CENTRAL NERVOUS SYSTEM

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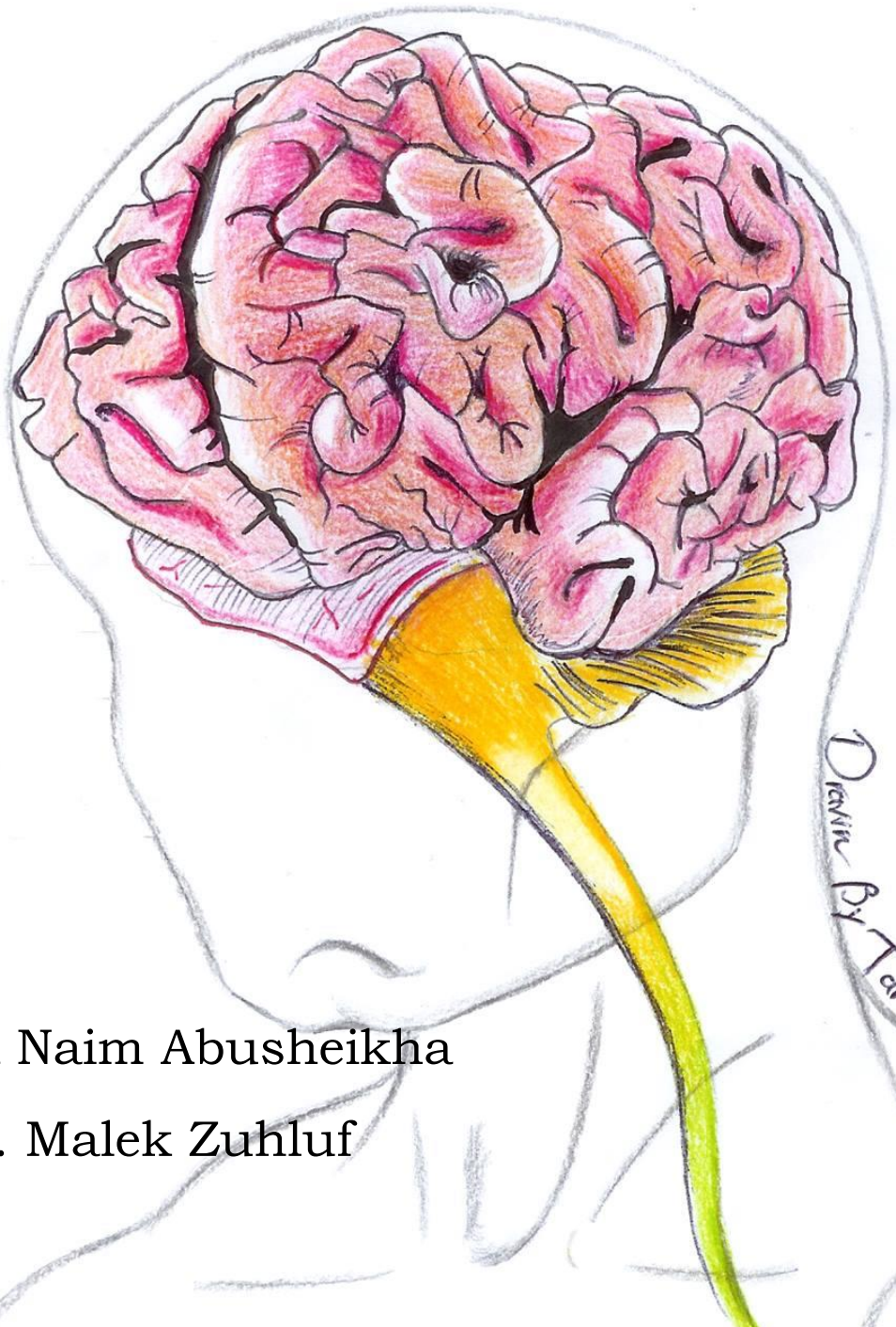

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Anticonvulsants, bipolar disorder and degenerative diseases

Please keep in mind that this sheet is only 7 pages, the rest is a summary and an article I wrote on a somewhat related topic and I'd love it if you read it. Thanks!

