

Utilizando abordagens computacionais para explorar o genoma humano e investigar os transtornos psiquiátricos

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Transtornos psiquiátricos: estrutura poligênica complexa

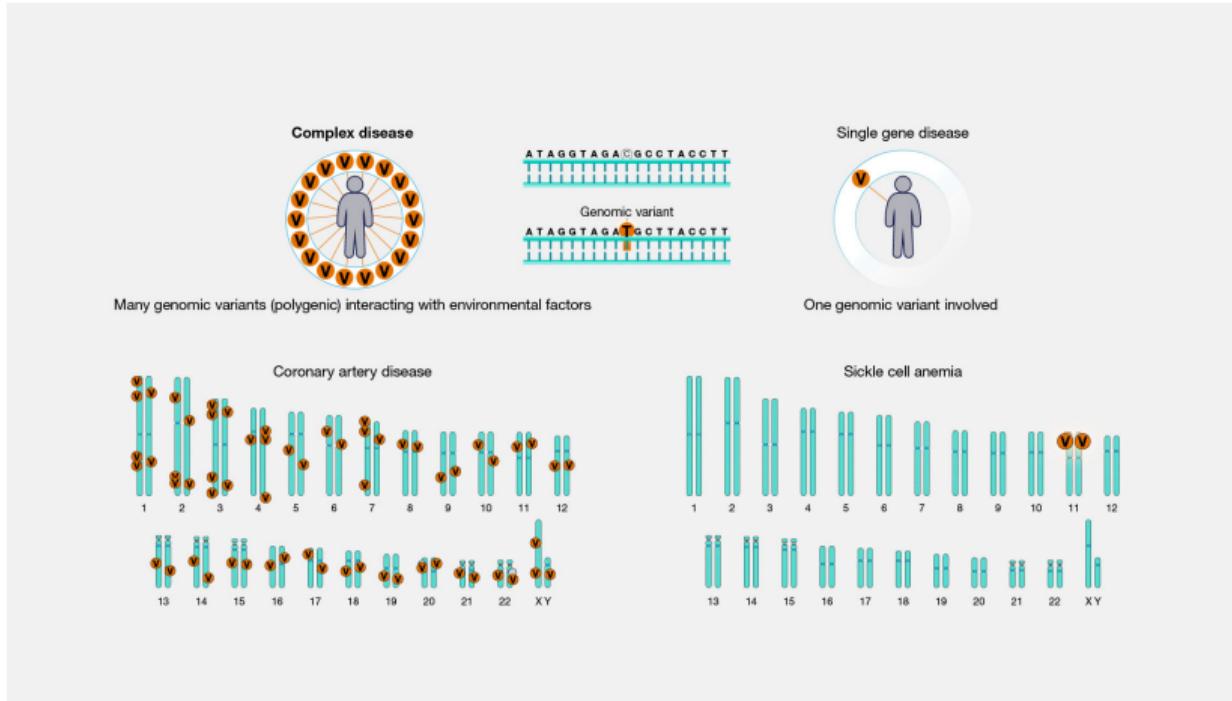


Figura 1: Doenças monogênicas vs doenças poligênicas (National Human Genome Research Institute, 2024).

Herdabilidade entre transtornos neuropsiquiátricos

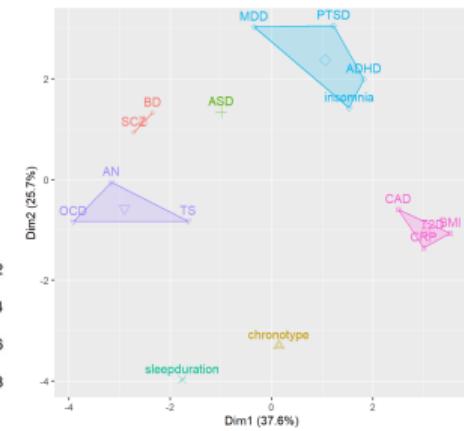
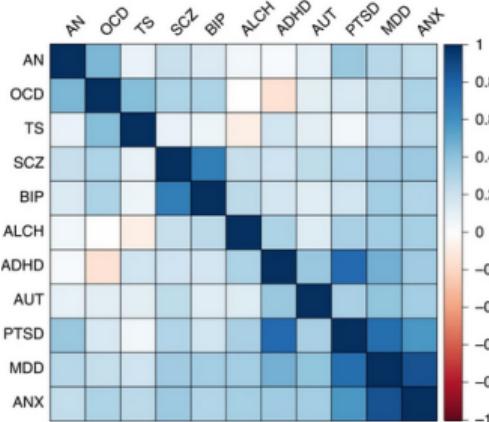
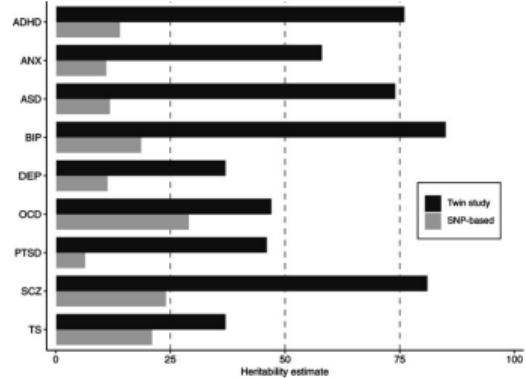


Figura 2: Herdabilidade e a correlação genética entre transtornos neuropsiquiátricos (Grotzinger et al., 2022, Krol et al., 2023).

Transtornos neuropsiquiátricos x neurodesenvolvimento

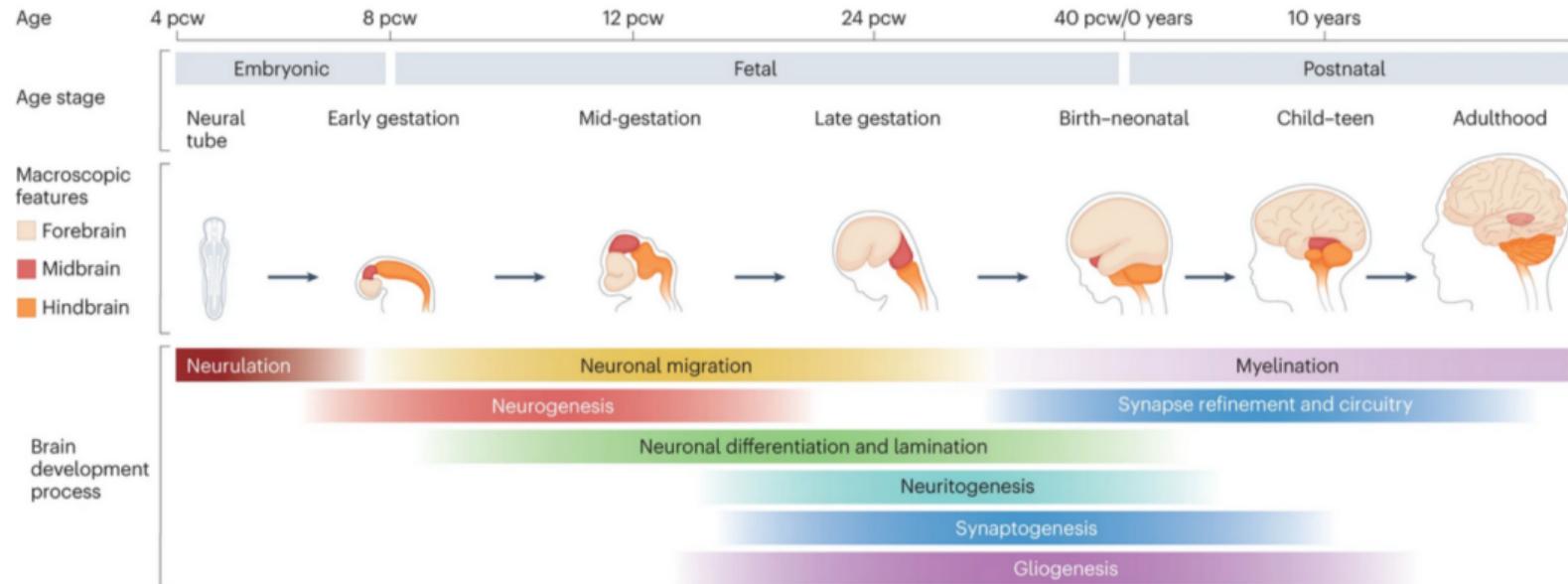


Figura 3: Processos chave do neurodesenvolvimento humano (Zhou et al., 2023).

