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Psychoneuroendocrinology

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Sustained urinary norepinephrine and epinephrine elevation in post-traumatic stress disorder

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Abstract

Urinary norepinephrine and epinephrine levels (µg/day) were measured at two-week intervals during the course of hospitalization in the following patient groups: post-traumatic stress disorder (PTSD); major depressive disorder (MDD); bipolar 1, manic (BP); paranoid...
schizophrenia (PS); and undifferentiated schizophrenia (US). The mean norepinephrine level during hospitalization was significantly higher in PTSD (76 ± 10.4 µg/day) than in BP (60.6 ± 8.4 µg/day), MDD (41.2 ± 4.7 µg/day), PS (33.4 ± 4.9 µg/day) and US (34.3 ± 5.9 µg/day) groups, according to Duncan's multiple range test, (F(4,39) = 6.94, p < 0.0003). The norepinephrine elevations in the PTSD group were sustained throughout hospitalization. The only other group to show mean levels in this range was the BP group in the first sample after hospital admission. This finding supports prior psychophysiological studies indicating increased sympathetic nervous system activity in PTSD patients. The mean epinephrine level during hospitalization was also significantly higher in PTSD (22.7 ± 2.4 µg/day) than in MDD (13.6 ± 1.7 µg/day), PS (14.7 ± 2.4 µg/day), and US (18.9 ± 1.8 µg/day), but not higher than in BP (21.5 ± 2.7 µg/day). The relationship of epinephrine levels among diagnostic groups was sustained throughout hospitalization. It appears likely that the main underlying mechanisms for elevations of both hormones are psychological, but further work will be required to establish the exact nature of these mechanisms.

There are no figures or tables for this document.

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THE CHALLENGES

I. THE ROLE OF GENES AND ENVIRONMENT

The investigation of the causes of Bipolar disorder is like the disease itself—with a lot of up and downs. Why is Bipolar disorder so challenging? First, we have known for a long time that it's caused by more than one gene. Family studies show that siblings of a person with bipolar disorder have only a 12% chance of being bipolar themselves. A statistical analysis shows that if genes were the only cause, then roughly 3-4 dominant genes may be required for bipolar disorder.

Identical twins share 100% of their genes; therefore, if genes alone are enough, then if one twin has bipolar disorder, the other twin will also. This is called concordance. However, various studies show that identical twins have a concordance of only 28-96%. This suggests that environment plays a role, with the number of genes involved perhaps as few as 1 or 2. Some rare bipolar-like diseases are indeed located to just one gene alone, such as Brunner Syndrome and Wolfram syndrome.

The wide variation in concordance also suggests that bipolar disorders may have different causes in different families, and this seems to be correct. How can environment affect genes? One way is via DNA methylation, which turns genes on and off, causing cells to develop into different types. Those variations can lead to a cascade of changes that make two identical twins different in personality. They can also be influenced by what happens to the body, with long lasting consequences. For instance, part of the difficulty of recovering from psychosis may be because psychosis triggers overactivity of DNA methylation in cortical interneurons deep in the brain that continue even after the episode passes.

Most family studies do not fully evaluate family members for 'mild' or 'partial forms' of bipolar disorder. Those studies that do find that some 'unaffected' relatives are in fact
affected in ways that show up on cognitive tests, personality measures, and medical histories. Those "partially" affected relatives may give valuable clues to how the patient developed the full-blown disorder.

II. DIAGNOSING AND STUDYING BIPOLAR DISORDER

Precise diagnosis is always a concern in any genetic study, since all evaluators need to be well trained. Unfortunately, bipolar disorder is not easy to identify, since manic episodes are rare, especially at the start of the disease. As a result, patients in the depressive phase of bipolar disorder are often misdiagnosed with unipolar depression. Other conditions such as thyroid hormone disorders can mimic or coexist with bipolar disorder, as well, which confuses the diagnoses. Patient education and counseling is part of the diagnostic challenge—patients want definite information on their disorder and their chances of passing it on to their children. Patients also hope that if the world knows more about bipolar disorder, it will help remove the stigma.

At present, bipolar disorder falls into two broad types, based on manic episode counts; Bipolar I with one or more manic episodes, Bipolar II which may never present with a full manic episode. This is pretty useless—treatment with lithium and other drugs for either disorder helps prevent future manic episodes. So, a patient with a family history of classic Bipolar I disorder may receive treatment at a very early stage, and never have a manic episode. Conversely, somebody who goes untreated could go from a diagnosis of bipolar II to bipolar I as the disorder progresses.