Seizures

Anti-epileptic drugs are 20 in number; we talked about 5 which are: **Phenytoin, Carbamazepine, Lamotrigine, Ethosuximide and Valproic acid**. We have to give drugs that decrease the electro-chemical activity in the brain; this is done by stabilizing the membrane by:

1) **Antagonism (blocking) of Na+ channels** to reduce excitability and increase the duration of inactivation. This is the method of action of **Phenytoin and Carbamazepine**, which are the drugs of choice for **partial seizures**. Phenytoin shows marked inter-individual variation among patients in the serum level achieved at any dosage. Patients taking Phenytoin require strict monitoring as **Phenytoin induces P450**, resulting in increase in its own metabolism. Carbamazepine is similar to Phenytoin, however, it shows much less inter-individual variation.
2) **K+ channel activation**. This is the method of action of **Valproic acid**, which also blocks Na+ channels and enhances GABAergic transmission, thus, it is highly pleiotropic. (*From wiki: pleiotropy refers to a drug's actions, usually unanticipated, other than those for which the agent was specifically developed. It may include* adverse effects *which are detrimental ones, but is often used to denote additional beneficial effects.*) Valproic acid is used for generalized seizures.
3) **Blocking Ca+2 channels**. This is the method of action of **Ethosuximide**.

These drugs have a very narrow therapeutic index and cause many side effects including a skin rash or even **Stevens-Johnson syndrome** (which is a very severe rash resulting from Lamotrigine) and cardiac arrhythmias in cases of toxicity.

We treat the patient from 2-3 or even 4 years, and if the patient doesn't show any seizures through the years, we start tapering down the dose until we stop the drug administration completely. If the patient goes back to having seizures we must go back to administering drugs. Around 50% of children could go 12 years without having a remission; they don't go back to having seizures after stopping drug administration.

Bipolar disorder

This disease is very difficult to treat as it's a very complex one, its complexity stems from the fact that it has 2 phenomena, so it's basically like treating two diseases instead of one. It is characterized by cyclic periods of depression and periods of elevated mood. Bipolar disorder is very difficult to live with and the incidence of suicide in these patients reaches 25 %.

How can we differentiate bipolar disorder from psychosis or schizophrenia? Bipolar patients tend to have **manic attacks** or manic episodes, which are characterized by periods of elevated, expansive or unusually irritable moods; patients are abnormally happy, outgoing, and more talkative than usual and might even hit others. (Check paragraph 4 of my article at the end of the sheet for a better understanding of bipolar disorder.)

Around 1% of the world population is estimated to have bipolar disorder. Bipolar patients' mood is highly unstable, so our job here is to stabilize the mood using mood-stabilizers. The **first-line pharmacological treatment** is an anti-epileptic drug called **Lithium** which is different than all other anti-seizure medications . It is the classical treatment for bipolar disorder.

In order to stabilize the mood, we must decrease the activity of the brain during manic episodes (where the patient has hyper-excitement of neurons) and elevate the patients' mood during depressive episodes. As mentioned, **Lithium is the best mood stabilizer** out there, as **it's the only drug that could control both manic and depressive attacks**. Lithium works by inhibiting Norepinephrine activity and increasing Serotonin activity (*from the internet: Lithium also enhances the effect of selective serotonin reuptake inhibitors (SSRIs), a type of drug commonly prescribed to treat depression*), therefore it has anti-manic activity and anti-depressive activity. If the patient doesn't respond to Lithium (40% of patients) we'll revert to anti-depressants, anti- Parkinson's and perhaps even anti-psychotics. We'll talk about all of this in a bit.

Psychiatrists in Jordan prefer not to deal with Lithium; it's an anti-epileptic drug which has a **very narrow therapeutic index** like Phenytoin or even worse.

Giving Lithium to a patient is like administering Na+; it has so many side-effects including arrhythmias, gastrointestinal side effects, memory difficulties, kidney dysfunction, sedation, drowsiness, confusion and hallucinations. More importantly, they produce **hypothyroidism, thirst and diabetes insipidus (urination).**

Keeping the dose within the therapeutic range, or 0.4 mmol-1 mmol, will produce no toxicity. You will, however, observe sedation, dizziness and very commonly, hypothyroidism, thirst and diabetes insipidus (urination).

Hypothyroidism results in drowsiness, hypothermia and dryness of skin.

