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Conference Highlights: Hallucinogenic Drugs in Experimental Psychiatric Research
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March 13th through 15th, 1997 at the Hotel Casteel Bloemendal in Vaals, Netherlands, I attended a three day workshop entitled Hallucinogenic Drugs in Experimental Psychiatric Research. Having a long standing interest in MDMA (Ecstasy), psychedelics, and schizophrenia, this was one conference I was not about to miss. The workshop was quite small and limited to forty people, so I felt relieved when, after some petitioning, I was allowed to attend. The "Tryptic-Workshop" was organized by the Depar tment of Psychiatry and Psychotherapy, Technical University of Aachen, Germany in collaboration with the Department of Psychiatry and Neuropsychology, University of Limburg, Maastricht, Netherlands and the Service de Psychiatrie, Centre Hospitalier Univer sitaire, Liege, Belgium.

The most impressive feature of this gathering, for me, was the professionality of the presentations. Serious scientific studies had been performed or were in progress, and their findings were presented in a manner similar to many pharmacologic conferences which I have attended - totally above board, with no excuses or innuendos. The data presented was geared to a doctorate level of understanding, with the majority of the presentors and audience members being M.D.'s and Ph.D.'s.

Opening Event

The weekend opened with a wine and cheese 'getting to know you' party on Friday evening. At this point in the weekend I met some recent MAPS Bulletin contributors (Alex Gamma from

Switzerland and John Halpern at Harvard) as well as the MAPS networks coordinator, Sylvia Thyssen. It was a pleasure to meet Sylvia after years of seeing her picture and carrying on an E-mail correspondence. I think it is important for MAPS members and other researchers to get a sense of what studies are going on, where, and by whom, and I found Sylvia to be a very able diplomat within the international psychedelic research community.

Saturday Morning

The proceedings were opened by Prof. Sass, who introduced the history of the tradition in Germany of experimental work with hallucinogens. Dr. Sass, a psychiatrist and psychopathologist, is not a specialist in psychedelics, but he is interested in the cha nges brought about by them. He described how the research tradition of working with hallucinogens has its roots in Heidelberg, with Kurt Beringer. Beringer described the effects of mescaline in detail in the 1927 Künstlisches Psychomodell which estab lished the groundwork for the experimental psychosis model.

Dr. Efi Gouzoulis-Mayfrank, a remarkable woman who is in the midst of performing MDE (methylene-dioxy-ethamphetamine, "Eve"), psilocybin and methamphetamine experiments, gave the first presentation. She reviewed the historical context of halluci nogen research, citing the mescaline phase of research as beginning in the late eighteen hundreds and giving way to the LSD phase beginning in 1943, and then finally describing research with PCP in the nineteen fifties.

Gouzoulis-Mayfrank discussed the problems and challenges of interpreting symptoms in schizophrenia, which are quite complex and which represent a wide variability of sub-syndromes. She stressed that her research seeks to shed light on the onset of psychot ic episodes, not schizophrenia as a whole, which she and others feel may be a syndrome, and not a disease.

1943-1960's: The LSD Phase

This phase of research was characterized by LSD, psilocybin, DMT, mescaline, phencyclidine and the anti-cholinergics. At the time, areas of interest in psychiatry were the model psychosis and the use of psychedelics for screening for latent schizophrenia. There was also a

prevalence of psychoanalytically oriented research on consciousness and personality, research on religious experience and psychotherapy research. In 1962, Hollister argued against the hallucinogen experience as a model for psychosis, des cribing the ongoing debate of the appropriateness of hallucinogens as psychotomimetics (mimicking psychosis). This phase of research thrived until research was restricted in 1966 following the wide use and abuse of these drugs in non-research contexts.