III. LACK OF POPULATION DATA

The World Health Organization places a great importance on bipolar disorder, citing it as one of the top 10 reasons for persistent disability worldwide, estimating it affects roughly 1% of the world population. There is not enough worldwide research to know if that estimate is true. The most comprehensive survey has been done in the United States, concluding that bipolar disorder affects every ethnic group at roughly the same rate. This survey has been used by other countries to extrapolate their number of bipolar patients, since they generally lack an infrastructure to track, treat, and/or report mental health issues. However a survey done in the United Kingdom yields a different result—the rates of bipolar disorder are significantly higher among minorities, for reasons unknown. We also have some evidence that the genetic bases for bipolar disorder vary widely, even in the same population. This challenges the assumption that all populations do in fact have bipolar disorders at similar frequencies.

Environmental causes, such as toxoplasmosis during pregnancy or viral diseases in pregnancy or in infancy, increase the risk of schizophrenia. However, there is no proof for this kind of environmental cause for bipolar disorder. Worldwide, scientists are studying different populations to determine the genetic causes of bipolar disorder, and establishing an international cooperation to standardize the exact diagnoses and traits studied in bipolar disorder. Such standardization may help identify and rule out environmental factors, such as diet. For instance, the Japanese are known to have remarkably lower
incidences of depression than Americans. This is because Japanese have a higher intake of omega-3 fatty acids from eating more fish. Now some psychiatrists are using omega-3 fatty acid supplements to help control depressive symptoms in their bipolar patients. Country-by-country studies could also turn up any hormonal roles in bipolar disorder, since diet and chemical exposure affecting hormone levels vary over the world.

IV. MODELLING & TESTING

One frustration in psychiatric genetics, in general, is the lack of good animal models. Mice are not very social animals and so not the best model for complex psychiatric disorders, particularly as they are nocturnal and researchers are not. Hope may come with the current drive to map the canine genome. Dogs are social animals that have been bred for very specific behaviors, and purebreds have low genetic variation, which makes it easier to locate candidate genes. Purebred dogs also have the advantage of having detailed pedigrees and relatives that can be located, tested, and bred, all great assets for genetic researchers. Finally, as animal models, they can also have their genes tested by lab techniques for their influence in a way human subjects cannot be.

Bipolar disorder is likely rarer in dogs than in humans, since unstable temperament is undesirable in dogs and often leads to early euthanasia. When bipolar disorder exists in dogs, it could manifest as unstable neurosis or "rage syndrome", a controversial diagnosis of behavior found in some pure breeds. The otherwise friendly dog can literally be sleeping one moment, and then the next moment attack without provocation. These attacks seem to resemble epileptic seizures, which is suggestive, since 10% of epileptic patients also have bipolar disorder, and almost all the new drugs used to treat bipolar disorder are epileptic drugs. Some of those dogs have thyroid problems and improve with treatment, showing that this syndrome is not due to "bad training." A project to diagnose and study the various causes and genetics of "rage syndrome" may prove promising.

THE DISCOVERIES:
WHEN AND WHY DOES BIPOLAR DISORDER APPEAR?

ADOLESCENT/ADULT-ONSET BIPOLAR DISORDER

Bipolar disorder usually unleashes its devastation in adolescence or early adulthood, particularly for women. Boys are more prone than girls to develop bipolar disorder before puberty, but also develop it as teenagers. Statistics indicate that bipolar disorder affects men and women roughly equally. However in some families, women seem to carry the gene without much affect, while the men develop full bipolar disorder. An X chromosome link seems likely in some families where the men have the full bipolar disorder inherited through their mothers who are not (as) affected. Click here for an introduction to X-chromosomal inheritance. An X-linked gene is being studied as a possible candidate. However, X-chromosome inheritance would not apply to the families in which the women are at greater risk than men.

Another possible explanation for the sex differences in bipolar disorder could be that hormonal interactions are crucial. Women and men react to stress differently at the
hormonal level, and estrogen plays a role in brain development, interacting with many other hormones. A possible hormonal role is supported by studies showing that bipolar patients have an abnormal stress hormone response and increased risk of thyroid hormone disorders.

