Reason For Project

- Inspired by the increasing number of mental health disorders prevalent in my generation
- Want to help those who currently struggle
- I know people who suffer from mental health issues
- I am aware of the stigma surrounding it
  - lack of how treatment can work and also not work
- Bipolar Disorder is a disease that many misdiagnosis and many judge

Note: All figures and images done by finalist.

Introduction

Bipolar Disorder (BD)

1. Affects 1/100 people in the world [1]
2. Types of Bipolar
    - Bipolar I
        - When the mania is very intense, and the depressive episodes are relatively short [2]
    - Bipolar II
        - The manic episodes are referred to as hypomania, and the depressive episodes are significantly longer than those in Bipolar I [2]
    - Cyclothymic
        - Episodes are shorter for both, it is typically considered outside of Bipolar I and Bipolar II [3]
3. Bipolar Disorder can lead to:
        - Liver Disease
        - Diabetes
        - Alcohol usage issues

Introduction

Signaling Pathways

The Wingless-related integration site (Wnt signaling pathway)

- The genes mutated (Fig. 1):
  - **Brain-Derived Neurotrophic Factor**
    - BDNF
    - Neuron stability
      - Survival of neurons [4]
    - Neuron growth

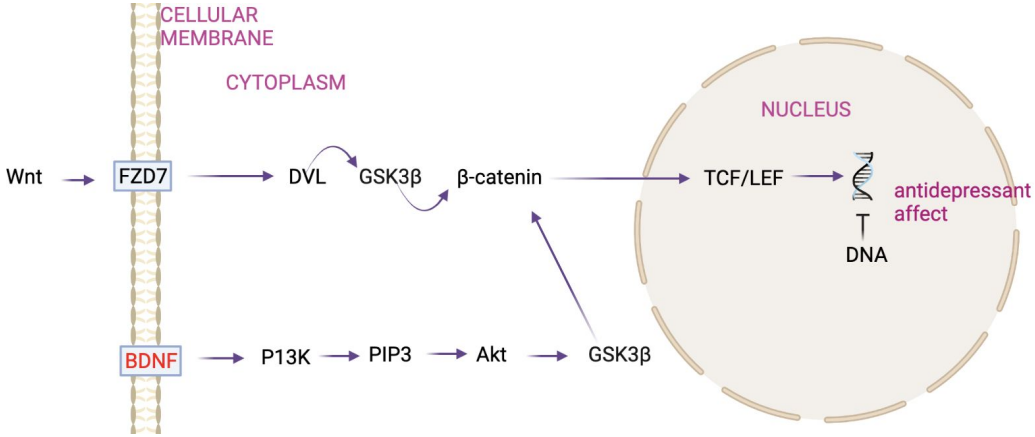

Figure 1. Diagram of the Wingless-related integration site as it functions in a person with Bipolar Disorder. The mentioned genes are: Frizzled homolog 7 (FZD7), Glycogen Synthase Kinase 3 Beta (GSK3B), Beta Catenin (B-catenin), T-cell factor/lymphoid enhancer factor (TCF/LEF), Brain-Derived Neurotrophic Factor (BDNF), Phosphoinositide 3-kinases (P13K), phosphoinositide 3 kinase (PIP3), Protein kinase B (Akt).

Introduction

Classifying Drugs Used in Current Treatment

Table 1. **Drugs currently used to treat Bipolar Disorder are classified to look at their functions, flaws, effectiveness, etc.** This was done before receiving data from the text-mining and organizing them (Table 2), in which the drugs found were based on manual research in Pubmed.