Dados biológicos disponíveis (ômicas)

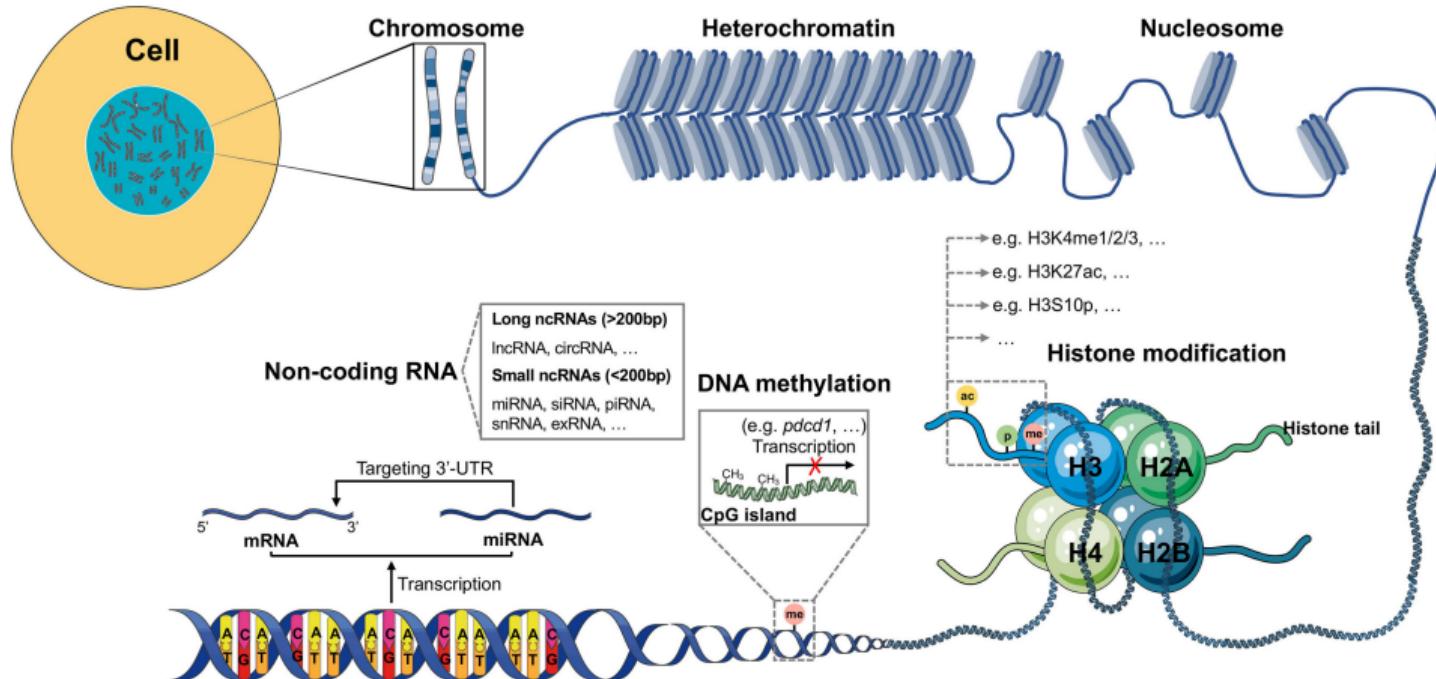


Figura 4: Modelo esquemático da regulação epigenética (Yang and Wang, 2021).

Sequenciamento genômico

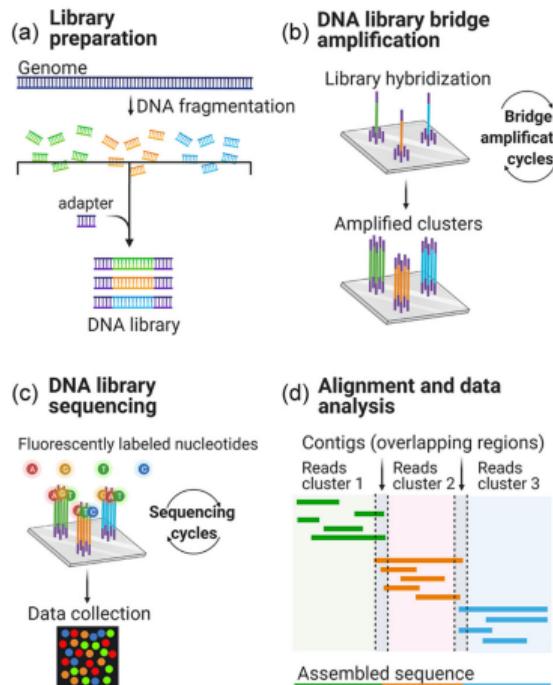


Figura 5: Processo de sequenciamento de nova geração (NGS ou next generation sequencing (Scholtz et al., 2021).

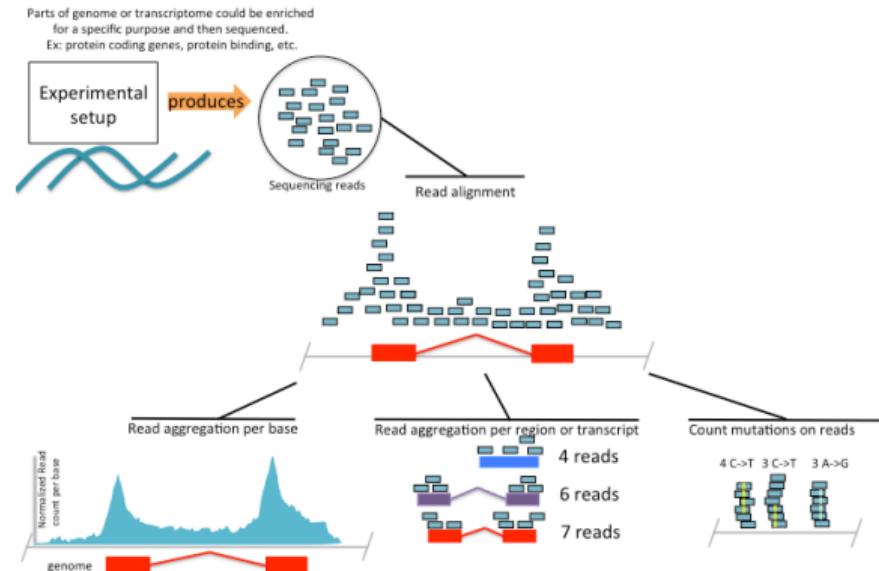


Figura 6: Challenges in interpreting GWAS associations (Akalin, 2020).