**CHILDHOOD-ONSET BIPOLAR DISORDER**

This newly discovered variant of bipolar disease is being diagnosed more and more at younger ages. This variant comes with more serious behavioral and thinking disturbances. Until recently, it was not realized that children could develop mania or depression. Childhood bipolar disorder is still harder to diagnose correctly than in adults, being often mistaken for other behavioral problems. Treatment is also harder. Most drugs for bipolar disorder have strong side effects and even adult patients vary in what drugs work best for them. The dosage levels for children are not always known, either. Cognitive therapy is being studied for its efficacy and may prove valuable for parents unwilling to risk using those drugs. Ultimately, doctors need a way to test for the specific type of bipolar disorder and the best treatment in order to prevent 'experimentation' while trying to treat children. Right now, the prognosis is much worse for children with bipolar disorder, and the research suggests that some cases of childhood-onset bipolar disorder are, in fact, distinct from other bipolar disorders.

It is always possible some cases develop early because of hormones, stress or other causes triggering bipolar disorder. Pesticides and other chemicals that have estrogen or other hormone-like effects on bodies have been increasing in the environment in the last 50 years. Also, childhood obesity and diabetes has increased dramatically, and sugar metabolism seems to play a role in bipolar disorder.

**ABUSE & STRESS AS A CAUSE?**

Where could the abnormal stress response come from? Many people with post-traumatic stress syndrome (PTSD) later develop bipolar disorder. Whether they would have had full-fledged bipolar disorder without the PTSD is uncertain. In both cases, the repetitive traumas suffered throw the body into a constant state of stress. Facultative hyperthyroidism is known to occur in people with PTSD under stress—probably an adaptation to being continually stressed and being unable to sleep or otherwise restore adrenaline levels, such as occurs in wartime or under severe abuse conditions. Research shows that stress can induce the hippocampus to remodel itself and shrink, but this process can be prevented by lithium and other drugs used to treat bipolar patients.

Childhood abuse could also help explain the partial connection between bipolar disorder and epilepsy. As it happens, surviving physical abuse (including blows to the head) is a very common cause of grand mal epilepsy in young adults. Roughly 10% of all epileptic patients have been diagnosed with bipolar disorder as well, and many epileptic drugs (e.g. lamictal) are now being applied to treat bipolar disorder.

Now to the genetics of stress: a gene called MAOB, related to the gene causing Brunner Syndrome and occurring on the X chromosome, is under study for its role in stress and bipolar disorder. When the gene is under-active, it seems to have some correlation with
bipolar disorder and increased reactivity to stress.

Smoking can reduce the levels of MAOB by 40%, and there may be other environmental effects on this gene expression. MAOB helps regulate dopamine, and variants of this gene influence the risk of Parkinson's disease. The fact that smoking influences MAOB, a protein related to another mental disorder and under study for bipolar disorder, is suggestive; smoking increases adrenaline, a stress hormone, with every cigarette. Drug abuse and smoking is also prevalent with bipolar disorder and induces stress and trauma on the brain, worsening symptoms. Bipolar patients under treatment are recommended to avoid even caffeine.

THE IMMUNE SYSTEM & STRESS?

It is well known that depression often occurs during illness and recovery—nobody feels happy when they feel sick and weak, and there are intricate biological causes for this. Interestingly, some studies also indicate that there seems to be a link between personality traits and immune system function. Other studies show that AIDS/HIV worsens the effects of bipolar disease. Also, bipolar patients have been shown to have abnormal immune system patterns in mania. Dopamine D2 receptors, which may play a role in bipolar disorder, are also involved in mediating suppression of the immune system. This is an underdeveloped line of research, but worth mentioning because calcium channels are involved in both bipolar disorder and immune system control. This may offer clues to identifying how bipolar depression occurs and better ways to treat it—current drugs for bipolar depression have strong side effects.

MANIA AND THE SUGAR TRAIL

Protein Kinase C, (PKC) the hottest discovery in the treatment of mania, is an enzyme known to rise with high blood sugar levels. It also plays a role in the immune system, apparently helping control infection by intracellular parasites. In fact Lyme disease, caused by intracellular bacteria, sometimes presents with bipolar disorder-like symptoms. PKC comes in a few different variants, all from the same gene. For example, genetic variants in PKC are also associated with alcohol intake (and alcoholism), which is a common problem in bipolar patients. Similarly to how alcoholics black out, bipolar patients report that they have no memory of what they did or said during their psychotic episodes. They have to depend on people around them to tell them that they were delusional and apparently hallucinating.

The "haze" of mania produced by excess PKC may be somewhat familiar to anybody who's ever been foggy after a really huge meal. The major difference between bipolar patients and people without bipolar disorder is that most people who have post-prandial high blood sugar tend to feel sleepy or otherwise relax. In contrast, those about to go into a manic episode will experience a burst of unlimited energy along with rapid and pressured action and speech, an overwhelming feeling of seeing it all, and a need to act NOW. Interestingly, both Wolfram syndrome and a rare form of bipolar disorder identified by Japanese scientists have been traced to defects in the endoplasmic reticulum,
a cell structure with many jobs, including that of taking up glucose into the cell. This suggests that sugar metabolism may play a role in other types of bipolar disorder.