Name of Drug	Flaws of Drug	Effectiveness with Depressive Episodes
Lithium	Lots of bloodwork, unkown consequences, unpleasent side effects, can cause diabetes, weight gain	Works well
Olanzapine	Difficulty walking, seizures, weight gain, unsual behavoir	Works moderately well
Quetiapine	Pain, loss of coordination, unsual dreams, excessive weight gain, difficulty speaking/concentrating	Works well
Risperidone	Vision issues, anxiety, weight gain, stomach pain, fever, difficulty breathing, irregular pulse	Works well
Carbamazepine	Dizzieness, balance issues	Works moderately well
Aripirazole	Pain, tiredness, nervousness, dizziness, seizures, tightening of muscles	Works well

- Current drug treatment have side effects that lead to other major issues, which include seizures, balance issues, pain, loss of coordination, and more. In addition to this, effectiveness doesn’t work for all aspects of BD.

Purpose

1. Create a database using abstract text-mining that can be used to link together genes and drugs used for Bipolar Disorder (BD)
    a. Compile list of abstract IDs that mention any genes related to BD
    b. Extract gene names from all abstracts
    c. Compile list of abstract IDs that mention any drugs related to BD
    d. Extract drug names from all abstracts
    e. Use cmapPy to determine any relationships between drugs and the genes
2. Elucidate novel connections between pre-existing drugs and genes directly affect patients with BD

Methods

Text-mining For Genes and Drugs

```
for abstractid in abstractids:
    abstract = fetch.article_by_pmid(abstractid).abstract
    #print(abstract)
    words = str(abstract)
    abstr = (words.replace('.', " ").replace('?'," ").replace(','," ").replace('!', " ").replace('('," ").replace(')'," ").replace('/', " "))
    results = (abstr.split())
    #print(results)
    intersection = (set(results)&set(drugs))
    list_result = []
    list_result.extend(intersection)

    for drug in list_result:
        y = open('drug_list_result.txt', 'a+')
        y.write('\n')
        y.write(abstractid)
        y.write("\t")
        y.write(drug)
        y.write("\t")
        y.close()
```

Figure 2. The code used to text-mine from abstracts in Pubmed to get the drugs currently used to treat Bipolar Disorder. In the figure, the code, using a file of related abstract IDs, removes all unrelated punctuation and searches for the drug names (based on a list). All other words are removed, and a list of drugs is generated.

Text-mining Abstract IDs (Fig. 2)

- Intended goals
  - Extracting gene/drug names by text-mining through abstracts on pubmed
- What the code does
  - Uses a previously generated list of abstract IDs and extract information from it

Methods - *Finding New Treatments*

- CmapPy
- Goals:
  - Relating drugs and genes
- Finding and validating new drug treatments
  - Expression data
- Expected results

Results
Genes

Information extracted from pubmed using query: ‘bipolar disorder genes’

Most common genes found:

- BDNF (Table 2)
  - Neuron stability
  - Negative correlation between BDNF levels and severity of episodes [3]

Takeaway: the gene to look at is BDNF

Table 2. **Number of times specific genes have been represented in relationship with Bipolar Disorder.** After receiving data from the code, the data was organized, and then validated.

Gene Name	Occurrence
BDNF	224
COMT	136
CACNA1C	130
DISC1	112
ANK3	86
DRD2	63
NRG1	57
DRD4	56
SLC6A4	49
CLOCK	45

Results
Drugs

Information extracted from pubmed using query: ‘bipolar disorder drugs’

Drugs used for BD:

- Lithium mentioned three times as much as Carbamazepine (Table 3)
- Lithium’s inability to target other areas of Bipolar Disorder
- Carbamazepine’s inability to successfully target all areas

Takeaway: Lithium & Carbamazepine are drugs to look at for the research

Table 3. **The number of times specific drugs have been represented in relationship with Bipolar Disorder.** After receiving data from the code, the data was organized, and then validated

Drug Name	Occurrence
lithium	1442
Carbamazepine	488
quetiapine	347
lamotrigine	342
risperidone	267
Aripiprazole	220
clozapine	169
haloperidol	152
ziprasidone	111
topiramate	93

Results
CMapPy

Information extracted from CMapPy files

- Gene Expression
- Carbamazepine
- Ketamine
  - Treatment
  - How it affects BDNF as a gene
- New Treatment possibilities (Table 4)

Table 4. **Effectiveness of drug treatments based on Gene Expression Data.** Data received from CMapPy and validated with research. BDNF is the Brain-Derived Neurotrophic Factor.

