%-100% and downregulation (0%). OE of genes positively regulating synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) along with OE of miR22 (repressed by MYC) / miR22 (activated by MYC) / CTCF/ MYC (activates miR22) / MYC (represses miR22)/ REST/ SOX2/ TCF3 downregulated synaptogenesis (0%). OE of genes positively regulating synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) along with OE of each miRNA/TF (except OE of miR22 (repressed by MYC) / miR22 (activated by MYC) / CTCF/

MYC (activates miR22) / MYC (represses miR22)/ REST/ SOX2/ TCF3) regulated synaptogenesis (between 0% - 100%).

e. Synaptogenesis (when BDNF is not expressed)

Simulations 1-4: OE of genes positively regulating synaptogenesis (when BDNF is not expressed) along with OE of each miRNA and each TF upregulated synaptogenesis (100%).

f. Neurodevelopment (when miR134 is expressed)

Simulation 1: Neurodevelopment was shown to be regulated in three different regulatory states (RS1), upregulation (100%), regulation between 0%-100% and downregulation (0%). OE of genes positively regulating neurodevelopment (when miR134 is expressed) and OE of TCF3, upregulated neurodevelopment (100%). However, OE of genes positively regulating neurodevelopment (when miR134 is expressed) and OE of STAT3, downregulated neurodevelopment (0%). OE of genes positively regulating neurodevelopment (when miR134 is expressed) and OE of STAT3/ TCF3, regulated neurodevelopment (between 0%-100%). OE of genes positively regulating neurodevelopment (when miR134 is expressed) and OE of each miRNA, regulated neurodevelopment (between 0%-100%).

Simulations 2, 3 and 4: OE of genes positively regulating neurodevelopment (when miR134 is expressed) and OE of each miRNA/TF, downregulated neurodevelopment (0%), as HDAC1 gene (self-regulated) represses BDNF gene expression.

g. Neurodevelopment (when miR134 is not expressed)

Simulation 1: Neurodevelopment was shown to be regulated in three different regulatory states (RS1), upregulation (100%), regulation between 0%-100% and downregulation (0%). OE of genes positively regulating synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) and OE of TCF3, upregulated neurodevelopment (100%). OE of genes positively regulating synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is

expressed)/ neurodevelopment (when miR134 is not expressed) and OE of STAT3, downregulated neurodevelopment (0%). OE of each TF (except TCF3/STAT3) and OE of genes positively regulating synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed), regulated neurodevelopment (between 0%-100%). OE of each miRNA and OE of genes positively regulating synaptogenesis (when BDNF is expressed)/ neurodevelopment (miR134 is expressed)/ neurodevelopment (when miR134 is not expressed), regulated neurodevelopment (between 0%-100%).

Simulation 2: Neurodevelopment was shown to be regulated in two different regulatory states (RS3), regulation between 0%-100% and downregulation (0%). OE of genes positively regulating synaptogenesis (when BDNF is expressed)/ neurodevelopment (miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) and OE of miR16, regulated neurodevelopment (between 0%-100%). OE of genes positively regulating synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) and OE of each miRNA/TF (except miR16), upregulated neurodevelopment (100%).

Simulation 3: OE of genes positively regulating neurodevelopment (when miR134 is not expressed) and OE of each miRNA and each TF, downregulated neurodevelopment (0%), as HDAC1 gene (self-regulated) represses BDNF gene expression.

Simulation 4: Neurodevelopment was shown to be regulated in two different regulatory states (RS3) regulation between 0%-100% and downregulation (0%). OE of genes positively regulating synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) along with OE of miR22 (repressed by MYC) / miR22 (activated by MYC) / CTCF/ MYC (activates miR22) / MYC

(represses miR22)/ REST/ SOX2/ TCF3 OE downregulated neurodevelopment (0%). OE of genes positively regulating synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) and OE of each miRNA/TF (except miR22 (repressed by MYC) / miR22 (activated by MYC) / CTCF/ MYC (activates miR22) / MYC (represses miR22)/ REST/ SOX2/ TCF3), regulated neurodevelopment (b/w 0% - 100%).

Perturbation condition 5: KO of genes positively regulating each stage of neurodevelopment (regulated by BDNF interactome) along with KO of each factor (miRNA/ TF) regulating BDNF interactome

Simulations 1-4: KO of all genes positively regulating each stage of neurodevelopment (differentiation/ neurite growth (when miR134 is expressed)/ neurite growth (when miR134 is not expressed)/ synaptogenesis (when BDNF is expressed)/ synaptogenesis (when BDNF is not expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed)) along with KO of each miRNA/TF, downregulated each same stage of neurodevelopment (0%).

Table 14: Perturbation results of BDNF interactome involved in postnatal development

Perturbed nodes	PC	Effect of perturbation on each stage at t =150 (Activation frequency for 1000 simulations at t = 150)															
		Differentiation				Neurite growth (when miR134 is expressed)				Neurite growth (when miR134 is not expressed)				Synaptogenesis (when BDNF is expressed)			
		Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4
Factors	1	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating differentiation and factors	2	100%	100%	100%	100%	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	RS1	RS4	RS1	RS4	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurite growth (when miR134 is expressed) and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	RS1	RS4	RS1	RS4	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurite growth (when miR134 is not expressed) and factors	2	100%	100%	100%	100%	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	RS1	RS4	RS1	RS4	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating synaptogenesis (when BDNF is expressed) and factors	2	100%	100%	100%	100%	0%	0%	0%	0%	100%	100%	100%	100%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	RS1	RS4	RS1	RS4	0%	0%	0%	0%	100%	100%	100%	100%	RS1	RS4	0%	RS3
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating synaptogenesis (when BDNF is not expressed) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment (when miR134 is	2	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

expressed) and factors	4	RS1	RS4	RS1	RS4	0%	0%	0%	0%	100%	100%	100%	100%	RS1	RS4	0%	RS3
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment (when miR134 is not expressed) and factors	2	100%	100%	100%	100%	0%	0%	0%	0%	100%	100%	100%	100%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	RS1	RS4	RS1	RS4	0%	0%	0%	0%	100%	100%	100%	100%	RS1	RS4	0%	RS3
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