On the Term "Hallucinogen"

I see that the term hallucinogen has come up more than once already, so I suppose I must acknowledge the ever present nomenclature debate: please understand that psychedelics are most frequently called hallucinogens in medicine, as in the title of the weekend conference. Hallucinogen is the accepted terminology in the American psychiatric diagnostic manual, for example. It is also an accepted legal term and the one used to group many scheduled drugs. The older term psychotomimetic was also used in both law and medicine, but much less so now. I, too, prefer the less pejorative term psychedelic, but the scientific research community at large, for the most part, seems only willing to discuss these neuromodulators as capable of creating models of psychosis, replete with hallucinations. Most of the presentations during the conference had to do with comparing acute drug intoxications with psychotic states found in illness, usually schizophrenia, and sometimes mania. There was some attention given to using these substances as treatments, certainly this was discussed with more enthusiasm privately than what was publically presented.

Classification Systems

Dr. Karl-Artur Kovar delineated the different classes of psychotropes to be discussed over the weekend: under the heading of phenethylamines are stimulants like amphetamine and methamphetamine, hallucinogens such as mescaline, 2CB, DOM and entactogens suc h as MDMA, MDE, MDA and MBDB. Dr. Kovar referred to MDMA, MDA and MDE as the "Ecstasy group" and described the complexity of their mode of action. Of course, there are many other psychedelics which fall under different headings, such as tryptami nes (DMT, 5 MeO-DMT, and others), phencyclohexylamines (PCP, ketamine and others), and indolalkylamines (LSD, psilocybin, ibogaine, bufotenine, and DMT). To confuse matters slightly, it should be noted that most of these indolalkylamines can also be class ified as tryptamines, as there is a tryptamine subclass of indole derivatives. Psilocybin is 4-phosphoryloxy-DMT, and bufotenine is 5-hydroxy-N,N,DMT, and LSD, although not a tryptamine, does have a molecular structure that includes a tryptamine molecule. During the Q&A after Kovar's presentation, the fluoxetine effect on reversing the "neurotoxic effect" of MDMA seen in laboratory animals was brought up.

Prepulse Inhibition (PPI) Research

The next presenter was Mark Geyer, Ph.D., UC San Diego, who explained the effects of various compounds on a measurement called prepulse inhibition (PPI) of startle response. PPI is a great, non-invasive way to measure something called sensorimotor gating, which could show a deficit in how someone filters out stimuli. Habituation, the process of 'tuning out' a repetitive stimulus, is a precursor of selective attention. Most schizophrenics show deficits in habituating to stimuli and in learning from a cue (like a prepulse-a smaller stimulus given before the larger one, to warn the subject of an impending cause for startle). In rats, hallucinogens such as LSD, and glutamate antagonists (also called NMDA antagonists for the type of glutamate receptor they interact with) like PCP and ketamine all disrupt prepulse inhibition and retard the process of habituation. In contrast, the amphetamines enhance the startle response, and low dose MDMA enhances prepulse inhibition in rats. A member of the audience, Franz Vollenweider, who was to present his MDMA findings the next day, reported the information that MDMA has enhanced prepulse inhibition in human volunteers as well, at a dose of 1.7 milligrams per kilogram body weight. (This comes out to 119 mg. for a 150 poun d individual. The commonly accepted 'recreational' dose of MDMA is 125 mg. initially, with an optional delayed 50 or 75 mg. "boost" dose.) These findings reported by Geyer and Vollenweider help to make the case that there may be a place for huma n studies with MDMA in the context of schizophrenia research. I have great hopes that low dose MDMA may help people with schizophrenia to pay closer attention, be less socially withdrawn and suspicious, perhaps talk more and connect with others. I have ce rtainly seen and read of these effects when MDMA is used in people without this disease. Research was conducted in the past to suggest that schizophrenics can benefit from low dose amphetamines to combat their negative symptoms. The concern is, will MDMA make people with schizophrenia more psychotic? I am in the process of collecting case studies of people with schizophrenia who have experimented with MDMA, if anyone reading this would like to contact me, I would appreciate any leads.

The APZ

Later in the morning of the first day, we heard about various ways to measure altered states of consciousness (ASC), with special attention paid to the German APZ questionnaire as described by Adolf Dittrich of Basel, Switzerland.