Pharmacodynamics of Lithium

Lithium has **no psychotropic effect on non-Bipolars (***from wiki: a psychotropic drug is a chemical substance that changes brain function and results in alterations in perception, mood, or consciousness*), it affects nerve membranes, multiple receptor systems and intracellular 2nd messenger impulse transduction systems, so it doesn't have a clear mechanism of action; it reduces the second messenger activity within the neuron, so it has an inhibitory activity on the CNS in general**.** It has potential to regulate CNS gene expression and stabilizing neurons. When treating a patient with Lithium, you'll notice that his Serotonin levels go up. So as mentioned, you're producing both anti-depressant and anti-manic activity using one drug.

Lithium is the second best drug <u>when it comes to manic attacks</u> (Valproic acid is the best). This point will be explained in a bit.

The diagnosis of bipolar disorder and especially type 2 is very difficult, if the diagnosis is correct and the patient tolerates Lithium he'll most likely have to take it for the rest of his life. Yes, he'll go back to normal and live a normal life but he'll have to take it for the rest of his life.

Constant monitoring of Lithium levels is necessary as it's a toxic drug affecting almost everything in the body. **Lithium blocks the action of ADH**, resulting in urination (diabetes insipidus + thirst), it also **blocks the building up of T3 and T4**, and also **interrupts the release of T3 and T4**, resulting in hypothyroidism. Anything affecting hemodynamics of the blood may increase Lithium toxicity**: Diuretics, NSAIDs and ACEIs**; all affect kidney perfusion and hemodynamics of the blood and therefore may elevate lithium levels in the blood.

Remember how we once said that over-the-counter drugs may interact with other drugs and produce toxicity? Well this is an example. **NSAIDs may interact with Lithium resulting in toxicity**. **DO NOT TAKE ASPIRIN, IBUPRUFEN OR DICLOFENAC (NSAIDS) WITH LITHIUM**, because they have effects on kidney perfusion, disrupting the body's ability to remove lithium from the body which can lead to a dangerous build-up of lithium levels. Diuretics will excrete Sodium from the blood, and as you know water will follow Na+, resulting in elevated levels of Lithium in the blood, causing toxicity.

What if lithium doesn't work?!

Antipsychotics (which is not a great option), or antiepileptics (the best drug is Valproic acid. Lamotrigine is also wonderful but the FDA approves better of Valproic acid.) Could be used. Valproic acid also has a very narrow therapeutic index and multiple side effects including thrombocytopenia, it also affects the liver and produces a skin rash, nausea and vomiting.

Valproic acid is even better than Lithium in **controlling manic episodes**. You might wonder why it isn't the first line of treatment if it's the best and the truth is Valproic acid **isn't very effective when it comes to treating depressive episodes**. So Valproic acid is the best drug in controlling manic episodes, but it isn't the first line of treatment because it doesn't control depressive episodes well.

So first you try Lithium, if Lithium doesn't work, you try Valproic acid in addition to an anti-depressant. This is used a lot here in Jordan. Keep in mind that you DO NOT GIVE ANTI-DEPRESSANTS DURING MANIC ATTACKS, this is because anti-depressants increase Serotonin levels. First you give ONLY Valproic acid (or Lamotrigine or Carbamazepine) and make sure manic episodes are under control and the patient's mood is somewhat stable, THEN you add antidepressants in order to further improve the mood of the patient by increasing Serotonin levels and inhibiting depressive episodes.

Which anti-depressants do we use? SSRI (Selective serotonin reuptake inhibitor), **DON'T GIVE** any SNRI (Serotonin and norepinephrine reuptake inhibitors), MAOI (Monoamine oxidase inhibitors) or anything increasing Norepinephrine level, because they might induce manic episodes.

If the patient doesn't respond to any of the above treatments, you then give him **antipsychotics**. Note how antipsychotics are used only as a last resort and not for long durations because they aren't very effective in treatment of depression in patients and so are only used in the treatment of manic attacks. **Clozapine, Olanzapine, Risperidone (Risperidal) and Arpiprazol** are the antipsychotics we use here.

Risperidone produces extrapyramidal side effects at high doses, Olanzapine doesn't produce extrapyramidal side effects but produces weight gain and diabetes, Clozapine produces agranulocytosis and Aripiprazole is a partial D2 agonist. They are also called **atypical antidepressants**.

Many antipsychotics and antidepressants (especially antidepressants) increase the suicidal effect (more in the US and western countries than Islamic ones, says Dr. Malik), but don't we treat depression to prevent suicide in the first place? The doctor didn't really answer this question, here's an answer from the internet:

"When a person's depression starts to lift, he or she may feel less hopeless and helpless. That sounds like an improvement, but when people feel less helpless but still feel depressed, they may think about suicide as a way out, whereas before they were too immobilized to make a suicide plan. For that reason, a decrease in the symptoms of depression can increase the risk of suicidal thoughts or actions"

Bipolar disorder has been linked towards criminal activity, Israelis and terrorists took advantage of this link by justifying their crimes and saying criminals are bipolar or mentally ill.