PC: Perturbation condition; Sim1: Simulation 1; Sim2: Simulation 2; Sim3: Simulation 3; Sim4: Simulation 4. RS1 represents regulatory state 1, where PC leads to upregulation (100%), regulation between 0%-100% and downregulation (0%). RS3 represents regulatory state regulatory state 3, where PC condition leads to downregulation (0%) and regulation between 0%-100%. RS4 represents regulatory state 4, where PC leads to upregulation (100%) and regulation between 0%-100%

Table 15: Perturbation results of BDNF interactome involved in postnatal development

Perturbed nodes	PC	Effect of perturbation on each stage at t =150 (Activation frequency for 1000 simulations at t = 150)											
		Synaptogenesis (when BDNF is not expressed)				Neurodevelopment (when miR134 is expressed)				Neurodevelopment (when miR134 is not expressed)			
		Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4
Factors	1	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating differentiation and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurite growth (when miR134 is expressed) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurite growth (when miR134 is not expressed) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

synaptogenesis (when BDNF is expressed) and factors	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating synaptogenesis (when BDNF is not expressed) and factors	2	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	0%	0%	0%	0%	RS1	RS3	0%	RS3
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment (when miR134 is expressed) and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	RS1	0%	0%	0%	RS1	RS3	0%	RS3
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment (when miR134 is not expressed) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	RS1	RS3	0%	RS3
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

PC: Perturbation condition; Sim1: Simulation 1; Sim2: Simulation 2; Sim3: Simulation 3; Sim4: Simulation 4. RS1 represents regulatory state 1, where PC leads to upregulation (100%), regulation between 0%-100% and downregulation (0%). RS3 represents regulatory state regulatory state 3, where PC condition leads to downregulation (0%) and regulation between 0%-100%.

Summary of node perturbation results of BDNF interactome regulating postnatal development

PC1 (Simulations 1-4): Perturbation of each factor, downregulated each stage of neurodevelopment (0%).

PC2 (Simulations 1-4): OE of genes positively regulating each stage of development along with OE of miRNAs and TFs, upregulated each same stage of development (100%).

Simulations 1-4: OE of genes positively regulating neurodevelopment (when miR134 is not expressed along with OE of factors, upregulated (100%) differentiation, synaptogenesis (when BDNF is expressed), neurodevelopment (miR134 is not expressed) and neurite growth (when miR134 is not expressed). Similarly, OE of genes positively regulating neurite growth (when miR134 is expressed)/ neurite growth (when miR134 is not expressed)/ synaptogenesis (when BDNF is expressed) along with OE of factors upregulated differentiation (100%). OE of genes positively regulating neurite growth (when miR134 is expressed)/ neurite growth (when miR134 is not expressed)/ synaptogenesis (when BDNF is expressed) along with OE of factors, upregulated (100%) neurite growth (when miR134 is not expressed).

PC3 (Simulations 1-4): KO of genes positively regulating each stage of development along with KO of miRNAs and TFs, downregulated each same stage of development (0%).

PC4 (Simulations 1-4): OE of genes positively regulating each stage of development along with OE of each miRNA/TF, upregulated each same stage of development (100%).

Simulations 1 and 3: OE of genes positively regulating differentiation/ neurite growth (when miR134 is expressed)/ neurite growth (when miR134 is not expressed)/ synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) along with OE of each factor, showed

overall regulation of differentiation in three different regulatory states (RS1), upregulation (100%), regulation between 0%-100% and downregulation (0%).

Simulations 2 and 4: OE of genes positively regulating differentiation/ neurite growth (when miR134 is expressed)/ neurite growth (when miR134 is not expressed)/ synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) along with OE of each factor, regulated differentiation in two different regulatory states (RS4), upregulation (100%) and regulation between 0%-100%.

Simulations 1-4: OE of genes positively regulating differentiation/ neurite growth (when miR134 is expressed)/ neurite growth (when miR134 is not expressed)/ synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) along with OE of each factor, upregulated neurite growth (when miR134 is not expressed) (100%).

Simulation 1: OE of genes positively regulating synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) along with OE of each factor showed regulation of synaptogenesis and neurodevelopment (when miR134 is not expressed) in three different regulatory states (RS1), upregulation (100%), regulation between 0%-100% and downregulation (0%). OE of genes positively regulating neurodevelopment (when miR134 is expressed) along with OE of each factor showed regulation of neurodevelopment in three different regulatory states (RS1), upregulation (100%), regulation between 0%-100% and downregulation (0%).

Simulation 2: OE of genes positively regulating synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) along with OE of each factor showed regulation of synaptogenesis as well as

neurodevelopment (when miR134 is not expressed) in two different regulatory states (RS4), upregulation (100%) and regulation between 0%-100%.

Simulation 3: OE of genes positively regulating synaptogenesis (when BDNF is expressed)/ neurodevelopment (miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) along with OE of each factor, downregulated synaptogenesis and neurodevelopment (when miR134 is not expressed) (0%).

Simulation 4: OE of genes positively regulating synaptogenesis (when BDNF is expressed)/ neurodevelopment (when miR134 is expressed)/ neurodevelopment (when miR134 is not expressed) along with OE of each factor showed regulation of synaptogenesis as well as neurodevelopment (when miR134 is not expressed) in two different regulatory states (RS3), downregulation (0%) and regulation between 0%-100%.

PC5 (Simulations 1-4): KO of genes positively regulating each stage of development along with KO of each factor, downregulated each same stage of development (0%).

Summary of the NP results for BDNF interactome is given in Table 14Table 14 and Table 15.

D. GRM5 interactome

During postnatal development, GRM5 interactome regulates proliferation, neurite growth and synaptogenesis. For performing node perturbation analysis, we have given two different Boolean rules for neurite growth stage, where HOMER1 is expressed along with GRM5 and regulates neurite growth. In the other rule, HOMER1 is not expressed and GRM5 is expressed. Similarly, GRM5 expression upregulates as well as downregulates synaptogenesis, so we have given two different Boolean rules for the stage, synaptogenesis. So, for the overall neurodevelopment process (combining all stages into one stage), we have given three different Boolean rules, where neurodevelopment is upregulated when GRM5 is

expressed (rule 1), neurodevelopment is upregulated when GRM5 and HOMER1 is expressed (rule 2) and neurodevelopment is upregulated when GRM5 is repressed (rule 3).