Dittrich developed the APZ in 1975. It is a 159 item survey, designed to assess specific states of consciousness rather than personality. Questions are presented in the first person singular. It

measures feelings of oceanic boundlessness, dread of ego-dissolution and visionary restructuralization. Dittrich drew parallels of these three to Huxley's Heaven and Hell and Visions. He went over the definition of altered state of consciousness and commonalities between ASCs achieved by different methods. He cite d a recent study done with 339 subjects tested with DMT, psilocybin, THC, NO2, perceptual deprivation, hypnagogic states, autogenic training, sensory overload and hypnosis. Subjective reports, keyed by independent reviewers, correlated well with APZ results.

The instrument itself has been rigorously tested, and it is the standard in Europe for assessing ASC. It has been translated into English. Psychometrically improved versions have been designed that utilize visual analog scales. Several of the European pre senters were using the APZ questionnaire as an outcome measurement of the subjects' experiences with study drugs. Unfortunately, no one was using Rick Strassman's Hallucinogen Rating Scale (HRS). According to Dittrich, the items in the HRS are not interna tionally accepted criteria and were tested in too few subjects. It has not been translated into German.

On Semantic Networks

After lunch there were two lectures on comparing schizophrenia with a psilocybin model of psychosis, with one looking at the analysis of facial expression and the other focusing on semantic networks and "loose associations," as tested by priming cues (related vs. unrelated words given before a test word, with the subject having to decide if it was a real or nonsense word). The results showed that in "psychosis" whether schizophrenic or psilocybin-induced, people widen their association s between words, so an indirect semantic primer will hasten the word choice much as a direct primer would ('lemon' before 'sweet' as opposed to 'black' before 'white'). This last study was eloquently presented by Dr. Manfred Spitzer, soon to be leaving He idelberg to become the chairman of a different psychiatric department elsewhere in Germany. Dr. Spitzer also capped the conference with an intriguing and somewhat daring summary including the possibility of an actual beneficial state from these substances , specifically the evolutionary advantage of "loosened associations." He feels that a decreased anxiety state is conducive to inducing change via these new pathways, created by broader activations. His capping lecture did seem to allude to the h orizons ahead, offering the possibility of treatment modalities involving psychedelics, and admitting that it was not fully discussed over the weekend but it was possible that "the use of hallucinogenic agents may actually have psychotherapeutic effe cts."

The Glutamate Hypothesis

The last two lectures of the first day covered familiar ground for me, the glutamate hypothesis of schizophrenia and experiments with NMDA type glutamate antagonists, specifically ketamine. Glutamate is the most abundant excitatory neurotransmitter in the brain, and the resulting intoxicated state that ketamine brings is felt to be reminiscent of many symptoms of schizophrenia, creating not only paranoia, delusions, hallucinations (all positive symptoms) and disorganized speech, but also negative symptoms - the group of behaviors manifest by social and emotional withdrawal. It is felt by many schizophrenia researchers that the glutamate antagonists ketamine and especially PCP, offe r the best model for schizophrenic psychosis, since they combine both positive and negative symptoms. One thing intriguing was that when discussing other drugs such as psilocybin or mescaline, the European researchers routinely specified the correlation o f their intoxications with the acutely psychotic state, but not the chronic residual phase, of schizophrenia. This is a differentiation not routinely made in American schizophrenia research, where we tend to clump schizophrenics into either "positive symptoms" or "negative symptoms" groups, and often specifically seek out one group or another for research subjects.

Ketamine

Two American M.D.'s, John Krystal from Yale and Henry Holcombe from University of Maryland, spoke of their clinical studies giving ketamine to healthy volunteers and schizophrenics. This is pretty much standard schizphrenia research fare, but was included in the conference due to ketamine's 'psychedelic' status, I presume. Dr. Krystal also tied in some prepulse inhibition data, reporting that in healthy volunteers, ketamine attenuates the sensory gating, and decreases the prepulse inhibition, thus mimicki ng results seen in schizophrenics. Dr Holcombe, commenting on work begun by Carol Tamminga, also correlated an area with the most increase in cerebral blood flow during the ketamine induced state, with the same brain region recently identified in PET stud ies during active auditory hallucination - the left superior temporal cortex. He brought up a repeated question for researchers: what does it mean when an area of the brain is turned on under pharmacological conditions?

