Using a stem cell-derived model to repurpose drugs for bipolar disorder

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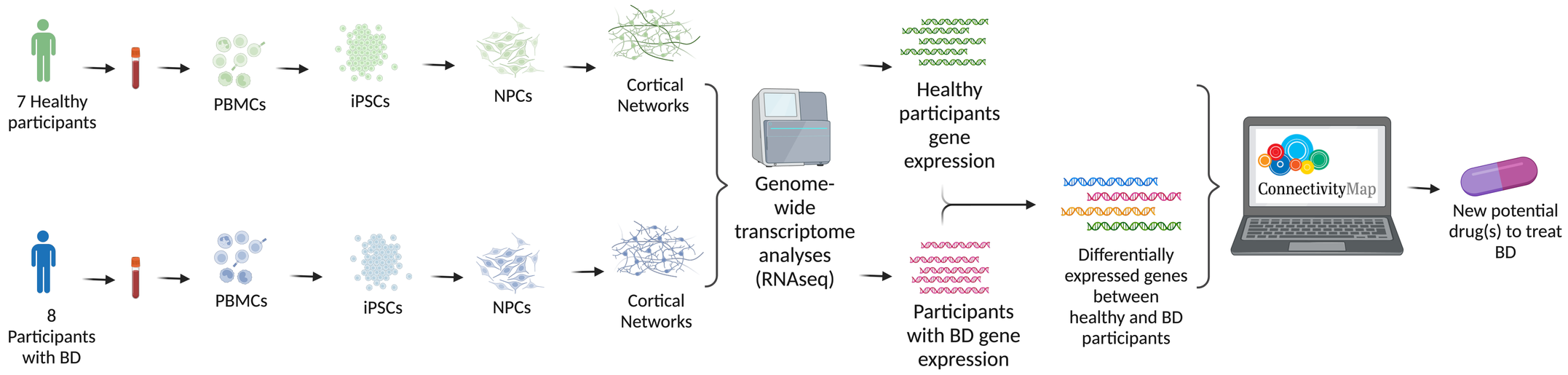
Introduction

Due to its episodic/cyclic nature, management of bipolar disorder (BD) is complex and reliant on medications from which many do not benefit. ***New treatment options for BD are urgently needed.*** We aim to identify off-patent drugs with known safety profiles that can rapidly translate to clinical practice to treat BD.

Hypothesis

We hypothesise that patient-derived cortical network cells (neurons and astrocytes) can be used to identify a gene expression signature (GES) that best differentiates between cells from participants with bipolar disorder and healthy control subjects and that the GES can be used to repurpose drugs to treat bipolar disorder.

Methods



Results

Gene expression:

Gene	Log2FC	Stat	p-value	adjusted p-value
NEUROD6	2.02	5.75	$8.80E^{-09}$	0.0001
LINC02488	1.09	5.74	$9.25E^{-09}$	0.0001
NMNAT3	-0.69	-5.03	$4.83E^{-07}$	0.0035
NEUROD2	1.24	4.94	$7.78E^{-07}$	0.0042
PTCHD1	0.77	4.76	$1.87E^{-06}$	0.0077
CTTNBP2	0.44	4.74	$2.11E^{-06}$	0.0077
EPHA6	0.79	4.67	$2.92E^{-06}$	0.0091
PCTP	-0.47	-4.50	$6.56E^{-06}$	0.0146

Table 1: Top 8 differentially expressed genes in cortical networks between BD and healthy controls.

Drug repurposing:

Compound	WTCS_FDR	Tau	MOAss
Gabazine	$5.79E^{-05}$	-99.48	GABA receptor antagonist
Triamterene	$5.79E^{-05}$	-99.03	Sodium channel blocker
Levonorgestrel	$5.79E^{-05}$	-98.88	Estrogen receptor agonist
Cirazoline	$5.79E^{-05}$	-99.27	Adrenergic receptor agonist
Loteprednol	$5.79E^{-05}$	-98.70	Glucocorticoid receptor agonist
Trapidil	$5.79E^{-05}$	-96.51	PDGFR receptor inhibitor
Diclofenac	$5.79E^{-05}$	-97.26	Cyclooxygenase inhibitor
Carmoxirole	$5.79E^{-05}$	-97.70	Dopamine receptor agonist
Ritanserin	$5.79E^{-05}$	-95.27	Serotonin receptor antagonist
Methantheline	$5.79E^{-05}$	-97.76	Acetylcholine receptor antagonist

Table 2: Top 10 drugs that might be suitable for repurposing for bipolar disorder treatment.

Discussion

DICLOFENAC

- Non-steroidal anti-inflammatory drug
- COX2 inhibitor
- Dose-dependent renal, gastrointestinal, and cardiovascular toxicities
- Statistical analysis of reports from the FDA Adverse Event Reporting System (FAERS) found a significant decrease in depression rates in patients who received diclofenac when compared to patients prescribed other pain medications (1)
- Clinical trials showed antidepressant activity in patients with chronic pain (2)
- Population scale retrospective analysis found antidepressant and anxiolytic effects of diclofenac in patients with pain (3)

Conclusion

We have identified a number of drugs that can potentially be repurposed to treat bipolar disorder. Further investigations including Mendelian randomisation, pharmacoepidemiology and animal behavioural studies will be performed to determine which of these drugs are most suitable for progressing to clinical testing in participants with bipolar disorder.

References

1. Sci Rep 2017;7(1):1450
2. J Affect Disord 2016;204:1–8
3. PLoS One 2018; 13(4): e0195521

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