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December 5, 2002
BBB 380

Pharmacological Evidence for the Role of Serotonin in Depersonalization Disorder

Depersonalization Disorder is a psychiatric disorder that, despite being first described over a century ago, still remains a relative mystery. Very little is known about its etiology, neuro-chemical mechanisms, or prevalence within the general population [1]. The disorder is characterized by a feeling of detachment from the self or from one's body, and there is a general sense that things have become unreal. Limbs may seem foreign and there can be a general disconnect from one's emotions, as if they belonged to someone else. Patients report that they feel like an automaton or an observer, and may have difficulty perceiving themselves in a mirror. "It is as if the real me is taken out and put on a shelf or stored somewhere inside of me. Whatever makes me me is not there. It is like an opaque curtain..." [1]

The external world may seem foggy, distant, or unreal, as if it were "made out of cardboard" or were frames from a movie [2]. Less frequently, objects may seem to have changed color or have become larger or smaller (macropsia or micropsia). It is important to note that individuals with Depersonalization-Derealization Disorder (as it is also known) are aware that their perceptions are simply feelings and carry no actual reality. In contrast to schizophrenia, patients maintain intact reality testing.

While the DSM-IV indicates that Depersonalization Disorder should only be diagnosed in the absence of other mental disorders, depersonalization symptoms may occur in a wide variety of disorders including panic disorder, generalized anxiety

disorder, phobias, obsessive-compulsive disorder, and posttraumatic stress disorder. Additionally, depersonalization disorder has been observed to have been temporally related to drug use and acute stress. While most patients of the disorder (70%) experience the symptoms continuously, episodes of depersonalization also occur with some frequency in the general population [1]. The DSM-IV states that approximately 40% of normal adults have experienced an episode of depersonalization, usually correlated with drug use or stress. Episodes tend vary in duration from a few minutes to a few weeks and, in more extreme cases, can last years [3].

Currently the cause of depersonalization is unknown, though there is evidence that it may be correlated with generalized anxiety disorder. Simeon, D found that in a population meeting the DSM-III-R criteria for depersonalization (N=30), the mean age of onset of depersonalization significantly correlated with the mean age of onset of generalized anxiety disorder. Moreover, it did not correlate with any other major psychiatric disorder. Depersonalization also appeared to be more severe in patients who also suffered from avoidant personality disorder, which lends support to the anxiety theory [1]. Apart from these correlations and a general correlation with trauma [1] and epilepsy [4], extremely little is known about the disorder's etiology, and as of yet, no neurological model has been validated.

The best way currently, it seems, to learn about the disorder's mechanism is through pharmacological evidence. This methodology uses information from both successful and unsuccessful treatments as well as reports from casual drug use. In this paper I will use pharmacological evidence to make the case that serotonin dysregulation

is implicated in Depersonalization Disorder and may in fact play a key role in its neuro-chemical mechanism.

There is a significant number of case studies in the literature that indicate Selective Serotonin Reuptake Inhibitors (SSRIs) have a positive effect on the disorder [5,6,7]. In many cases, the disorder is presented with other conditions that respond to treatment while the depersonalization feelings are only alleviated once the patient is started on a SSRI. Abbas S reports the case of a 21-year-old woman suffering from depersonalization disorder whose moderate depressive symptoms were alleviated with non-SSRI anti-depressants, but whose depersonalization persisted until she was treated with fluoxetine. After treatment began, she eventually experienced a complete resolution of her symptoms and was able to maintain the improvement during 6 months of follow-up [5]. Sachdev P reports similar findings using a combination of Citalopram and Clonazepam, and found that the results were robust, even upon multiple re-challenges [6]. Finally, in a case report of eight patients, Hollander E reported that six out of the eight patients experienced resolution of their chronic depersonalization through the use of either fluoxetine or fluvoxamine. This data, along with several other case studies including Fichtner et al 1992, Ratliff and Kerski 1995, and Simeon D's partially completed trial with Clomipramine [8] all suggest that serotonin plays a significant role in depersonalization disorder.