Single node perturbation

Perturbation condition 1: OE and KO of each miRNA and each TF regulating GRM5 interactome

Simulations 1-4: OE and KO of each miRNA and each TF downregulated proliferation, neurite growth (when GRM5 is expressed), neurite growth (when GRM5 and HOMER1 is expressed), synaptogenesis (when GRM5 is expressed), synaptogenesis (when GRM5 is not expressed), neurodevelopment (when GRM5 is repressed), neurodevelopment (when GRM5 and HOMER1 is expressed) and neurodevelopment (when GRM5 is expressed) (0%).

Perturbation condition 2: OE of genes positively regulating each stage of neurodevelopment (regulated by GRM5 interactome) and OE of miRNAs and TFs regulating GRM5 interactome

Simulations 1-4: OE of genes positively regulating each stage of neurodevelopment (proliferation, neurite growth (when GRM5 is expressed), neurite growth (when GRM5 and HOMER is expressed), synaptogenesis (when GRM5 is expressed), synaptogenesis (when GRM5 is not expressed), neurodevelopment (when GRM5 and HOMER1 is expressed), neurodevelopment (when GRM5 is repressed) and neurodevelopment (when GRM5 is expressed)) along with OE of miRNAs and TFs, upregulated each same stage of neurodevelopment (100%). Similarly, OE of genes positively regulating neurodevelopment (when GRM5 is expressed) along with OE of miRNAs and TFs, upregulated proliferation, neurite growth (when GRM5 is expressed), synaptogenesis (when GRM5 is expressed) and neurodevelopment (when GRM5 is expressed) (100%).

Perturbation condition 3: KO of genes regulating each stage of neurodevelopment (regulated by GRM5 interactome) and KO of miRNAs and TFs regulating GRM5 interactome)

Simulations 1-4: KO of genes positively regulating each stage of neurodevelopment (proliferation, neurite growth (when GRM5 is expressed), neurite growth (when GRM5 and HOMER is expressed), synaptogenesis (when GRM5 is expressed), synaptogenesis (when GRM5 is not expressed), neurodevelopment (when GRM5 and HOMER1 is expressed), neurodevelopment (when GRM5 is repressed) along with KO of miRNAs and TFs regulating GRM5 interactome, downregulated each same stage of neurodevelopment (0%).

Perturbation condition 4: OE of genes regulating each stage of neurodevelopment (regulated by GRM5 interactome) along with OE of each factor (miRNA/ TF) regulating GRM5 interactome

a. Proliferation

Simulations 1-4: OE of genes positively regulating proliferation/ neurodevelopment (when GRM5 is expressed) and OE of each miRNA/ TF, upregulated proliferation (100%).

Simulations 1 and 3: OE of genes positively regulating neurite growth (when GRM5 is expressed)/ synaptogenesis (when GRM5 is expressed) and OE of REST/ RUNX2/ NEUROD2 regulated proliferation (between 0%-100%). OE of genes positively regulating neurite growth (when GRM5 is expressed)/ synaptogenesis (when GRM5 is expressed) and OE of each factor (except REST/ RUNX2/ NEUROD2), downregulated proliferation (0%). Thus, proliferation is shown to be regulated by other stages of development in two different regulatory states (RS3), downregulation (0%) and regulation between 0%-100%.

b. Neurite growth (when GRM5 and HOMER1 is expressed)

Simulations 1-4: OE of genes positively regulating neurite growth (when GRM5 and HOMER1 is expressed)/ neurodevelopment (when GRM5 and HOMER1 is expressed) along with OE of each miRNA/ TF, upregulated neurite growth (100%).

c. Neurite growth (when GRM5 is expressed)

Simulations 1-4: OE of genes positively regulating neurite growth (when GRM5 is expressed)/ neurodevelopment (when GRM5 is expressed along with OE of each miRNA/ TF, upregulated neurite growth (100%).

d. Synaptogenesis (when GRM5 is expressed)

Simulations 1-4: OE of genes positively regulating neurodevelopment (when GRM5 is expressed)/ synaptogenesis (when GRM5 is expressed) along with OE of each miRNA/ TF, upregulated synaptogenesis (100%).

e. Synaptogenesis (when GRM5 is not expressed)

Simulations 1-4: OE of genes positively regulating synaptogenesis (when GRM5 is repressed) along with OE of each miRNA/ TF, upregulated synaptogenesis (100%).

f. Neurodevelopment (when GRM5 and HOMER1 is expressed)

Simulations 1-4: OE of genes positively regulating neurodevelopment (when GRM5 and HOMER1 is expressed) along with OE of each miRNA/ TF, upregulated neurodevelopment (100%).

g. Neurodevelopment (when GRM5 is expressed)

Simulations 1-4: OE of genes positively regulating neurodevelopment (when GRM5 is expressed) along with OE of each miRNA/ TF, upregulated neurodevelopment (100%).

h. Neurodevelopment (when GRM5 is repressed)

Simulations 1-4: OE of genes positively regulating neurodevelopment (when GRM5 is repressed) along with OE of each miRNA/ TF, upregulated neurodevelopment (100%).

Perturbation condition 5: KO of all genes positively regulating each stage of neurodevelopment (regulated by GRM5 interactome) along with KO of each factor (miRNA/ TF) regulating GRM5 interactome

Simulations 1-4: KO of all genes positively regulating each stage of neurodevelopment (proliferation, neurite growth (when GRM5 is expressed), neurite growth (when GRM5 and HOMER is expressed), synaptogenesis (when GRM5 is expressed), synaptogenesis (when

GRM5 is not expressed), neurodevelopment (when GRM5 and HOMER1 is expressed), neurodevelopment (when GRM5 is repressed) along with KO of each factor (miRNA/ TF), downregulated each same stage of neurodevelopment (0%).