Neurodegenerative diseases

Neurodegenerative diseases include Alzheimer's, Parkinson and Huntington. The complexity of Parkinson's disease is that it isn't a stable disease; it is a degenerative disease, so the treatment of the patient's going to change as the disease progresses. It's somewhat similar to diabetes, where we start treating the patient orally and if oral medications become ineffective, treatment with insulin is initiated.

In addition to tremors, muscular rigidity, imbalance and bradykinesia, the patient also suffers emotionally. The patient might also suffer from cognitive dysfunction and hallucinations.

The doctor reads from the slides: Alzheimer affects some 4 million Americans while Parkinson is affecting 1.5 million Americans. They are devastating (destructive) illness, characterized by the progressive loss of selected neurons in discrete brain areas, resulting in characteristic disorders of movements, cognition or both. For example, Alzheimer is characterized by loss of cholinergic neurons, whereas Parkinson is associated with a loss of dopaminergic neurons.

Parkinson

Patients have decreased Dopamine levels and increased Ach levels. Ach is excitatory whereas Dopamine is inhibitory, so what we're supposed to do is increase Dopamine levels and decreases Ach levels. Regarding Dopamine, levels can only be elevated for 2-3 years. Using endocrine replacement therapy we can produce similar activity, however some activities and movements in the patient can't go back to normal.

Levodopa is combined with Carbidopa,, or we could give Selegiline, or Monoamine oxidase (MAO) inhibitors, Dopamine receptors agonists (very new and effective) or two types of anti-cholinergics (not very effective and not very commonly used), so we either augment Dopamine levels or we inhibit cholinergic activity in the brain.

Dopamine, however, causes hallucinations which are characteristic of psychosis and schizophrenia. So we should monitor the patient and titrate the drug, which means starting with a low dose and then increasing it. **Over-activation of Dopamine receptors results in tardive dyskinesia.**

Levodopa

Levodopa is a precursor of dopamine, and is used to restore the dopamine level in brain.

Why don't we just give Dopamine to the patient? It can't cross the blood brain barrier. In the new patient, the therapeutic response is consistent. While in advanced cases (year 3 or 4), the number of neurons decrease and fewer cells are capable of taking up Levodopa and converting it to dopamine for subsequent storage and release.

Levodopa is decarboxylated in dopaminergic neurons, however in Parkinson's patients, these dopaminergic neurons continuously degenerate, resulting in decreased amount of activate Levodopa, resulting in fluctuation or 'wearing off'. The half-life of the drug decreases; it was initially 6 hours and now it's 1 hour for example, so the drug disappears quickly from the body. Wearing off is also called "On and off", off means off Dopamine, resulting in sudden return of muscular rigidity, imbalance and bradykinesia. We solve this problem by increasing the frequency of dosing; if we used to dose him 3 times we begin to dose him 6 times. Relief provided by Levodopa is only symptomatic, and it lasts only while the drug is present in the body.

Dopamine

Dopamine is the best vasopressor, meaning it results in high elevation of the blood pressure. Dopamine can be administered at three doses: Kidney dose, pressor dose, cardiac dose. (*From Dr. Yaqoub's slides: at normal concentrations, Dopamine activates D1 receptors and produces vasodilation, which is especially clinically important in renal vascular beds → increases renal blood flow. It also activates presynaptic D2 receptors suppressing norepinephrine release. At higher doses, dopamine activates β1 receptors in the heart. At even higher concentrations, it activates vascular α receptors leading to vasoconstriction including the renal vascular bed*.)

It activates β1 receptors in the heart. At high concentrations, it activates vascular α receptors leading to vasoconstriction including the renal vascular bed. (So apparently I went through the trouble of referring to Dr. Yacoub's slides before realizing Dr. Malik was going to say the same thing.)

To solve the problems Dopamine causes in the periphery, Levodopa is combined with Carbidopa, which is a dopamine decarboxylase inhibitor that does not cross the blood brain barrier. Thus, Carbidopa, diminishes the metabolism of the Levodopa in the peripheral tissues, and increase the availability of Levodopa to the CNS (lower the dose four to five folds).