If we are to infer that depersonalization symptoms arise from a deficiency in serotonin and that SSRIs are effective by preventing reuptake, thereby increasing the levels of serotonin, Sakar J's case report of an actual induction of depersonalization is of especial interest owing to the fact that it may have arisen through an induced serotonin

deficiency [2]. He reports of a 65-year-old man who was receiving treatment for schizophrenia that manifested thought disturbances and hallucinations in multiple modalities. He was started on a course of quetiapine, an atypical antipsychotic medication that works acts as both a dopamine and a serotonin antagonist [9]. Within 6 weeks of medication, his schizophrenic symptoms had showed improvement but he also reported the onset of clear episodes of depersonalization, some of which lasted up to 5 minutes at a time. When the quetiapine treatment was halted, the depersonalization symptoms ceased, but the schizophrenic psychoses returned. It was decided that he would rather live with the depersonalization than the psychosis, and so was restarted on quetiapine, upon which time the depersonalization returned. Sakar's case is very interesting because the depersonalization may have occurred due to the 5-HT antagonistic properties of quetiapine. If this is the case, it would lend credence to the theory that a serotonin deficiency is involved in depersonalization.

Another area that is yielding some very interesting results is the study of the effects of 3,4-methylenedioxymethamphetamine (MDMA), otherwise known by its street name, Ecstasy. MDMA is a compound that was first patented in 1914 by Merck and has become in the last twenty years one of the most popular recreational drugs in the world. Primarily used in dance clubs and rave scenes, MDMA produces a feeling of euphoria, usually accompanied by enhanced mood, sensitivity, and sociability. In addition to these sought-after effects, a high percentage of MDMA users experience some amount of depersonalization/derealization during their trips, an effect typical of psychoactive drugs such as cannabis and LSD. This effect is usually welcomed by the user as part of their altered experience.

Perhaps one of the clearest demonstrations of this effect is Vollenweider FX's 1998 study, in which 13 MDMA-naïve subjects were entered into a double-blind placebo-controlled study in order to determine the effects of MDMA on cognitive functioning [12]. This study was one of the first, if not the first, to study ecstasy's effect in naïve subjects – a condition that is extremely important due to the possible confounding effect that repeated, long-term use may have (to be discussed later). In the study, subjects ingested a typical recreational dose of MDMA (1.7 mg/kg) or placebo and then were tested after 75 minutes in order to obtain a reading during the peak effect of the MDMA. They were rated using the Altered State of Consciousness (APZ-OAV) rating scale which reliably measures changes in self-perception, mood, and thinking during altered and normal states of consciousness. Vollenweider found that subjects who ingested MDMA reliably showed moderate increases in feelings of depersonalization and derealization ($p < .001$) compared to placebo.

What makes MDMA especially interesting for research in this area is the fact that it has a strong effect on the serotonergic systems in the brain. MDMA seems to cause an efflux of vesicular serotonin – it has been shown that acute doses can release up to 80% of central serotonin stores [10]. Additionally, new research is emerging that shows that MDMA can cause severe serotonergic impairment with long-term use [11]. Croft RJ, et al using EEG and an auditory intensity dependence paradigm showed that regular MDMA users exhibit significantly lower levels of serotonin function compared to both cannabis users and normal subjects. In consideration of this evidence and the evidence that depersonalization is associated with low levels of serotonin, we can then hypothesize that as current casual MDMA users become long-term users, more incidences of

depersonalization may be seen due to this progressive serotonergic impairment. Though the evidence is rather weak, Wodarz N's case study of a 21-year-old woman who exhibited a protracted psychotic depersonalization disorder after ingesting two ecstasy tablets for the first time may point in this direction [13].

Evidence from this sort of research indicates that MDMA may represent another method of studying the effects of serotonin manipulation, both in the agonist and antagonist cases. Even though drug-induced depersonalization is not technically considered to be a form of the disorder, many researchers still feel that it is a valid research approach due to the phenomenal similarities with the canonical condition [3]. It is important to note, however, that evidence derived from MDMA should be considered "messy" at best because the drug also boosts dopamine, noradrenalin, acetylcholine, and histamine levels [10]. Such interrelation prevents us from making any definitive claims about serotonin, but it can be extremely useful in pointing out new directions for research.

While nearly all of the research presented so far has suggested that decreased levels of serotonin are implicated in depersonalization, Vollenweider's experiment marks an important departure from this trend. Clinical studies show that MDMA ingestion leads to a temporary increase in serotonin levels [10], consequently the subjects in his study were experiencing depersonalization during a period of increased serotonin. While this study seems to run contrary to most of the data available (the numerous successes of the SSRIs, etc), one very important study seems to back it up, and suggests that an increase in serotonin may also cause depersonalization.