Table 16: Perturbation results of GRM5 interactome involved in postnatal development

Perturbed nodes	PC	Effect of perturbation on each stage at t =150 (Activation frequency for 1000 simulations at t = 150)															
		Proliferation				Neurite growth (when GRM5 and HOMER1 is expressed)				Neurite growth (when GRM5 is expressed)				Synaptogenesis (when GRM5 is expressed)			
		Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4
Factors	1	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating proliferation and factors	2	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes negatively regulating neurite growth (when GRM5 and HOMER1 is expressed) and factors	2	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurite growth (when GRM5 is expressed) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	RS3	0%	RS3	0%	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating synaptogenesis (when GRM5 is expressed) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	RS3	0%	RS3	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating synaptogenesis (when GRM5 is not expressed) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

Genes positively regulating neurodevelopment (GRM5 and HOMER1 is expressed) and factors	2	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment (GRM5 expressed) and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment (GRM5 repressed) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

PC: Perturbation condition; Sim1: Simulation 1; Sim2: Simulation 2; Sim3: Simulation 3; Sim4: Simulation 4; RS3 represents regulatory state 3, where PC leads to upregulation (100%), regulation between 0%-100% and downregulation (0%)

Table 17: Perturbation results of GRM5 interactome involved in postnatal development (contd)

Perturbed nodes	PC	Effect of perturbation on each stage at t =150 (Activation frequency for 1000 simulations at t = 150)															
		Synaptogenesis (when GRM5 is not expressed)				Neurodevelopment (when GRM5 and HOMER1 is expressed)				Neurodevelopment (when GRM5 is expressed)				Neurodevelopment (when GRM5 is repressed)			
		Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4
Factors	1	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating proliferation and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurite growth (when GRM5 and HOMER1 is expressed) and	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

factors	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurite growth (when GRM5 is expressed) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating synaptogenesis (when GRM5 is expressed) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating synaptogenesis (when GRM5 is not expressed) and factors	2	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment (when GRM5 and HOMER1 is expressed) and factors	2	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment (when GRM5 is expressed) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment (when GRM5 is repressed) and factors	2	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

PC: Perturbation condition; Sim1: Simulation 1; Sim2: Simulation 2; Sim3: Simulation 3; Sim4: Simulation 4; Upregulation (100%), downregulation (0%)

Summary of node perturbation results of GRM5 interactome involved in postnatal development

PC1 (Simulations 1-4): Perturbation of each factor downregulated each of development. Perturbation of each factor showed upregulation (100%) of neurite growth (when GRM5 is not expressed).

PC2 (Simulations 1-4): OE of genes positively regulating each stage of development along with OE of all factors regulating GRM5 interactome, upregulated each same stage of development (100%). OE of genes positively regulating neurodevelopment (when GRM5 is expressed) along with OE of all factors, upregulated (100%) each stage of development (synaptogenesis (when GRM5 is not expressed) and neurodevelopment (when GRM5 is not expressed)).

PC3 (Simulations 1-4): KO of genes positively regulating each stage of development along with KO of all factors regulating GRM5 interactome, downregulated each same stage of development (0%).

PC4 (Simulations 1-4): OE of genes positively regulating each stage of development along with OE of each factor, showed upregulation of each same stage of development (100%). OE of genes positively regulating neurodevelopment (when GRM5 is expressed) along with OE of each factor, upregulated (100%) each stage of development (except synaptogenesis (when GRM5 is not expressed) and neurodevelopment (when GRM5 is not expressed)). OE of genes positively regulating neurodevelopment (when GRM5 and HOMER1 is expressed) along with OE of each factor, showed upregulation of neurite growth (when GRM5 and HOMER is expressed) (100%).

Simulations 1 and 3: OE of genes positively regulating neurite growth (when GRM5 is expressed), synaptogenesis (when GRM5 is expressed) along with OE of each factor, showed

overall proliferation process to be regulated in two regulatory states (RS3), downregulation (0%) and regulation between 0%-100%.

PC5 (Simulations 1-4): KO of genes positively regulating each stage of development along with KO of all factors regulating GRM5 interactome, downregulated each same stage of development (0%).

Summary the NP results for GRM5 interactome is given in Table 16 and Table 17.

E. NRG1 interactome

NRG1 regulates differentiation, myelination and synaptogenesis. NRG1 gene has been shown to be regulated only by miR124, in turn miR124 is regulated by TFs, STAT3, REST and EGR1. The direction of regulation of miRNA by these four TFs has been experimentally shown. Therefore, Boolean rules for simulation 1 and 3 remains same, as TF upregulates gene expression in both simulations and the TF regulation of miRNA expression also does not change in both the simulations. Similarly, Boolean rules for simulations 2 and 4 are same, as TF downregulates gene expression in both the simulations and the TF regulation of miRNA expression does not change in both the simulations. We have given two different Boolean rules for synaptogenesis, where DISC1 expression upregulates synaptogenesis (rule 1) and NRG1 expression upregulates synaptogenesis (rule 2).

Single node perturbation

Perturbation condition 1: OE and KO of each miRNA and each TF regulating NRG1 interactome

Simulations 1-4: OE of each miRNA and each TF, downregulated (0%) each stage of development (proliferation, differentiation, myelination, synaptogenesis (DISC1 is expressed), synaptogenesis (when NRG1 is expressed), neurodevelopment). KO of each miRNA downregulated proliferation, differentiation, myelination and synaptogenesis (when NRG1 is expressed) (0%). KO of each TF downregulated proliferation, differentiation,

myelination, synaptogenesis (when DISC1 is expressed) and synaptogenesis (when NRG1 is expressed) (0%).

a. Synaptogenesis (when DISC1 is expressed)

Simulations 1 and 3: We observed regulation of synaptogenesis in two different regulatory states (RS2), downregulation (0%) and upregulation (100%). KO of miR124 upregulated (100%) synaptogenesis (when DISC1 is expressed). KO of each factor (except miR124), downregulated (0%) synaptogenesis (when DISC1 is expressed).

Perturbation condition 2: OE of genes regulating each stage of neurodevelopment (regulated by NRG1 interactome) and OE of miRNAs and TFs regulating NRG1 interactome)

Simulations 1-4: OE of genes positively regulating each stage of neurodevelopment (proliferation, differentiation, myelination, synaptogenesis (when DISC1 is expressed), synaptogenesis (when NRG1 is expressed) and neurodevelopment) and OE of all miRNAs and TFs, upregulated each same stage of neurodevelopment (100%). OE of genes positively regulating neurodevelopment along with OE of miRNAs and TFs, upregulated proliferation, differentiation, myelination, synaptogenesis (when NRG1 is expressed), neurodevelopment (100%).

a. Proliferation

Simulations 1-4: OE of genes positively regulating differentiation/myelination/ synaptogenesis (when NRG1 is expressed) along with OE of miRNAs and TFs, upregulated proliferation (100%).

b. Differentiation

Simulations 1-4: OE of genes positively regulating proliferation/myelination/ synaptogenesis (when NRG1 is expressed) along with OE of miRNAs and TFs, upregulated differentiation (100%).

c. Myelination

Simulations 1-4: OE of genes positively regulating proliferation/ differentiation/ synaptogenesis (when NRG1 is expressed) along with OE of miRNAs and TFs upregulated myelination (100%).