Arquivos importantes: .fasta/.fastq e .sam/.bam

```
Identifier  • @SRR566546_970 HWUSI-EAS1673_11067_FC7070M:4:1:2299:1109 length=50
Sequence   • TTGCCCTGCCTATCATTTTACTGCTCTGTCAGGTGACATGTGACGATCAGT
'-' sign   • +
Quality scores • hhhhhhhhhhhghhhhhhhhhhhfffffe'ee['X]b[died'[Y[-Y
Identifier  • @SRR566546_971 HWUSI-EAS1673_11067_FC7070M:4:1:2374:1108 length=50
Sequence   • GATTGTATGAACTATACTAACTCGCAGGTGGATCAGACTAAGTC
'-' sign   • +
Quality scores • hhggfhhcgghgffcfdfrehhhhcehdchhdbahheffffdde'bVd
```

Figura 7: Exemplo de um arquivo .fastq (Hosseini et al., 2016).

@HD VN:1.5 SO:coordinate							
@SQ SN:ref LN:45							
r001	99	ref	7	30	8M2I4M1D3M	=	37 39 TTAGATAAAGGATACTG *
r002	0	ref	9	30	3S6M1P1I4M	*	0 0 AAAAGATAAGGATA *
r003	0	ref	9	30	5S6M	*	0 0 GCCTAACGCTAA * SA:Z:ref,29,-,6H5M,17,0;
r004	0	ref	16	30	6M14N5M	*	0 0 ATAGCTTCAGC *
r003	2064	ref	29	17	6H5M	*	0 0 TAGGC * SA:Z:ref,9,+,5S6M,30,1;
r001	147	ref	37	30	9M	=	7 -39 CAGCGGCAT * NM:i:1

Optional fields in the format of TAG:TYPE:VALUE

SEQ: read sequence

TLEN: the number of bases covered by the reads from the same fragment. Plus/minus means the current read is the leftmost/rightmost read. E.g. compare first and last lines.

PNEXT: Position of the primary alignment of the NEXT read in the template. Set as 0 when the information is unavailable. It corresponds to POS column.

RNAME: reference sequence name of the primary alignment of the NEXT read. For paired-end sequencing, NEXT read is the paired read, corresponding to the RNAME column.

CIGAR: summary of alignment, e.g. insertion, deletion

MAPQ: mapping quality

POS: 1-based position

RNAME: reference sequence name, e.g. chromosome/transcript id

FLAG: indicates alignment information about the read, e.g. paired, aligned, etc.

QNAME: query template name, aka. read ID

Figura 8: Exemplo de um arquivo .sam (zyxue.github, 2017).

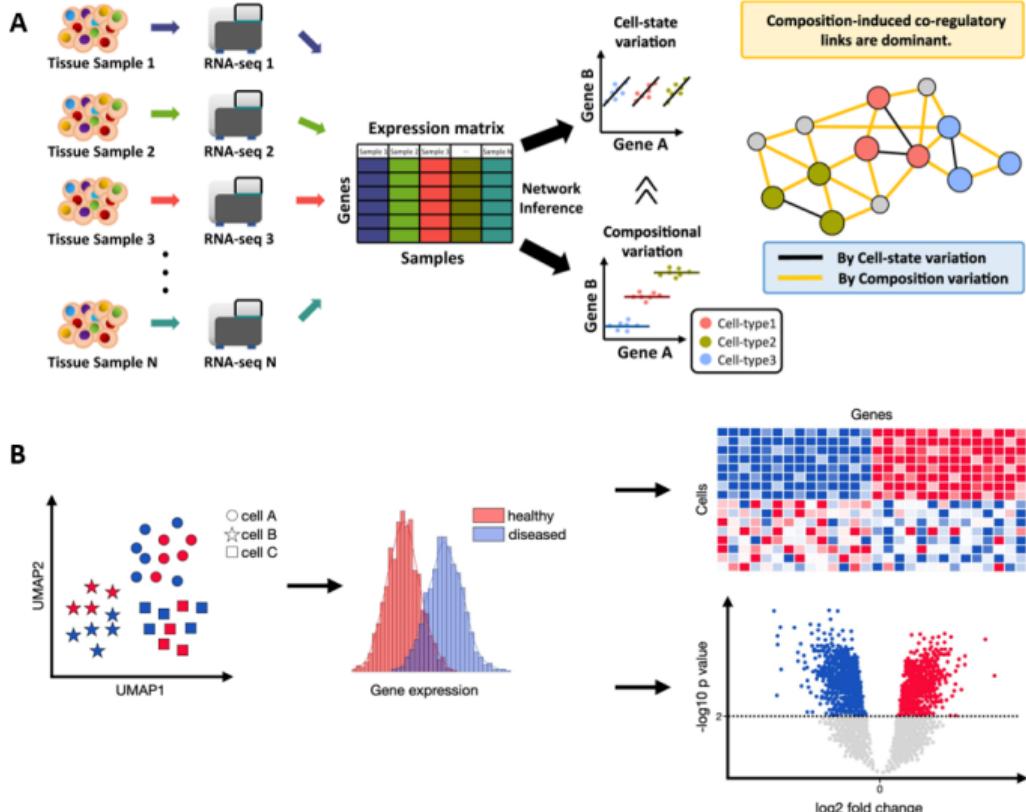


Figura 10: Tipos de análises possíveis com dados de sequenciamento (Cha and Lee, 2020).

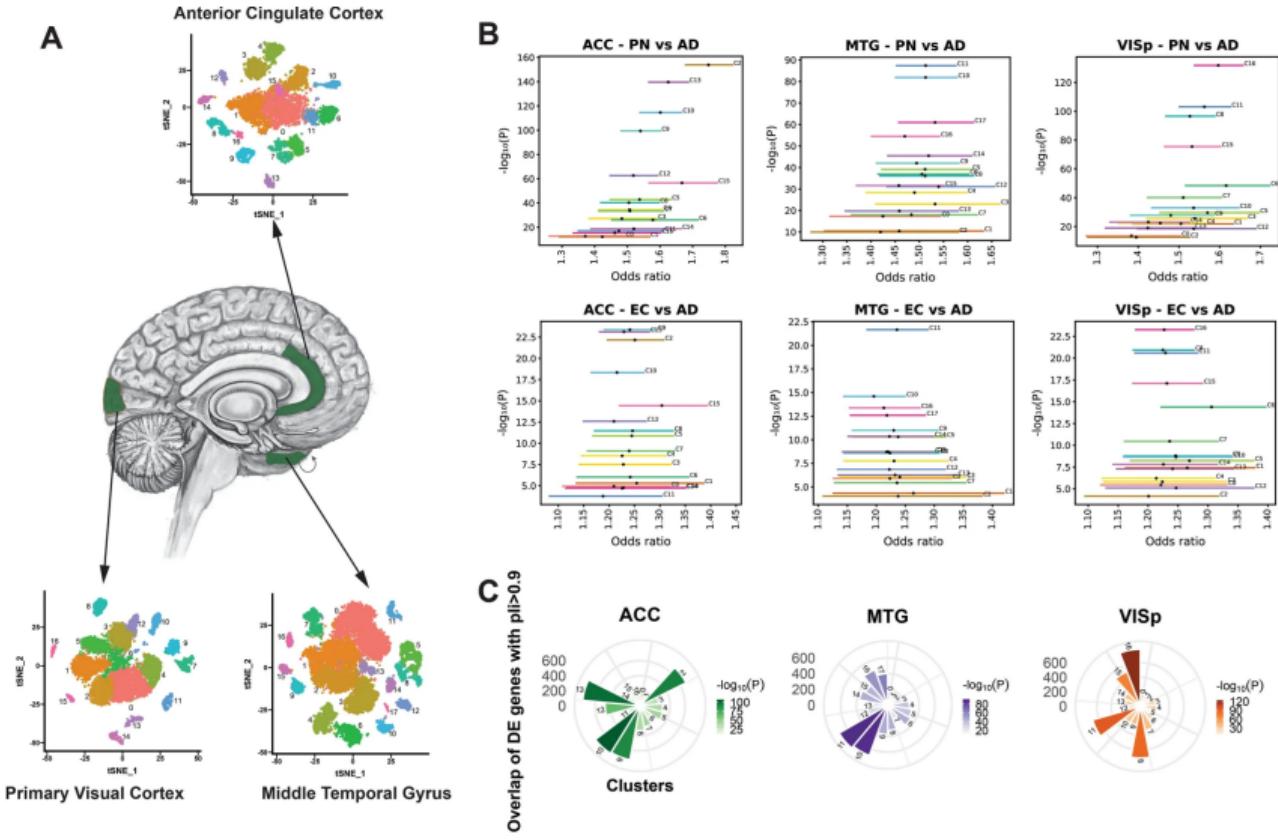


Figura 11: Analise de transcriptoma de 3 regioes cerebrais distintas proveniente de tecido postmortem (Nassir et al., 2021).