This new discovery linking PKC to bipolar disorder also hints to a possible mechanism in which lack of sleep causes high blood sugar AND manic episodes in people with bipolar disorder. Researchers hope that developing drugs to inhibit PKC will mean that doctors in the emergency room can rapidly bring down people from the manic state within hours.

NEW WAYS TO RESEARCH BIPOLAR DISORDER

Now, if we had a magic wand to wave over a person to find out if they are bipolar or not, it would simplify research and diagnosis considerably. We are nearing that day.

GENE EXPRESSION:
Significantly, all of the genes in the body are used in one form or another in the brain, but never all in the same cell type. In the last decade, we have been making great progress in actually tracking which genes in each cell type are being used at any given time; this is called gene expression. Just a few cells extracted can be tested with cDNA microarrays, a lab technique that simultaneously tests for thousands of genes at the same time to capture which genes have been just turned on or off. This test is heavily used in cancer research and now is an important part of neuroscience. cDNA microarrays can be used to detect molecular abnormalities in bipolar patients without knowing the precise genetics. This is how the latest, hottest discoveries in bipolar disorder were made. A blood test now exists to distinguish bipolar disorder from schizophrenia using cDNA microarrays alone—both diseases have characteristically different gene expression patterns.

An interesting discovery will help research gene expression levels in bipolar disorder. Bipolar patients have a lower concentration of calcium in their olfactory bulbs, and a lowered calcium-sensitive response to smells. It has been shown that bipolar patients have a defect in calcium regulation in their neurons, and with a simple five minute biopsy, actual living olfactory receptor neurons can be studied and directly correlated to what is happening in bipolar disorder. If those neurons can be used to study drugs' effects and also measure changes in various stages of bipolar disorder, this will be a huge boost to the gene expression studies, which right now rely on blood tests and cell cultures.

CALCIUM MAKES THE BRAIN STRONG

Interestingly enough, calcium is required not only for normal neurotransmission and smell; it also plays a role in blocking persistent smells. After a few minutes of being exposed to an odor, extracellular calcium enters olfactory neurons and prevents them from sending signals—turning down the volume. It would be interesting to study if the sense of smell differs in bipolar patients.

Calcium channels also play a role in other sensory neurons in the eye and in the ear. Studies in salamanders and mice show that low extracellular calcium increases calcium signaling between neurons in the eye as well as in the nose. What effect a drop in
extracellular calcium would have on vision is uncertain; it cannot be completely bad considering that artists have 20 times the rate of bipolar disorder as the normal population.

Also, at least one type of calcium channel seems to have a role in synchronizing brain cells. A type of epilepsy that sometimes occurs after a stroke has been directly tied to increased extracellular calcium, probably by leakage from dying cells. Epilepsy occurs when a part of the brain strongly synchronizes its firing. Omega-3 acids, which play a protective role against depression, have recently been shown to control calcium channels and other ion channels also involved in our senses, further suggesting that diet SHOULD play a difference in bipolar disorder management.

THE BRAIN ELECTRIC
The brain, which can be compared to an electric circuit, produces a strong electric field. This is why EEGs (electrocardiograms) have been useful for 100 years to observe some basic disturbances in the brain. Unlike a circuit, however, the brain does not use simply one kind of 'wiring', but has many subtypes of cells called neurons and glia.

![Diagram of neuron, astrocyte, oligodendrocyte, and microglia](image)

The types of glial cells versus a typical neuron

Neurons exchange neurotransmitters with each other to communicate and form various networks, such as the reticular formation that functions to suppress sleep. It is thought that bipolar disorder is due to a disruption of cell-cell communication in the part of the brain
governing emotion, but researchers can not pinpoint where. Now a physical difference has been pinpointed— but in the glia, not the neurons.

New, sophisticated imaging techniques— especially fMRI (functional Magnetic resonance imaging) are able to track what is happening in the brain on an electric level in a more precise manner, and thereby allow researchers to deduce some of the molecular activity. fMRI has found that patients with bipolar disorder have very few oligodendrocytes in the left hippocampus of the brain, a significant finding, because this area controls emotion and memory processing. Remember, stress affects the hippocampus— but why bipolar patients have asymmetrical hippocampuses is unknown.