Perturbation condition 3: KO of genes positively regulating each stage of neurodevelopment (regulated by NRG1 interactome) and KO of miRNAs and TFs regulating NRG1 interactome

Simulations 1-4: KO of genes positively regulating each stage of neurodevelopment (proliferation, differentiation, myelination, synaptogenesis (when DISC1 is expressed), synaptogenesis (when NRG1 is expressed), neurodevelopment (when DISC1 is expressed), neurodevelopment) and KO of all miRNAs and TFs, downregulated each same stage of neurodevelopment (0%).

a. Synaptogenesis (DISC1 is expressed)

Simulations 2 and 4: KO of genes positively regulating proliferation/ differentiation/ myelination/ synaptogenesis (when NRG1 is expressed)/ neurodevelopment and KO of all miRNAs and TFs, upregulated synaptogenesis (when DISC1 is expressed) (100%).

Perturbation condition 4: OE of genes positively regulating each stage of neurodevelopment (regulated by NRG1 interactome) along with OE of each factor (miRNA/ TF) regulating NRG1 interactome

a. Proliferation

Simulations 1-4: OE of genes positively regulating proliferation/ differentiation/ myelination/ synaptogenesis (when NRG1 is expressed)/ neurodevelopment and OE of each miRNA/ TF, upregulated proliferation (100%).

b. Differentiation

Simulations 1-4: OE of genes positively regulating proliferation/ differentiation/ myelination/ synaptogenesis (when NRG1 is expressed)/ neurodevelopment and OE of each miRNA/ TF, upregulated differentiation (100%).

c. Myelination

Simulations 1 and 3: OE of genes positively regulating proliferation/ differentiation along with OE of each miRNA/TF (except OE of EGR1) showed upregulation of myelination (100%). OE of genes positively regulating differentiation along with OE of EGR1 showed regulation of myelination between 0%-100%. OE of genes positively regulating myelination/ synaptogenesis (when NRG1 is expressed)/ neurodevelopment and OE of each miRNA/ TF, upregulated myelination (100%).

Simulations 2 and 4: OE of genes positively regulating proliferation/ differentiation/ myelination/ synaptogenesis (when NRG1 is expressed)/ neurodevelopment and OE of each miRNA/ TF, upregulated myelination (100%).

c. Synaptogenesis (when NRG1 is expressed)

Simulations 1-4: OE of genes positively regulating synaptogenesis (when NRG1 is expressed)/ neurodevelopment and OE of each miRNA/TF, upregulated synaptogenesis (100%).

d. Synaptogenesis (when DISC1 is expressed)

Simulations 1-4: OE of genes positively regulating synaptogenesis (when DISC1 is expressed) and OE of each miRNA/TF, upregulated synaptogenesis (100%).

Simulations 1 and 3: Synaptogenesis was shown to be regulated in all three regulatory states (RS1), upregulation (100%), regulation between 0%-100% and downregulation (0%). OE of genes positively regulating proliferation/ differentiation/ myelination and OE of miR124, downregulated synaptogenesis (0%). OE of genes positively regulating proliferation/ differentiation/ myelination and OE of EGR1 regulated synaptogenesis (between 0%-100%). OE of genes positively regulating proliferation/

differentiation/myelination and OE of each miRNA/TF (except OE of miR124 or EGR1) upregulated synaptogenesis (100%).

e. Neurodevelopment

Simulations 1-4: OE of genes positively regulating synaptogenesis (when NRG1 is expressed)/ neurodevelopment and OE of each miRNA/TF, upregulated neurodevelopment (100%).

Perturbation condition 5: KO of all genes positively regulating each stage of neurodevelopment (regulated by NRG1 interactome) along with KO of each factor (miRNA/TF) regulating NRG1 interactome

Simulations 1-4: KO of genes positively regulating each stage of neurodevelopment (proliferation, differentiation, myelination, synaptogenesis (when NRG1 is expressed), synaptogenesis (when DISC1 is expressed) and neurodevelopment) along with KO of each miRNA/ TF regulating NRG1 interactome, downregulated each same stage of neurodevelopment (0%).

a. Synaptogenesis (when DISC1 is expressed)

Simulations 1 and 3: KO of genes positively regulating proliferation/ differentiation/ myelination/ synaptogenesis (when NRG1 is expressed)/ neurodevelopment and each miRNA/TF KO upregulated synaptogenesis (100%).

Table 18: Perturbation results of NRG1 interactome involved in postnatal development

Perturbed nodes	PC	Effect of perturbation on each stage at t =150 (Activation frequency for 1000 simulations at t = 150)											
		Proliferation				Differentiation				Myelination			
		Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4
Factors	1	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating proliferation and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%	RS4	100%	RS4	100%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating differentiation and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%	RS4	100%	RS4	100%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating myelination and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating synaptogenesis (when NRG1 is expressed) and factors	2	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating synaptogenesis (when DISC1 is expressed) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating	2	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%

neurodevelopment and factors	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4					100%	100%	100%	100%	100%	100%	100%	100%
	5					0%	0%	0%	0%	0%	0%	0%	0%

PC: Perturbation condition; Sim1: Simulation 1; Sim2: Simulation 2; Simulation 3; Sim4: Simulation 4; RS1 represents regulatory state 1, where PC leads to upregulation (100%), regulation between 0%-100% and downregulation (0%); RS2 represents regulatory state 2, where PC leads to upregulation (100%) and downregulation (0%); RS4 represents regulatory state 4, where PC leads to upregulation (100%) and regulation between 0%-100%

Table 19: Perturbation results of NRG1 interactome involved in postnatal development (contd)