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Transtorno Obsessivo-Compulsivo (TOC ou OCD)

Environmental factors

- Perinatal events
- Stress
- Trauma
- Neuroinflammation

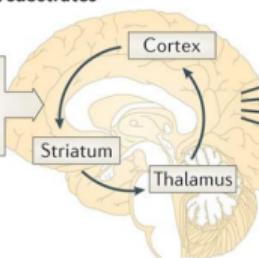
Triggers

Vulnerability

Neural substrates

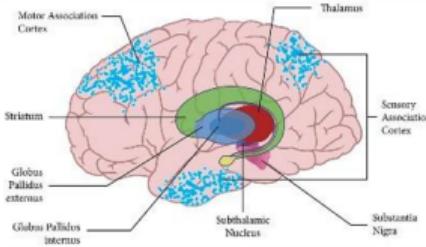
Transmission

- Glutamate
- Serotonin
- Dopamine



OCD dimensions

- Symmetry
- Taboo thoughts
- Contamination
- Hoarding



Genetic factors

- Gene variants
- Gene expression

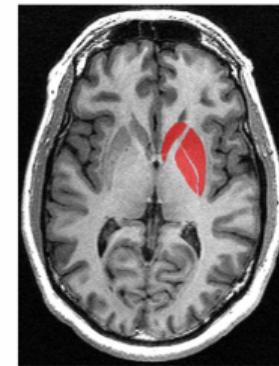
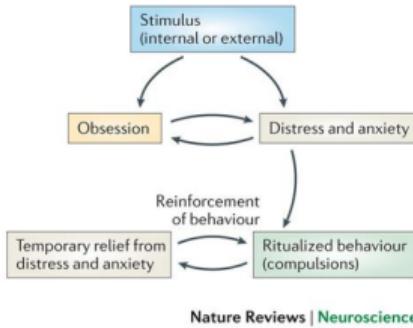
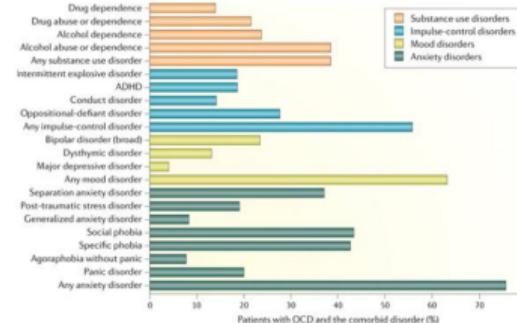


Figura 12: Prevalência de comorbidades no TOC (Stein et al., 2019, Pauls et al., 2014).

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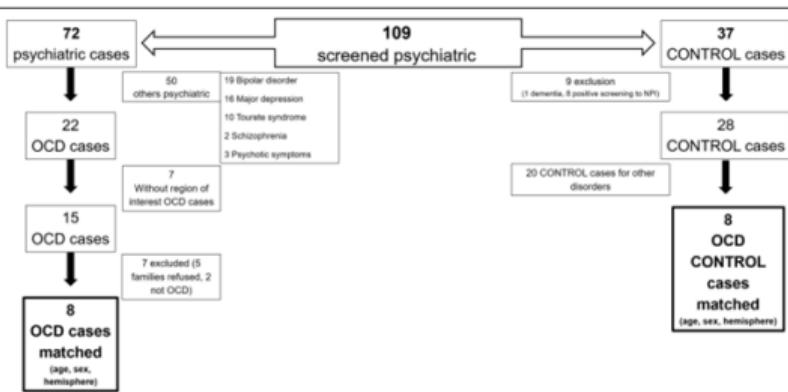
Initial findings of *striatum tripartite* model in OCD brain samples based on transcriptome analysis

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Supplementary Figure 1. Flowchart of samples collected and selected for this study.

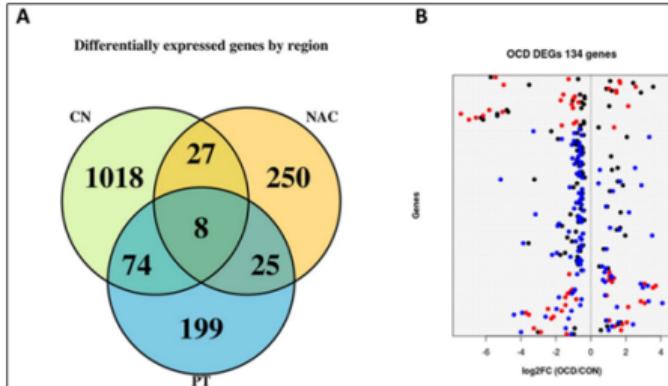


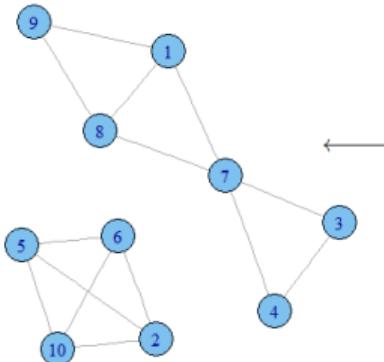
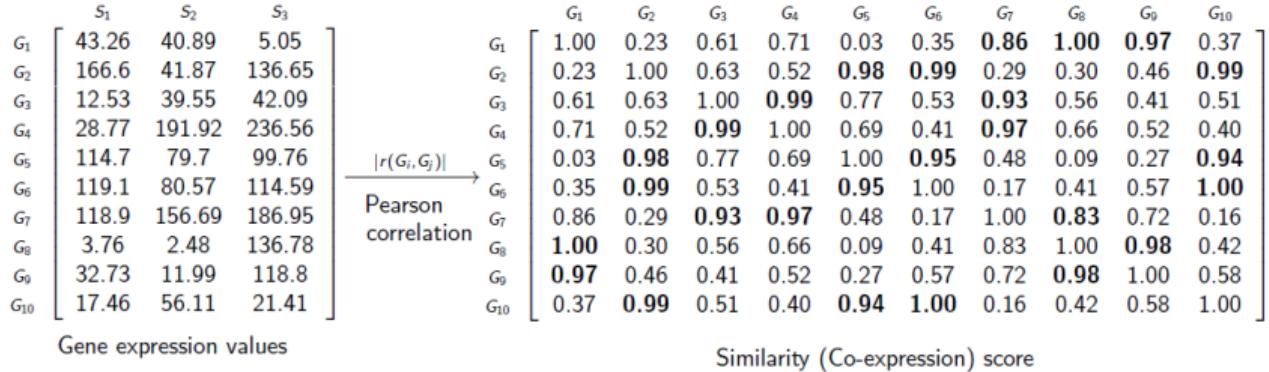
Figure 1. (A) Venn diagram of DEGs ($p\text{-value} \leq 0.01$) of each striatal region CN, NAC and PT. (B) Dot blot of log2FC (OCD/CON) on the x-axis, genes are represented on the y-axis. Each color corresponds to a striatal area CN (black), NAC (red) and PT (blue).