Mescaline and SPECT Brainmapping

Sunday morning gave us four lectures. Leo Hermle, a researcher from Göppingen, Germany presented some data from a 1989 study of twelve healthy volunteers (nine of which were M.D.'s) who had ingested 500 milligrams of mescaline and underwent cerebral blood flow studies utilizing SPECT analysis (single positron emission computed tomography: it gives you

the pretty color pictures of the brain's blood flow like PET does, but with less resolution). His results showed an increased frontal uptake and decreased occipital uptake with mescaline, as well as an improved left hemisphere performance over right on a facial recognition task. Mescaline seemed to reverse normal hemispheric assymetry, but the phenomenon did not attain statistical significance.

The face/non-face decision picture was presented to one side of the brain or another with a specialized projection system called a tachistoscope. Dr. Hermle also presented some more recent data of eight male subjects who had ingested 140 milligrams of MDE and underwent sleep EEG's (electroencephalograph, a non-invasive brain wave study) and multiple psychological tests and assessments. All subjects showed an increased desire to communicate verbally, and seven out of eight showed a decrease in anxiety. One subject noted a "good, deep sadness" and unfortunately, one subject was noted to have hallucinations, delusions, and increased anxiety.

REM Suppression

Efi Gouzoulis-Mayfrank followed Dr. Hermle's lecture with more details of the experiments she had performed with him (published in 1992) and new data from an ongoing study begun in Summer 1995 comparing MDE, methamphetamine, psilocybin, and a placebo. Are as that were studied were some that are relevant in the study of endogenous psychosis: working memory, gating mechanism, alteration in psychological effects (thought disturbances) and brain metabolism. In this large study, eight subjects are needed for ea ch compound, and each subject takes the compound on two different occassions, once at noon and another time at eleven p.m. Of note, those subjects taking the entactogen MDE at night experienced complete rapid eye movement (REM) suppression, as shown by th eir sleep EEGs. Few of these patients slept through the night after the eleven p.m. dose, as one might imagine. A similar picture of REM suppression was seen with the amphetamine group. The significance of this is not fully known, but it should be noted t hat antidepressant therapies often supress REM stage sleep, and people with untreated depression show a faster onset of REM when going to sleep than healthy normal volunteers. There are also abnormalities of REM sleep in schizophrenics, one being that eve n after sleep deprivation they do not compensate with more REM once allowed to sleep, as healthy volunteers do.

PET Brainmapping

Franz Vollenweider, M.D. from Zürich, Switzerland, presented his PET data (cerebral glucose utilization studies) obtained under three experimental conditions: during exposure to ketamine, psilocybin and amphetamine. Dr. Vollenweider attempted to corr elate different brain regions whose blood flow and glucose metabolism changed as a result of the intoxication, and map this onto various parameters or clusters of the APZ scale, such as oceanic boundlessness, dread of ego dissolution, or visionary restruc turalization. Dr. Vollenweider had mentioned from the audience during Holcombe's talk, that the area of interest that showed increased cerebral blood flow during mania, the anterior cingulate gyrus, also showed increased flow at a higher amphetamine dose. Other research of his that is currently underway, with the help of Alex Gamma, is PET and MDMA research, however, these results were not yet available.

Receptor Antagonists

The last presentation by Dr. Schneider of Hanover, Germany involved intoxication of delta 9 THC (tetrahydrocannabinol) in healthy volunteers. He compared their results on a visual perception task of 3D inversion of familiar photographs with results from a group of schizophrenics, and found similarities in the groups' disturbances of internal regulation of perceptual processes. Also discussed was the concept of endogenous cannabis receptors, and the recently discovered (1992) endogenous ligand for these receptors, anandamide, and the current development of newer schizophrenic medications based on antagonizing these receptors, such as SR14166A, a CB1 receptor antagonist. Another promising new treatment for schizophrenia which was mentioned in an earlier talk by Mark Geyer was the compound MDL 100,907, currently undergoing clinical trials nationwide (including my home away from home, Bellevue). This is a specific 5HT2A antagonist, thus theoretically antagonizing such psychedlics as psilocybin (a presumed 2A and 2C agonist) and completely blocking the effects of DOI, a serotonin agonist which disrups pre-pulse inhibition. MDL 100,907 is thus considered by some to be a "hallucinogen receptor antagonist," and has been shown to improve sensory motor gating.