Perturbed nodes	PC	Effect of perturbation on each stage at t =150 (Activation frequency for 1000 simulations at t = 150)							
		Synaptogenesis (when DISC1 is expressed)				Neurodevelopment			
		Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4
Factors	1	RS2	0%	RS2	0%	0%	0%	0%	0%
Genes positively regulating proliferation and factors	2	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	100%	0%	100%	0%	0%	0%	0%
	4	RS1	0%	RS1	0%	0%	0%	0%	0%
	5	100%	0%	100%	0%	0%	0%	0%	0%
Genes positively regulating differentiation and factors	2	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	100%	0%	100%	0%	0%	0%	0%
	4	RS1	0%	RS1	0%	0%	0%	0%	0%
	5	100%	0%	100%	0%	0%	0%	0%	0%
Genes positively regulating myelination and factors	2	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	100%	0%	100%	0%	0%	0%	0%
	4	RS1	0%	RS1	0%	0%	0%	0%	0%
	5	100%	0%	100%	0%	0%	0%	0%	0%
Genes positively regulating synaptogenesis (when NRG1 is expressed) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	100%	0%	100%	0%	0%	0%	0%
	4	0%	0%	0%	0%	100%	100%	100%	100%

	5	100%	0%	100%	0%	0%	0%	0%	0%
Genes positively regulating synaptogenesis (when DISC1 is expressed) and factors	2	100%	100%	100%	100%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating neurodevelopment and factors	2	0%	0%	0%	0%	100%	100%	100%	100%
	3	0%	100%	0%	100%	0%	0%	0%	0%
	4	0%	0%	0%	0%	100%	100%	100%	100%
	5	100%	0%	100%	0%	0%	0%	0%	0%

PC: Perturbation condition; Sim1: Simulation 1; Sim2: Simulation 2; Simulation 3; Sim4: Simulation 4; RS1 represents regulatory state 1, where PC leads to upregulation (100%), regulation between 0%-100% and downregulation (0%); RS2 represents regulatory state 2, where PC leads to upregulation (100%) and downregulation (0%); RS4 represents regulatory state 4, where PC leads to upregulation (100%) and regulation between 0%-100%

Summary of node perturbation results regulating NRG1 interactome involved in postnatal development

PC1 (Simulations 1-4): Perturbation of each factor, downregulated each stage (except synaptogenesis (when NRG1 is expressed) of development (0%).

Simulations 1 and 3: Perturbation of each factor showed overall regulation of synaptogenesis in two different regulatory states (RS2), downregulation (0%) and regulation between 0%-100%.

PC2 (Simulations 1-4): OE of genes positively each stage along with OE of factors upregulated each same stage of development (100%). OE of genes positively regulating neurodevelopment, showed upregulation (100%) of each stage (except synaptogenesis (when DISC1 is expressed)). OE of genes positively regulating differentiation/ myelination/ synaptogenesis (when NRG1 is expressed) along with OE of factors, upregulated proliferation (100%). OE of genes positively regulating proliferation/ myelination/ synaptogenesis (when NRG1 is expressed) along with OE of factors, upregulated differentiation (100%). Similarly, OE of genes positively regulating proliferation/ differentiation/ synaptogenesis (when NRG1 is expressed) along with OE of factors, showed upregulation of myelination (100%).

PC3 (Simulations 1-4): KO of genes positively regulating each stage of development along with KO of all factors regulating NRG1 interactome, downregulated each same stage of development (0%).

Simulations 2 and 4: KO of genes positively regulating proliferation/ differentiation/ myelination/ synaptogenesis (when NRG1 is expressed)/ neurodevelopment along with KO of all factors, upregulated (100%) synaptogenesis (when DISC1 is expressed).

PC4 (Simulations 1-4): OE of genes positively each stage along with OE of each factor upregulated each same stage of development (100%). OE of genes positively regulating

neurodevelopment, showed upregulation (100%) of each stage (except synaptogenesis (when DISC1 is expressed)). OE of genes positively regulating differentiation/ myelination/ synaptogenesis (when NRG1 is expressed) along with OE of each factor, upregulated differentiation (100%). OE of genes positively regulating proliferation/ myelination/ synaptogenesis (when NRG1 is expressed) along with OE of each factor, upregulated differentiation (100%). Similarly, OE of genes positively regulating proliferation/ differentiation/ synaptogenesis (when NRG1 is expressed) along with OE of each factor, showed upregulation of myelination (100%).

OE of genes positively regulating synaptogenesis (when NRG1 is expressed)/ neurodevelopment and OE of each factor, showed upregulation of neurodevelopment (100%).

Simulations 1 and 3: OE of genes positively regulating proliferation/ myelination/ differentiation along with OE of each factor, showed overall regulation of synaptogenesis (when DISC1 is expressed) in all three different regulatory states (RS1), upregulation (100%), regulation between 0%-100% and downregulation (0%). Similarly, OE of genes positively regulating proliferation/ differentiation along with OE of each factor, showed overall regulation of myelination in two different regulatory states (RS4), upregulation (100%) and regulation between 0%-100%.

PC5 (Simulations 1-4): KO of genes positively regulating each stage of development along with KO of each factor regulating NRG1 interactome, downregulated each same stage of development (0%).

Simulations 1 and 3: KO of genes positively regulating proliferation/ differentiation/ myelination/ synaptogenesis (when NRG1 is expressed)/ neurodevelopment (when NRG1 is

expressed) along with KO of each factor, upregulated (100%) synaptogenesis (when DISC1 is expressed).

Summary of the NP results for NRG1 interactome is given in Table 18Table 18 and Table 19Table 19.

F. YWHAE interactome

During prenatal development, YWHAE interactome regulates neurite growth

Single gene perturbation

Perturbation condition 1: OE and KO of each miRNA and each TF regulating YWHAE interactome

Simulations 1-4: OE and KO of each miRNA and each TF regulating YWHAE interactome, downregulated neurite growth (0%).

Multiple gene perturbation

Perturbation condition 2: OE of genes positively regulating each stage of neurodevelopment (regulated by YWHAE interactome) and OE of miRNAs and TFs regulating YWHAE interactome

Simulations 1-4: OE of all genes positively regulating neurite growth and OE of all miRNAs and TFs upregulated neurite growth (100%).

Perturbation condition 3: KO of genes positively regulating each stage of neurodevelopment (regulated by YWHAE interactome) and OE of miRNAs and TFs regulating YWHAE interactome

Simulations 1-4: KO of all genes positively regulating neurite growth and KO of all miRNAs and TFs downregulated neurite growth (0%).

Perturbation condition 4: OE of all genes positively regulating each stage of neurodevelopment (regulated by YWHAE interactome) along with OE of each factor (miRNA/TF) regulating YWHAE interactome

Simulations 1-4: OE of all genes positively regulating neurite growth and OE of each miRNA/TF upregulated neurite growth (100%).