So never give Levodopa alone, we always combine it with Carbidopa which prevents Peripheral metabolism of Carbidopa, causing its buildup in the brain. Without carbidopa only 1% of levodopa will cross the blood brain barrier but with carbidopa, you end up with 10-20% crossing the blood brain barrier and those are enough at first, but as the disease progresses, wearing off decreases the percentage crossing the blood brain barrier.

The end.

"Men have called me mad; but the question is not yet settled, whether madness is or is not the loftiest intelligence. They who dream by day are cognizant of many things which escape those who dream only by night. In their gray visions they obtain glimpses of eternity, and thrill, in awakening, to find that they have been upon the verge of the great secret. In snatches, they learn something of the wisdom which is of good, and more of the mere knowledge which is of evil."

Summary

Drugs of choice	
Drugs of choice for partial seizures	**Phenytoin/Carbamazepine**
Generalized seizures	**Valproic acid**
First-line pharmacological treatment for bipolar disorder	**Lithium**
Best drug in controlling manic episodes (most widely used anti-manic drug)	**Valproic acid**
If Lithium doesn't work?	**Valproic acid (or Lamotrigine or Carbamazepine)** + **anti-depressants** (after a while, once mood is stabilized)
Patient doesn't respond to Lithium or (Valproic acid or Lamotrigine or Carbamazepine + antidepressants)	**Antipsychotics: Clozapine, Olanzapine, Risperidone (Risperidal) and Arpiprazol**
Parkinson's	**Levodopa + Carbidopa/ Selegiline/Monoamine oxidase (MAO) inhibitors/ Dopamine receptors agonists /anti-cholinergics**
Contraindications	
Diuretics/NSAIDs/ACEIs	**Lithium**
SNRI / MAOI	**Bipolar disorder (they are anti-depressants, but might induce manic attacks)**
Side effects	
Lamotrigine	**Stevens-Johnson syndrome**
Lithium	**Neurological, gastrointestinal, hypothyroidism, rash, weight gain, memory difficulty, kidney dysfunction, cardiovascular.**
Valproic acid	**Thrombocytopenia, it also affects the liver and produces a skin rash, nausea and vomiting.**
Risperidone	**Extrapyramidal side effects**
Olanzapine	**Weight gain and diabetes**
Clozapine	**Agranulocytosis**

The curse of brilliance: creativity and mental illness

"Men have called me mad," writes Edgar Allan Poe in his short story Eleonora, which is often regarded as autobiographical, "but the question is not yet settled, whether madness is or is not the loftiest intelligence."

The idea of the 'tortured artist' roots all the way back to ancient Greece, when Aristotle noted: "**Those who have been eminent in philosophy, politics, poetry, and the arts have all had tendencies toward melancholia**." But is it just another dramatic ancient myth, or is there a scientifically proven genetic link between mental illness and creativity? Is creativity a side effect of suffering, or is mental illness the price creative people have to pay for their unique abilities? Or is the relationship between the two a lot more complex?

Van Gogh, Self-Portrait with Bandaged Ear

From Virginia Woolf's suicide note to Van Gogh chopping off his own ear, Sylvia Plath placing her head in an oven to Leo Tolstoy's diary of depression, the painful pages of history offer no shortage of evidence linking mental illness to creativity, bringing the myth to life.

Numerous studies have conclusively found correlations between creativity and mental illness, especially **bipolar disorder**. Bipolar disorder, previously known as manic-depressive illness, is a brain disorder that causes extreme and drastic shifts in mood and energy that include mania (or hypomania, a less severe form) and depression. During a manic episode, one feels euphoric and has very high self-esteem and an exaggerated sense of importance and skills; the world seems full of possibilities, causing them to make choices they'll later regret and take very dangerous risks. They need very little sleep and their minds are race like rockets. During a depressive episode one feels worthless, hopeless, drained, and sad or even devoid of emotion, their ability to think and concentrate is hugely diminished and they just have a loss of pleasure even when something good happens.

But what exactly is creativity? An article published by King's College London in 2015 describes a creative person as **"Someone who takes novel approaches requiring cognitive processes that are different from prevailing modes of thought or expression."**

Nancy Andreasen, a neuroscientist and neuropsychiatrist who was declared a genius after taking an IQ test in Kindergarten, has shown huge interest in this subject. She conducted a study **in which she interviewed and tested 30 gifted and distinguished writers from the Iowa Writers' Workshop; a famous creative-writing program in the University of Iowa where she had completed her residency in psychiatry, and compared them with 30 educationally matched control subjects.** The results of this study bewildered Nancy herself, what she found is summarized in *the table below*. She found that **rates of mood disorder were extremely high in the writers; 80% had some type of mood disorder**, a rate significantly different from the control subjects.