Reflections

Again, you can see the focus of the conference was using these powerful substances as tools to study behavior, cognition, emotion, and to build treatments, but not exactly how every MAPS member would hope for. The general theme of this conference was that these psychedelic-induced states were models of unwanted behavior to be quantified and analyzed in order to provide understanding of and ideally treatment for those people suffering from psychiatric illnesses. The catch words for the weekend were definit ely "model psychosis." I know this idea offends some MAPS members. You know these drugs have more to offer. I am

just happy anyone anywhere is allowed to do these studies at all. I think they are crucial, they must be done, any work involving human consumption of psychedelics is inherently good work and anywhere to start is a good place. After the talks had ended, the conference slowly shifted into the usual casual formation of small groups, where there was some talk of who has tried what drugs and what's the best way to take what. On the side, some of these researchers will acknowledge the benefits these drugs can give the average normal healthy volunteer, and some will even privately allow that these drugs have helped the scientists themselves to achieve desired states. The bravest ones will be doing both, publically. Amen.

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Comments by Sylvia Thyssen, MAPS Networks Coordinator

The purpose of my attending this small gathering was two-fold: to gain a better understanding of the type of research that is currently underway with psychedelic drugs in Germany, Switzerland and the United States, and to seek out new opportunities to stimulate psychedelic psychotherapy research.Traditions of research and approaches differ between Europe and America. This workshop's topics were very specifically focused on the use of psychedelic drugs in schizophrenia, or model psychosis, research. Th e 40 or so people attending were primarily psychiatrists and psychiatry researchers. The forum's small size offered the opportunity for researchers to bring up yet-unpublished preliminary data and discuss more deeply aspects of their research. Many of the presenters utilized brain imaging technologies illustrated by slides. To tease out what relevance this has for MAPS' agenda was no small task.

American audience members' questions were focused on MDMA and the psychotherapy agenda. One mention of Prof. Hanscarl Leuner and his work with psycholytic psychotherapy was made during the introductory period of the workshop. When I talked with Prof. Sass , one of the organizers of the workshop, he suggested that Dr. Gouzoulis-Mayfrank's work may stimulate therapy research somewhat in Germany, since if a researcher there studies other aspects of psychedelics first, they may have a better chance of eventually gaining permission to do therapy research.

Manfred Spitzer wrapped up the workshop. He mentioned several times the psychotherapeutic applications of psychedelics and how they can enhance the psychotherapeutic process. This raised the eyebrows of some of the presenters who focus on model psychosis or related research and have little knowledge of this aspect of psychedelics.

MAPS as Metaphor

Surprisingly, Spitzer mentioned MAPS from the podium, noting that there were "representatives of MAPS" (just myself) at the workshop. He brought this up in the context of the metaphor of the map. He went on to elaborate considerably on this metaphor, mentioning neural-network models and the example of phantom pain. He explained how psychedelics are tools that can be used to describe the maps of networks and brain regions and their interaction.

When we want to introduce changes into these maps, we want to learn more about which neuromodulators do what. Psychedelics can be useful for that. But mapping is one thing, changing and adapting the (brain) maps is another. Commenting on the next step, the possible therapeutic use of these agents, Spitzer went into detail. Change involves activating and forming new associations, which requires broad activation, an idea reminiscent of Grof's "non-specific amplifiers." Put another way, "noise " is good for learning and reorganization. The concept of signal to noise ratio is an often used analogy in neurophysiology. As an example, anxious people have a narrow range of activation. To change anxiousness, an agent that introduces a state of broad activation - like a psychedelic drug - may be involved in the process of change.

This was a surprising and encouraging end to a workshop that wasn't designed to discuss the use of psychedelics outside of schizophrenia research.