Name of Drug	Effectiveness to Treat Bipolar Based on Gene Expression (BDNF)
Lithium	Raises BDNF, but there are some flaws
Carbamazepine	Simply attempts to prevent abnormal levels of BDNF, there are flaws
Ketamine	Raises BDNF, research seems promising

Conclusions

Conclusions

- Carbamazepine and lithium
  - Inability to treat all parts of Bipolar
- Ketamine
  - Increases BDNF levels

Further Ideas

- Optimizing
  - how to find the most optimal treatment

Applications

- New treatment options
- Treatments that work, less side effects, know what it does

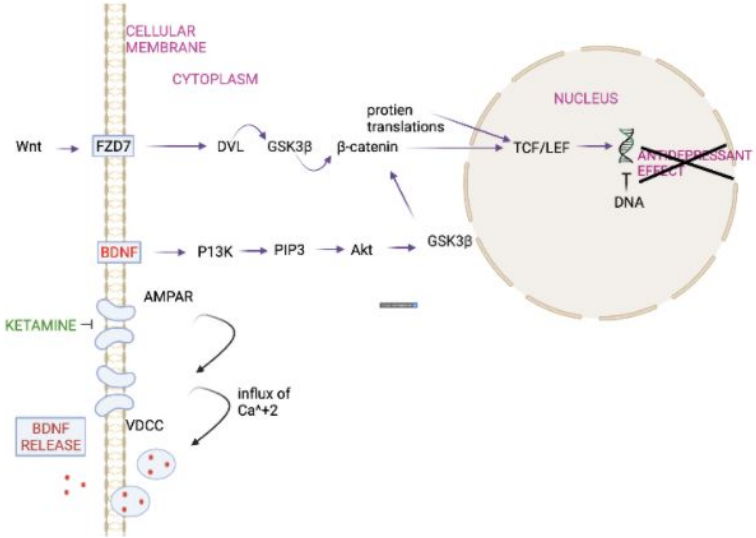

Figure 3. Diagram of the Wingless-related integration site as it functions in a person with Bipolar Disorder with Ketamine as a treatment. The mentioned genes and proteins are: Frizzled homolog 7 (FZD7), Glycogen Synthase Kinase 3 Beta (GSK3B), BETA-catenin, T-cell factor/lymphoid enhancer factor (TCF/LEF), Brain-Derived Neurotrophic Factor (BDNF), Phosphoinositide 3-kinases (P13K), phosphoinositide 3 kinase (PIP3), Protein kinase B (Akt), AMPAR(α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor), and VDCC (Voltage-gated calcium channel). The figure depicts how ketamine affects the WNT pathway IN ORDER TO increase the release of BDNF.

References

[1] “15 Mental Health Facts You Should Know,” *USC Suzanne Dworak-Peck School of Social Work*. https://dworakpeck.usc.edu/news/15-mental-health-facts-you-should-know (accessed Jul. 23, 2021).

[2]. Gitlin, “Lithium side effects and toxicity: prevalence and management strategies,” *Int J Bipolar Disord*, vol. 4, p. 27, Dec. 2016, doi: 10.1186/s40345-016-0068-y.

[3]“BDNF gene: MedlinePlus Genetics.” https://medlineplus.gov/genetics/gene/bdnf/ (accessed Jul. 28, 2021).

[4] I. Grande, G. R. Fries, M. Kunz, and F. Kapczinski, “The Role of BDNF as a Mediator of Neuroplasticity in Bipolar Disorder,” *Psychiatry Investig*, vol. 7, no. 4, pp. 243–250, Dec. 2010, doi: 10.4306/pi.2010.7.4.243.