Perturbation condition 5: KO of all genes positively regulating each stage of neurodevelopment (regulated by YWHAE interactome) along with KO of each factor (miRNA/ TF) regulating YWHAE interactome

Simulations 1-4: KO of genes positively regulating neurite growth and KO of each miRNA/ TF downregulated neurite growth (0%).

Table 20: Perturbation results of YWHAE interactome involved in postnatal development

Perturbed nodes	PC	Effect of perturbation on each stage at t =150 (Activation frequency for 1000 simulations at t = 150)			
		Neurite growth			
		Sim1	Sim2	Sim3	Sim4
Factors	1	0%	0%	0%	0%
Genes positively regulating neurite growth and factors	2	100%	100%	100%	100%
	3	0%	0%	0%	0%
	4	100%	100%	100%	100%
	5	0%	0%	0%	0%

PC: Perturbation condition; Sim1: Simulation 1; Sim2: Simulation 2; Sim3: Simulation 3; Sim4: Simulation 4; Upregulation (100%), Downregulation (0)

Summary of node perturbation results of YWHAE interactome involved in postnatal development

YWHAE interactome regulated neurite growth during postnatal development. At all four simulations, perturbation of each factor (PC1) regulating YWHAE interactome showed downregulation of neurite growth (0%). Similarly, KO of genes positively regulating neurite growth along with KO of all factors (PC3)/ each factor (PC5), also showed downregulation of neurite growth (0%). But, OE of genes positively regulating neurite growth along with OE of all factors (PC2)/ each factor (PC4), showed upregulation of neurite growth (100%).

Summary of the NP results for YWHAE interactome is given in Table 20.

G. DLG2 interactome

During postnatal development, DLG2 interactome is shown to regulate synaptogenesis. DLG2 interactome has been shown to regulated by miR873 and EP300 (TF-miRNA FFLs).

Single node perturbation

Perturbation condition 1: OE and KO of each miRNA and each TF regulating DLG2 interactome

Simulations 1-4: OE and KO of miR873 and EP300 downregulated synaptogenesis (0%)

Multiple node perturbation

Perturbation condition 2: OE of genes positively regulating each stage of neurodevelopment (regulated by DLG2 interactome) and OE of miRNAs and TFs regulating DLG2 interactome

Simulations 1-4: OE of genes positively regulating synaptogenesis and OE of miR873 and EP300 regulating DLG2 interactome, upregulated synaptogenesis (100%).

Perturbation condition 3: KO of genes positively regulating each stage of neurodevelopment (regulated by DLG2 interactome) and KO of miRNAs, TFs regulating DLG2 interactome

Simulations 1-4: KO of genes positively regulating synaptogenesis and KO of miR873 and EP300 regulating DLG2 interactome, downregulated synaptogenesis (0%).

Perturbation condition 4: OE of genes positively regulating each stage of neurodevelopment (regulated by DLG2 interactome) along with OE of each factor (miRNA/ TF) regulating DLG2 interactome

Simulations 1-4: OE of genes positively regulating synaptogenesis and OE of EP300/ miR873, upregulated synaptogenesis (100%).

Perturbation condition 5: KO of genes positively regulating each stage of neurodevelopment (regulated by DLG2 interactome) along with KO of each factor (miRNA/TF) regulating DLG2 interactome

Simulations 1-4: KO of genes positively regulating synaptogenesis and KO of EP300/ miR873, downregulated synaptogenesis (0%).

Table 21: Perturbation results of DLG2 interactome involved in postnatal development

Perturbed nodes	PC	Effect of perturbation on each stage at t =150 (Activation frequency for 1000 simulations at t = 150)

		Synaptogenesis			
		Sim1	Sim2	Sim3	Sim4
Factors	1	0%	0%	0%	0%
Genes positively regulating synaptogenesis and factors	2	100%	100%	100%	100%
	3	0%	0%	0%	0%
	4	100%	100%	100%	100%
	5	0%	0%	0%	0%

PC: Perturbation condition; Sim1: Simulation 1; Sim2: Simulation 2; Sim3: Simulation 3; Sim4: Simulation 4; Upregulation (100%), Downregulation (0%)

Summary of node perturbation results of DLG2 interactome involved in postnatal development

DLG2 interactome regulated synaptogenesis during postnatal development. At all four simulations, perturbation of each factor (PC1) regulating DLG2 interactome showed downregulation of synaptogenesis (0%). Similarly, KO of genes positively regulating synaptogenesis along with KO of all factors (PC3)/ each factor (PC5), also showed downregulation of synaptogenesis (0%). But, OE of genes positively regulating synaptogenesis along with OE of all factors (PC2)/ each factor (PC4), showed upregulation of synaptogenesis (100%). Summary of the NP results for DLG2 interactome is given in Table 21Table 21.

h. GRIN2A interactome

During postnatal development, GRIN2A interactome regulates synaptogenesis. We have given two different Boolean rules for synaptogenesis, where GRIN2B expression upregulates synaptogenesis (rule 1) and GRIN2A expression downregulates synaptogenesis (rule 2).

Single gene perturbation

Perturbation condition 1: OE and KO of each miRNA and each TF regulating GRIN2A interactome

Simulations 1-4: OE and KO of each miRNA and each TF downregulated (0%) synaptogenesis (when GRIN2A is expressed) and synaptogenesis (when GRIN2B is expressed). OE and KO of

each miRNA and each TF (except KO of miR411/HNF4A) downregulated synaptogenesis (when GRIN2A is not expressed) (0%).

a. Synaptogenesis (when GRIN2A is not expressed)

Simulations 1 and 3: We observed that the overall synaptogenesis process to be regulated in two different regulatory states (RS3), regulation between 0%-100% and downregulation (0%). KO of miR411 regulated synaptogenesis (between 0%-100%).

Simulation 2 and 4: We observed that the overall synaptogenesis process is regulated in two different regulatory states (RS3), regulation between 0%-100% and downregulation (0%). KO of HNF4A regulates synaptogenesis (between 0%-100%)

Multiple node perturbation

Perturbation condition 2: OE of genes positively regulating each stage of neurodevelopment (regulated by GRIN2A interactome) and OE of miRNAs and TFs regulating GRIN2A interactome

a. Synaptogenesis (when GRIN2B is expressed)

Simulations 1-4: OE of genes positively regulating synaptogenesis (when GRIN2B is expressed) and OE of miRNAs and TFs regulating GRIN2A interactome, upregulated synaptogenesis (100%).

b. Synaptogenesis (when GRIN2A is expressed)

Simulations 1-4: OE of genes positively regulating synaptogenesis (when GRIN2A is expressed) and OE of miRNAs and TFs regulating GRIN2A interactome, upregulated synaptogenesis (100%).

c. Synaptogenesis (when GRIN2A is not expressed)

Simulations 1-4: OE of genes positively regulating synaptogenesis (when GRIN2A is not expressed) and OE of miRNAs and TFs regulating GRIN2A interactome, upregulated synaptogenesis (100%).