DEGs	Caudate Nucleus (CN)		Accumbens Nucleus (NAC)		Putamen (PT)	
	p-value	N matched genes	p-value	N matched genes	p-value	N matched genes
CNV's	0.1134	38	0.1930	11	0.8011	6
SNVs de novo	0.5010	1	1.0000	0	1.0000	0
GWAS	0.0514	10	0.7608	1	0.3971	2
Tourette syndrome	0.0001	159	0.0001	23	0.0001	35
Microglia	0.0001	108	0.5865	5	0.0290	10
Astrocytes	0.0186	32	0.3236	7	0.4389	6
Cortical Neuron 05	0.0411	12	0.0001	14	0.0988	4
Cortical Neuron 10	0.0001	51	0.0001	32	0.0001	20
Oligodendrocyte 01	0.1059	4	0.0867	2	0.0886	2
Oligodendrocyte 04	0.0001	14	1.0000	0	0.6662	1
Oligodendrocyte 2.5	0.0805	4	0.0078	3	0.0620	2

Table 2. Enrichment results for genes previously described in OCD studies and different brain cell types.

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	G_1	G_2	G_3	G_4	G_5	G_6	G_7	G_8	G_9	G_{10}
G_1	0	0	0	0	0	0	1	1	1	0
G_2	0	0	0	0	1	1	0	0	0	1
G_3	0	0	0	1	0	0	1	0	0	0
G_4	0	0	1	0	0	0	1	0	0	0
G_5	0	1	0	0	0	1	0	0	0	1
G_6	0	1	0	0	1	0	0	0	0	1
G_7	1	0	1	1	0	0	0	1	0	0
G_8	1	0	0	0	0	0	1	0	1	0
G_9	1	0	0	0	0	0	0	1	0	0
G_{10}	0	1	0	0	1	1	0	0	0	0

Network adjacency matrix $|r(G_i, G_j)| \geq 0.8$ Significance threshold

Figura 13: Criação de uma rede de co-expresão (S. Mohammad H. Oloomi, 2014).

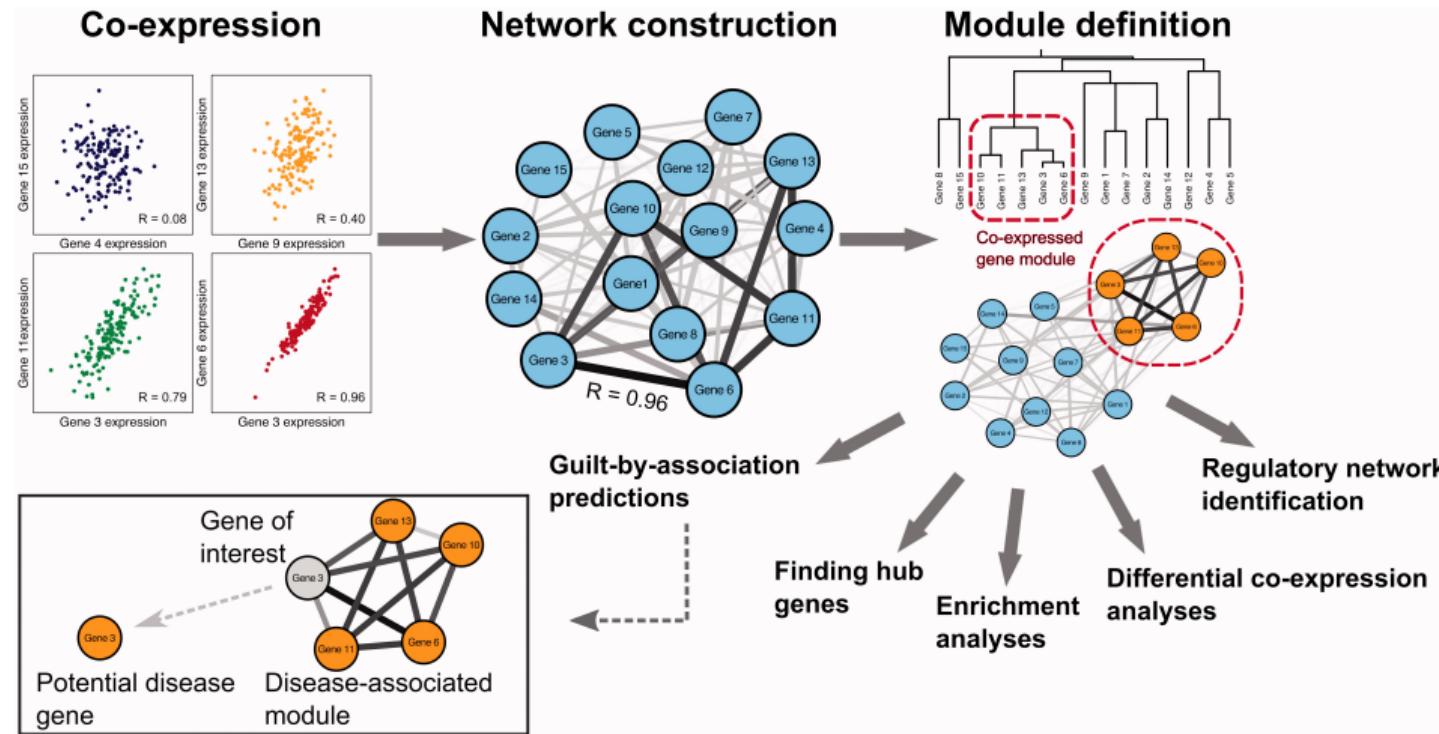


Figura 14: Analises possíveis de uma rede de co-expresão genica (van Dam et al., 2017).

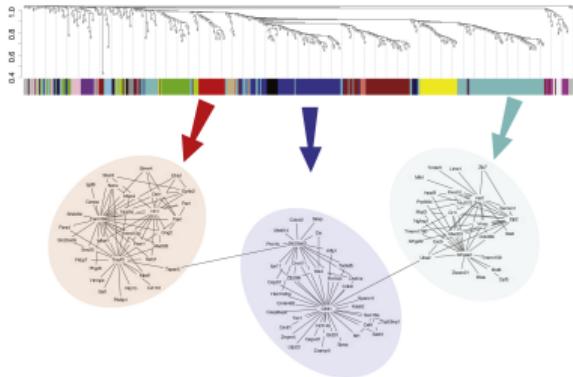
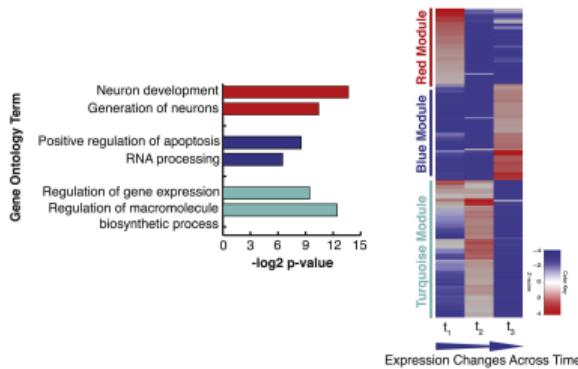
A.**B.**

Figura 15: Identificação de módulos em redes de co-expresão gênica (Silverman et al., 2016).