Table 4-3. The Iowa Writers' Workshop Study: Psychiatric Illness in 30 Writers versus 30 Controls*

	Writers		Controls			
	N	%	N	%	X^2	P
Bipolar I	4	13	0	0	–	ns
Bipolar II	9	30	3	10	2.60	ns
Unipolar	11	37	5	17	2.13	ns
Any Bipolar Disorder	13	43	3	10	6.90	0.01
Any Mood Disorder	24	80	9	30	13.20	0.001
Alcoholism	9	30	2	7	4.01	0.05
Drug Abuse	2	7	2	7	–	ns

*Some people had more than one diagnosis, so the numbers add up to more than 30. The last two columns are statistical tests of how significant the differences are. A P greater than .05 is considered statistically significant.

Surprisingly, writers she interviewed made it quite clear that their altered mood states affected their creativity, and that they were unable to be creative when either depressed or manic.

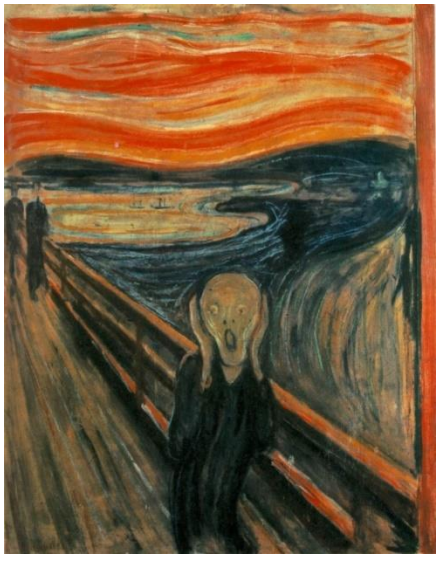
Another study tested the intelligence of 700,000 Swedish 16-year-olds who were followed up a decade later. Results published in 2010 showed that those who were outstanding when they were 16 years old were **four times as likely** to develop bipolar disorder. The list of studies and researchers searching for a link goes on and on, but what do the results mean? How do they even make sense?

When someone is at rest and not focused on a certain task, such as during day-dreaming, fantasizing, thinking about the past, picturing the future or just allowing

their minds to wander, a network in the brain called the **default mode network** is automatically activated. In most people, this network is also supressed by default when one is focusing on a task involving attention. Hikaru Takeuchi and his colleagues mapped the brain activity of mentally healthy individuals while they engaged in difficult working memory tasks. They found that **as creativity of the participant increased, their ability to suppress and deactivate the precuneus (an area of the default mode network) decreased**. The ability to come up with novel ideas has been linked to the inability of individuals to supress the precuneus during creative thinking. The researchers noted that "Such an inability to supress seemingly unnecessary cognitive activity may actually help creative subjects in associating two ideas represented in different networks." **Those scoring high in schizotypy, a less intense form if schizophrenia, also had difficulty supressing the precuneus.**

It's important to note that although the idea of the 'mad genius' or the 'tortured artist' might be charming or fascinating, it shouldn't be. As Nancy Andreasen emphasized, "**these women and men had become successful writers not *because* of their tortuous mental health but *despite* it**." Mental illness does *not* make one creative, and great creativity can indeed exist without mental illness. They are just likely to exist together, hinting at an indirect genetic link that remains to this day somewhat vague.

When certain risk factors like abuse or severe stress are present, creativity genes may express themselves as mental illness. Which has always made so much sense seeing as creative people are a lot more vulnerable in many aspects; they see connections other people don't, they think outside the box, they are always open to new ideas and experiences, and as Andreasen says, **"Their inner world is complex, ambiguous, and filled with shades of gray rather than black and white. Too much openness means living on the edge. Sometimes the person may drop over the edge… into depression, mania, or perhaps schizophrenia. "**



The Scream, 1893 by Edvard Munch

By Aya Naim Abusheikha

Resources:

https://en.wikipedia.org/wiki/Creativity_and_mental_illness

https://en.wikipedia.org/wiki/Edgar_Allan_Poe#Publishing_career

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