Perturbation condition 3: KO of genes regulating each stage of neurodevelopment (regulated by GRIN2A interactome) and KO of miRNAs and TFs regulating GRIN2A interactome

a. Synaptogenesis (when GRIN2B is expressed)

Simulations 1-4: KO of genes positively regulating synaptogenesis (GRIN2B is expressed) and KO of miRNAs and TFs, downregulated synaptogenesis (0%).

b. Synaptogenesis (when GRIN2A is expressed)

Simulations 1-4: KO of genes positively regulating synaptogenesis (when GRIN2A is expressed) and KO of miRNAs and TFs, downregulated synaptogenesis (0%).

c. Synaptogenesis (when GRIN2A is not expressed)

Simulations 1-4: KO of genes positively regulating synaptogenesis (when GRIN2A is not expressed) and KO of miRNAs and TFs, downregulated synaptogenesis (0%).

Perturbation condition 4: OE of genes positively regulating each stage of neurodevelopment (regulated by GRIN2A interactome) along with OE of each factor (miRNA/TF) regulating GRIN2A interactome

a. Synaptogenesis (when GRIN2B is expressed)

Simulations 1-4: OE of genes positively regulating synaptogenesis (when GRIN2B is expressed) and OE of each miRNA and each TF, upregulated synaptogenesis (100%).

b. Synaptogenesis (when GRIN2A is expressed)

Simulations 1-4: OE of genes positively regulating synaptogenesis (when GRIN2A is expressed) and OE of each miRNA and each TF, upregulated synaptogenesis (100%).

c. Synaptogenesis (GRIN2A is not expressed)

Simulations 1-4: OE of genes positively regulating synaptogenesis (when GRIN2A is not expressed) and OE of each miRNA and each TF, upregulated synaptogenesis (100%).

Perturbation condition 5: KO of genes positively regulating each stage of neurodevelopment (regulated by GRIN2A interactome) along with KO of each factor (miRNA/ TF) regulating GRIN2A interactome

a. Synaptogenesis (when GRIN2B is expressed)

Simulations 1-4: KO of genes positively regulating synaptogenesis (when GRIN2B is expressed) and KO of each miRNA and TF, downregulated synaptogenesis (0%).

b. Synaptogenesis (GRIN2A is expressed)

Simulations 1-4: KO of genes positively regulating synaptogenesis (when GRIN2A is expressed) and KO of each miRNA and each TF, downregulated synaptogenesis (0%).

c. Synaptogenesis (GRIN2A is not expressed)

Simulations 1-4: KO of genes positively regulating synaptogenesis (when GRIN2A is not expressed) and KO of each miRNA and each TF, downregulated synaptogenesis (0%).

Table 22: Perturbation results of GRIN2A interactome involved in postnatal development

Perturbed nodes	PC	Effect of perturbation on each stage at t =150 (Activation frequency for 1000 simulations at t = 150)											
		Synaptogenesis (when GRIN2B is not expressed)				Synaptogenesis (when GRIN2A is expressed)				Synaptogenesis (when GRIN2A is not expressed)			
		Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4	Sim1	Sim2	Sim3	Sim4
Factors	1	0%	0%	0%	0%	0%	0%	0%	0%	RS3	RS3	RS3	RS3
Genes positively regulating synaptogenesis (when GRIN2B is expressed) and factors	2	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	100%	100%	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating synaptogenesis (when GRIN2A is expressed) and factors	2	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	100%	100%	100%	100%	0%	0%	0%	0%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Genes positively regulating synaptogenesis (when GRIN2A is not expressed) and factors	2	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%
	3	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
	4	0%	0%	0%	0%	0%	0%	0%	0%	100%	100%	100%	100%
	5	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

PC: Perturbation condition; Sim1: Simulation 1, Sim2: Simulation 2; Sim3: Simulation 3; Sim4: Simulation 4

Summary of node perturbation results of GRIN2A interactome regulating postnatal development

GRIN2A interactome regulated synaptogenesis during postnatal development. From the curated experimental evidence, we observed that synaptogenesis is regulated in three different conditions, when GRIN2A and GRIN2B is expressed, when GRIN2A is not expressed and when GRIN2B is not expressed.

PC1 (Simulations 1-4): Perturbation of each factor, downregulated (0%) synaptogenesis (when GRIN2B is not expressed) and synaptogenesis (when GRIN2A is expressed).

We observed overall regulation of synaptogenesis (when GRIN2A is not expressed) in two different regulatory states (RS3), downregulation (0%) and regulation between 0%-100%. GRM3 (one of the positively regulating gene involved in synaptogenesis) has been shown to regulated by miR411-HNF4A composite FFLS. When either one of the factors is KO (miR411 in simulations 1 and 3 and HNF4A in simulations 2 and 4) synaptogenesis was shown to be regulated between 0%-100%.

Regulation of synaptogenesis (at PC2, PC3, PC4 and PC5)

OE of genes positively regulating synaptogenesis (when GRIN2A is expressed)/ synaptogenesis (when GRIN2A is not expressed)/ synaptogenesis (when GRIN2B is not expressed) along with OE of all factors (PC2) or OE of each factor (PC4), showed upregulation (100%) of synaptogenesis (when GRIN2A is expressed)/ synaptogenesis (when GRIN2A is not expressed)/ synaptogenesis (when GRIN2B is not expressed)

KO of genes positively regulating synaptogenesis (when GRIN2A is expressed)/ synaptogenesis (when GRIN2A is not expressed)/ synaptogenesis (when GRIN2B is not expressed) along with KO of all factors (PC3) or KO of each factor (PC5), showed downregulation (0%) of

synaptogenesis (when GRIN2A is expressed)/ synaptogenesis (when GRIN2A is not expressed)/ synaptogenesis (when GRIN2B is not expressed).

Summary of the NP results for GRIN2A interactome is given in Table 22Table 22.

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