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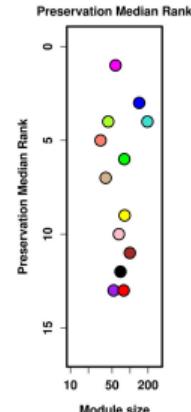
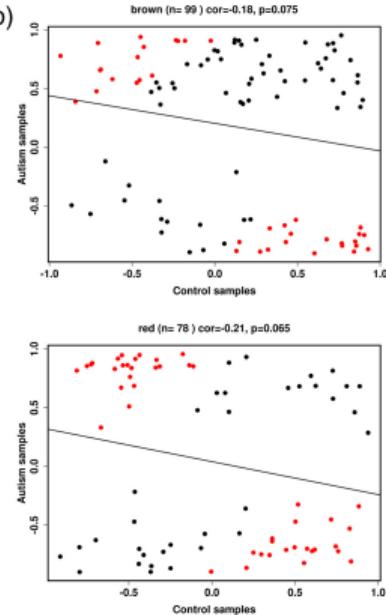
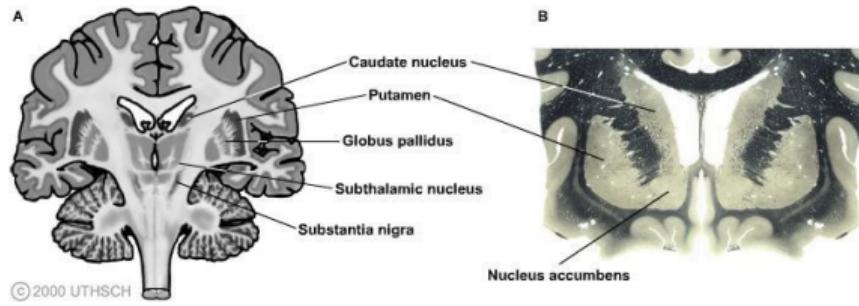
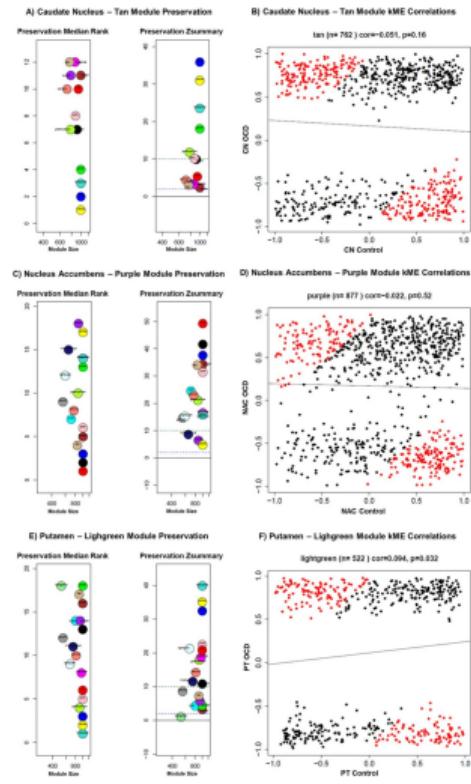
(a)**(b)**

Figura 16: Analise de preservação de módulos entre duas redes de co-expresão gênica (Tahira et al., 2019).



WGCNA	Caudate Nucleus (CN)		Accumbens Nucleus (NAC)		Putamen (PT)	
	p-value	N matched genes	p-value	N matched genes	p-value	N matched genes
CNVs	0.6897	24	0.9537	22	0.1908	22
SNVs <i>de novo</i>	1	0	0.4506	1	0.2982	1
GWAS	0.3103	6	0.7699	4	1	0
Tourette syndrome	0.7404	20	0.9642	18	0.5893	15
Adult Microglia	0.184	20	0.9883	10	0.9889	5
Astrocytes	0.1788	22	0.9716	13	0.0057	22
Cortical Neuron 05	0.9239	3	0.989	2	0.195	6
Cortical Neuron 10	0.9978	5	0.9889	8	6.00E-04	21
Oligodendrocyte 01	0.8266	1	0.3136	3	1	0
Oligodendrocyte 04	0.8996	2	0.9367	2	0.9268	1
Oligodendrocyte 2.5	0.8275	1	0.5891	2	0.6925	1

Figura 17: Comparação das redes de co-expresão do núcleo caudado, núcleo accumbens e putamen entre doadores com e sem TOC. Acima, diagrama com o plano coronal das principais estruturas cerebrais deste estudo (Byrne, 1997).

Especro da Esquizofrenia

DSM-5 diagnostic criteria for schizophrenia

Diagnostic criteria for schizophrenia from the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5)¹⁸⁴:

- A. Two or more of:
 - Delusions
 - Hallucinations
 - Disorganized speech
 - Grossly disorganized or catatonic behaviour
 - Negative symptoms, such as diminished emotional expression, avolition and anhedonia.
- B. Marked functional impairment, including interpersonal, academic and occupational.
- C. Continuous disturbance for at least 6 months, including 1 month of list A symptoms and can include a prodromal or residual period.
- D. Mood disorder excluded as a primary diagnosis.
- E. Symptoms not caused by physiological effects of a substance or another medical condition.
- F. In the context of autism spectrum disorder or communication issues, prominent delusions or hallucinations must be present to make a diagnosis.

Symptom glossary

- Delusions — fixed, culturally inappropriate false beliefs
- Hallucinations — false perception in any sensory modality
- Catatonia — immobility and extreme withdrawal
- Avolition — inability to execute self-directed activities
- Anhedonia — loss of enjoyment in pleasurable activities

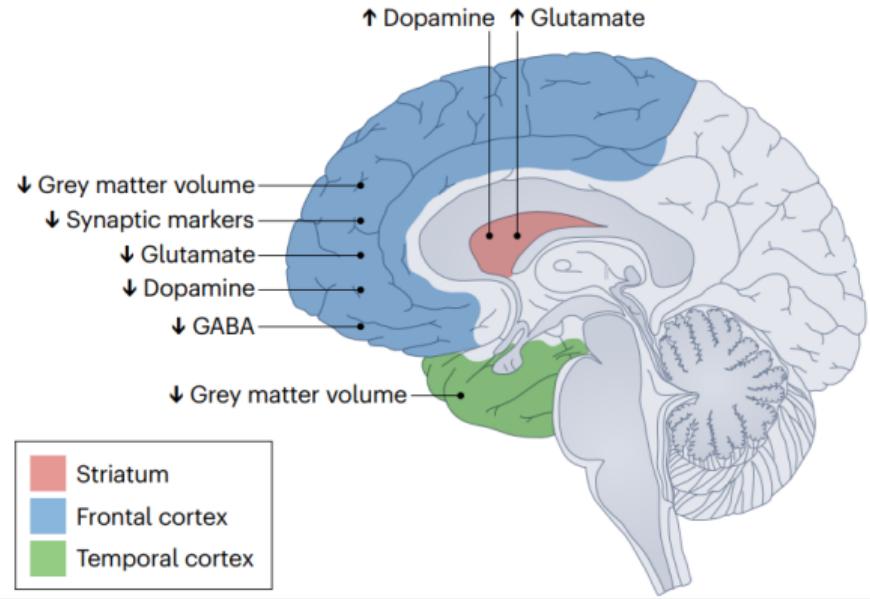


Figura 18: Sintomatologia da esquizofrenia (esq.) e disfunção do circuito dopaminérgica (dir) (Howes et al., 2023).