In some ways Simeon D's study [3] is a distillation of many of the critical aspects of the experiments mentioned above. It attempts to integrate their important aspects and test them in manner that isn't marred by confounding factors. In the other studies, when depersonalization was induced by an antipsychotic, we are not able to rule out the effect dopamine inhibition might have had. Similarly, in the MDMA studies, many other neurotransmitters are affected by the drug, and in the reports of SSRI treatment, depersonalization may have been co-morbid with many other psychological and neurological conditions. While co-morbidity is generally a normal state of the disorder, a clear dissociation must be shown both in incidence and treatment.

Simeon D's study is the first experiment to attempt to induce depersonalization purely by affecting the serotonergic system.[1] Subjects were given doses of meta-chlorophenylpiperazine (m-CPP), a known serotonin agonist, in a double-blind comparison with placebo. The subjects included 18 patients with social phobia, 16 patients with borderline personality disorder, 22 patients with obsessive-compulsive disorder, and 11 normal controls. Once a 0.5 mg/kg dose of m-CPP or placebo was administered, subjects were asked to rate their feelings of depersonalization ("Do you feel detached from part or all of your body?"), derealization ("Do things and people seem unreal?"), as well as anxiety, nervousness, sadness, drowsiness, depression, and panic. Ratings were obtained every hour for the four hours following m-CPP administration, with a typical m-CPP effect peak at approximately 2 hours.

[1] Strictly speaking, this study is not the first to induce depersonalization by targeting the serotonergic system. Hollander E et al published an article the year before using the same m-CPP induction paradigm but the study was aimed more at determining the role of serotonin in borderline personality disorder than actually probing the mechanisms of depersonalization.

Simeon found that the number of subjects who experienced depersonalization was significantly higher in the m-CPP group than in the placebo group. Similar results were found in the mean change of depersonalization score (a measure of severity from the subject's own baseline), with significantly higher scores in the m-CPP group. Of the 12 m-CPP group subjects who experienced depersonalization, 6 had borderline personality disorder, 3 had obsessive-compulsive disorder and 3 had social phobia. In total, depersonalization was induced in 18% of the study's subjects.

While the study did not induce depersonalization in any normal controls, it was extremely successful at inducing it in patients who already possessed a psychiatric condition. This may suggest that these patient populations have varying degrees of serotonergic vulnerability and/or it may be indicative of some common underlying mechanism. Nevertheless, the essential finding here is that there seems to be a rather clear link between serotonin dysregulation and episodes of depersonalization. Even more significant is that episodes can be triggered with nothing more than the introduction of serotonin, strongly suggesting that it plays crucial role in the phenomenon. Whether serotonergic dysregulation is at the heart of chronic Depersonalization Disorder, or is involved simply in the induced variety, it has yet to be proven.

Looking back at all of the experiments presented here, it seems that it is reasonable for us to conclude that serotonin very likely plays an important, if not crucial role in the experience of depersonalization. We have evidence for a lack of serotonin in naturally occurring cases of depersonalization disorder, evidence that a lack of serotonin may be implicated in episodic depersonalization, and we also have evidence that too

much serotonin may have similar effects in both high doses (MDMA usage) and in vulnerable patients (m-CPP).

What is now required is a two-fold effort to further pin down serotonin's role and to place it in the larger picture of the disorder. First, more dissociating experiments should be carried out to show that the effects we are seeing truly are due to abnormal serotonin levels. I propose a battery of at least 4 experiments[2]: attempt to induce depersonalization with a serotonin antagonist; attempt to match MDMA-induced levels of serotonin with an agonist; replicate Simeon's experiment with another agonist, varying the dosage and attempting to measure the levels of serotonin; and finally, monitor the levels of serotonin in patients at risk for developing the disorder. The first experiment would try to mimic naturally occurring Depersonalization Disorder (at least to the extent that serotonin is involved) while the second would try to disambiguate serotonin's role in MDMA-induced depersonalization. The third experiment simply makes Simeon's experiment more rigorous, and the forth attempts to study more closely the role of serotonin in natural cases of the disorder.

The second step would be to determine the role of serotonin in the larger neurological picture. It has been suggested that the pre-frontal cortex is somehow over-regulating the amygdala and anterior cingulate. Another model has suggested that there is a failure to integrate neocortical perceptions and thoughts with previously acquired information, causing a split in the person's experience. Emotional modulation by the limbic system and basal ganglia may also fail to occur, further distancing the individual (Hollander et al, 1992). Whichever theory is developed must be able to explain

[2] I am not knowledgeable enough to determine whether these experiments are actually safe enough to be carried out, but I imagine some version of them should be possible.

depersonalization's interaction with other disorders (the connections to OCD, epilepsy, and anxiety), why it occurs, and how the transitory drug- and stress-induced episodes are related to the natural disorder.

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