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- Esquizofrenia é um transtorno que afeta 1% da população mundial e com alta herdabilidade;
- Mais de 270 regiões genômicas associadas ao risco da esquizofrenia,
- Sabemos (a mais de 60 anos) que modulação dopamínérígica excessiva seria a mais provável causa para a psicose (antipsicóticos são muito eficientes em bloquear os receptores de dopamina D2)
- **PROBLEMA:** a maioria dos estudos *postmortem* se focou em regiões corticais (ex. córtex pré-frontal), locais com pouca expressão de receptores D2.
- Receptores de dopamina D2 são abundantes no corpo estriado

Analysis of the caudate nucleus transcriptome in individuals with schizophrenia highlights effects of antipsychotics and new risk genes

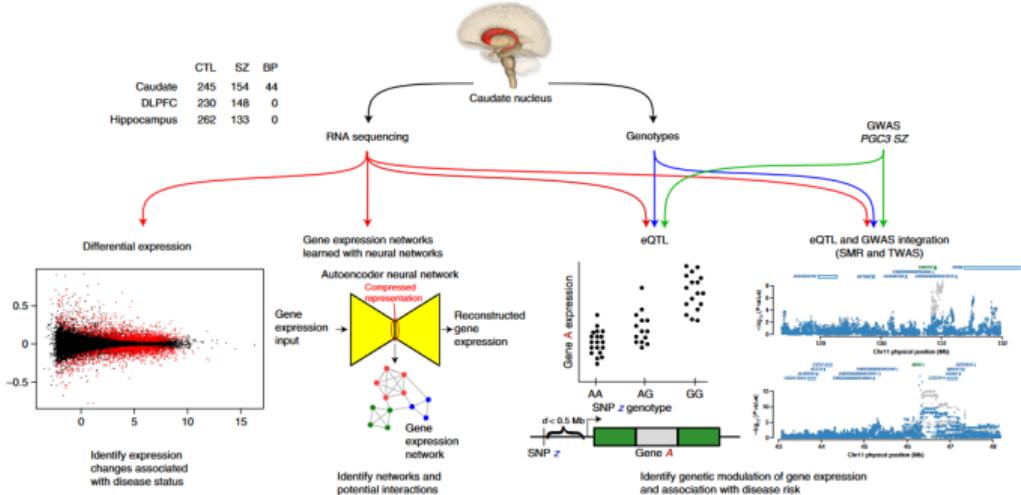
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 Daniel R. Weinberger^{1,2,3,4,5,6,7,8} & Apúia C. M. Paquola^{1,3,12}



GNVAE - Gene Networks with Variational AutoEncoders ¹

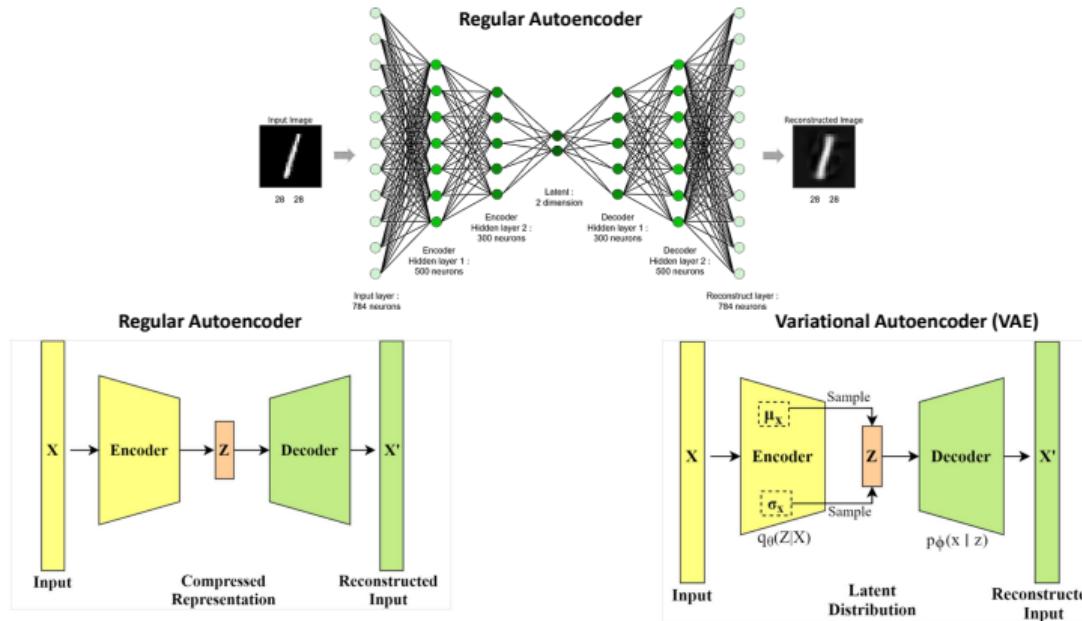
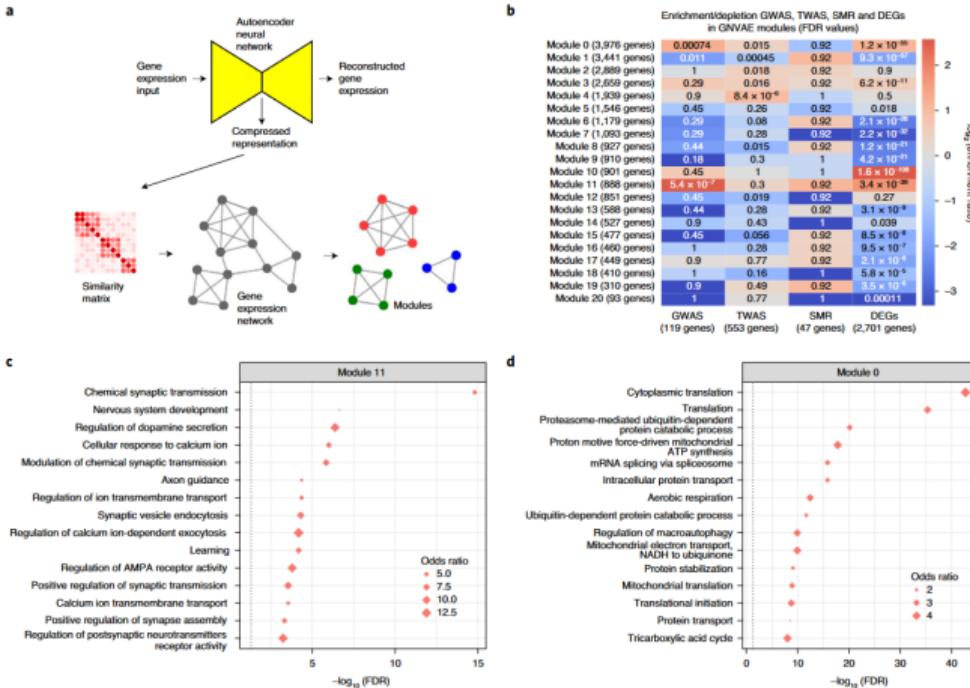


Figura 19: Autoencoder x Variational Autoencoder (<https://encodebox.medium.com/auto-encoder-in-biology-9264da118b83>)

¹<https://github.com/apuapaquola/GNVAE>

GNVAE - Gene Networks with Variational AutoEncoders ¹

- Mapeamento do perfil transcripcional do núcleo caudado no maior dataset *postmortem* relacionado a esquizofrenia publicado até agora;
- Identificação de 2701 genes diferencialmente expressos no núcleo caudado entre indivíduos neurotípicos e com esquizofrenia;
- Identificação de uma isoforma do gene DRD2 (receptor de Dopamina D2): **DRD2 short**. Diferencialmente expressa em indivíduos com esquizofrenia.
- São classificados como autoreceptores - responsáveis por regular a produção e recaptura de dopamina. Baixa produção de receptores **DRD2 short**.



¹ <https://github.com/apuapaquola/GNVAE>

Organoides cerebrais: criação de células-tronco de pluripotência induzida (iPSC)

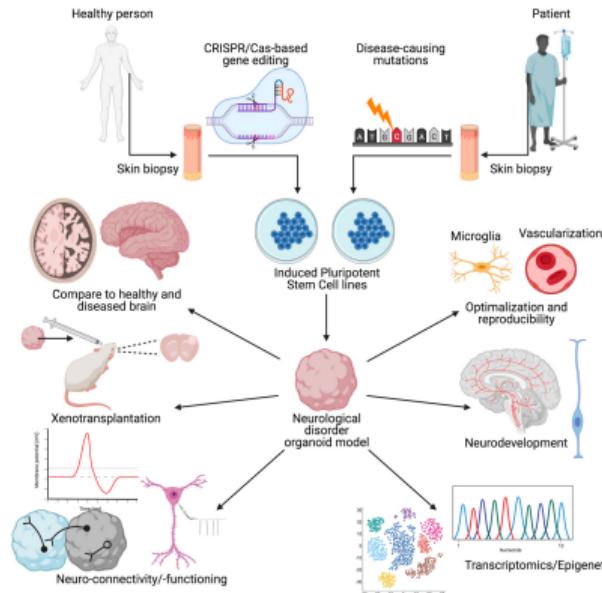


Figura 20: Aplicações biomédicas da utilização de (*induced pluripotent stem cell* ou iPSC) (Zarate-Sanchez et al., 2021).

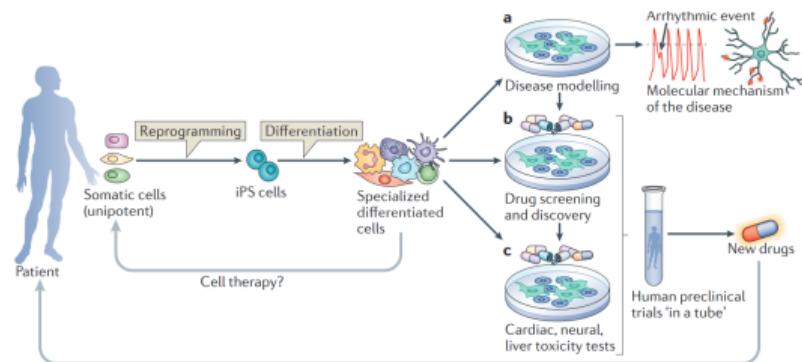


Figura 21: Criação de células-tronco de pluripotência induzida (*induced pluripotent stem cell* ou iPSC) (Bellin et al., 2012).

FULL ACCESS | Article | Published Online: 2 November 2023

Recapitulation of Perturbed Striatal Gene Expression Dynamics of Donors' Brains With Ventral Forebrain Organoids Derived From the Same Individuals With Schizophrenia

Tomoyo Sawada, Ph.D., André R. Barbosa, Ph.D., Bruno Araújo, Ph.D., Alejandra E. McCord, B.A., Laura D'Ignazio, Ph.D., Kynon J.M. Benjamin, Ph.D., Bonna Sheehan, B.Sc., Michael Zabolocki, B.Sc., Arthur Feltrin, Ph.D., Ria Arora, B.Sc., Anna C. Brandtjen, B.A., Joel E. Kleinman, M.D., Ph.D., Thomas M.

Hyde, M.D., Cedric Bardy, Ph.D., Daniel R. Weinberger, M.D., Apuā C.M. Paquola, Ph.D., and Jennifer A. Erwin, Ph.D. [SHOW FEWER](#) | [AUTHOR](#)**INFO & AFFILIATIONS**Publication: American Journal of Psychiatry • Volume 181, Number 6 • <https://doi.org/10.1176/appi.ajp.20220723>

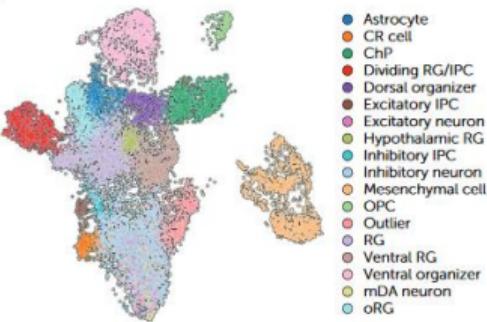
a

iPSC line ID	Brain ID	Diagnosis	Race	Sex	PRS	Age of death	PMI
LIBD2c1	Br2371	Control	Caucasian	Male	-58.33	23	18.5
LIBD6c2	Br5207	Control	Caucasian	Male	-58.27	62	29
LIBD7c6	Br5287	Control	Caucasian	Male	-56.70	40	28
LIBD9c1	Br5212	Control	Caucasian	Male	-54.87	52	38.5
LIBD3c5	Br5224	Schizophrenia	Caucasian	Male	-52.52	46	22.5
LIBD5c7	Br5446	Schizophrenia	Caucasian	Male	-52.94	23	32.5
LIBD8c4	Br2346	Schizophrenia	Caucasian	Male	-51.07	21	56
L0019A_Y03	Br2423	Schizophrenia	Caucasian	Male	-52.68	61	31.5

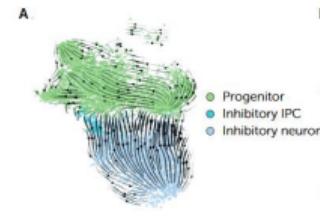
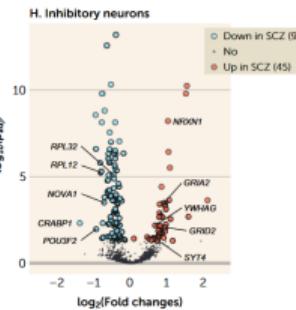
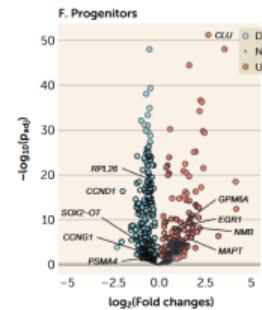
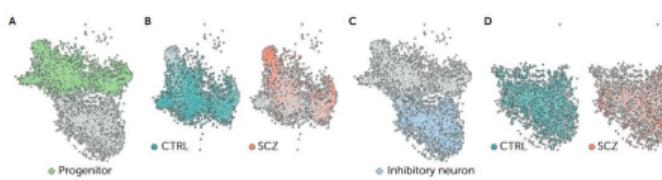
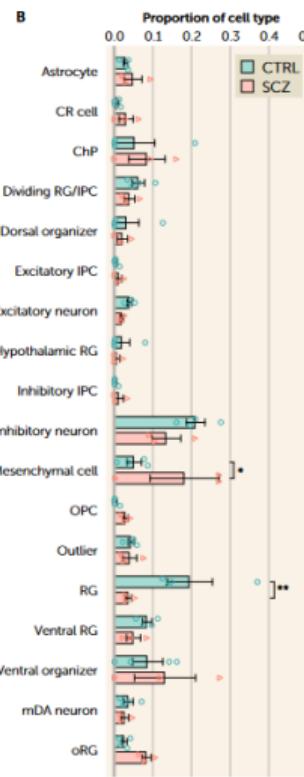
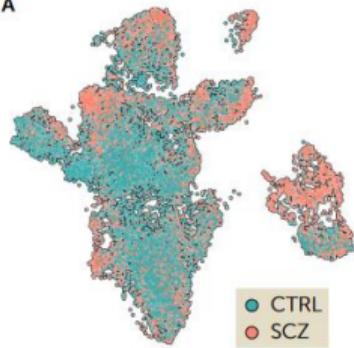
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F



A



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