DISCUSSION

Audience and Panel Participants: David Comings, Scott Lukas, Howard Moss, Meyer Glantz, RonHerning, Remi Cadoret, EricDevor, Dan Hummer, RitaLiu, and Jag Khalsav

Dr. Comings: I was very impressed by the studies published a number of years ago using the Wisconsin Card Sort during a PET scan in schizophrenia. Dr. Lukas talked about functional studies. Can you do that kind of testing with your little air puff machine?

Dr. Lukas: There's a mirror in the magnet itself and we're testing that ability right now. The key will be to get a nonferrous screen that can be placed near the magnet and won't get sucked into the magnet. We're working with small LCDs and on a unit that projects it on the back with a magnifier that then brings the image right in so that the child can actually see the task at a distance.

Dr. Moss: We're using video projection as a way of getting the image.

Dr. Comings: Do you get a video screen far enough from the magnet so that it doesn't destroy it?

Dr. Moss: We have it all the way across the room.

Dr. Glantz: But you also have to have some kind of control for things like kids, who otherwise would perform normally, that have claustrophobic responses.

Dr. Lukas: Sure. That's a good point. We've actually played around with vanilla extract to try to allay some of the fears. It's a funny thing that straight olfactory stimulation tends to reduce some of the claustro-phobia, and those of you who are working with a magnet may want to try it. It doesn't work for everybody, but it's a very good issue, not a trivial matter. How many of you have ever been in one of these things? It's a tight squeeze and you do get a feeling of being blocked in. I think the mirror does help a lot, and so does good subject preparation. We actually spend a lot of time on our informed consent. We have this fully detailed procedure that explains exactly the types of sounds in layman's terms. For example, some of the sounds sound like a backfire of a car; others sound like you've lost

your drive train or something like that—things that people can identify with.

Dr. Moss: We also go through a procedure in which we pick up a metal wastepaper basket and we bang on it a few times and you say to the kid, "This is what the scanner sounds like." We also permit the parent to come in and talk to the child while the child is in the scanner and that seems to allay a lot of fears as well. And, of course, at any point that the child wants to terminate the procedure, that's what happens.

Dr. Lukas: Do you let the parent touch the child?

Dr. Moss: No. But the parent can be there and talk to the child over the course of the procedure. I might add that as this technology improves, and with the use of larger magnets, acquisition time is much, much faster. In fact, echoplanar acquisition time is something like 100 milliseconds. So, you can do a procedure that now may take half an hour in the scanner within a matter of minutes, and that may make it much more useful for children.

Dr. Lukas: That's a very good point, Dr. Moss. That's the way to go, I think.

Dr. Comings: Both of you talked about cost. What is the cost of an hour in one of these?

Dr. Moss: It depends on the center. It's about $650 a scan in Pittsburgh, and then we have to pay for the time we spend on the data processing unit in addition. So, it's $650 just for the procedure itself, and then for the postscan analysis also the price can be very high.

Dr. Lukas: It's similar at McLean Hospital. We charge $750 for the hour in the scanner, but then there's no charge for time on a computer. Some small grants—like Digital for example—will provide a lot of the hardware for you. We were able to get one of those small grants to put up a couple of computer workstations. So, right now we're not charging for that. We may as more people use it.

Dr. Herning: One question comes to mind. We've seen—in terms of brain potentials, particularly sensory brain potentials—the auditory ones that are delayed in some of these populations. There’s always been a question as to whether it's a delay in myelination that causes

the delay in the potentials. Will this technique tell us something about myelination?

Dr. Moss: Yes. Because the process of myelination is the process of laying down biological membrane, we should be able to see that reflected in decreases in the precursors, the PMEs, and possibly static levels of the breakdown products.

Dr. Herning: In this population, then, it might be interesting to look at, in addition to the longer latency brain potentials that you are collecting, perhaps the earlier ones in which you see clear delays that can be directly linked to myelination.

Dr. Moss: Absolutely. Dr. Brigham and I talked quite early about trying to find ways that we could incorporate her ERP data with our P31 data because we all share the same subject population.

Dr. Cadoret: This goes back to more of the clinical issue. At your school I think that Dr. Tarter has been interested in looking at develop-ment of different types of convert disorder—the overt and the covert. Do you have access to that sample, and do you plan to use it?

Dr. Moss: Dr. Tarter has the Pittsburgh Longitudinal Study sample, he's a member of our center, and he collaborates quite closely with us. But we are accessing a different sample. We do utilize Dr.Tarter's expertise, of course, in helping us with taxonomic issues as far as conduct disorder goes.

Dr. Cadoret: I think it would be very interesting to see if this correlates with some taxonomic variety of conduct disorder that may be very relevant to the substance abuse issue.

Dr. Moss: Absolutely.

Dr. Hummer: That's very exciting methodology, Dr. Moss, and I congratulate you on it. I had two questions. One is what is the actual spatial resolution of the scanner in this situation? The reason I'm asking is if you want to look at white matter versus gray matter in terms of the phosphoesters, you'd like to be able to say, "Well, this is clearly from white matter and this region is clearly from gray matter." Can you do that now given the technology?

Dr. Moss: For other atoms of interest—like protons for example—you have much better spatial resolution. You have much less so with phos-phorus and that's a problem. You're getting crude regions, rather than highly specific anatomic areas, which is why quantitative metabolic mapping may ultimately be a more satisfying technology where the anatomy is revealed by the proton MRI and then the metabolite concentrations laid out on the anatomic map. I think that will be very nice, and we are working on that. But, at this juncture, even saying that we're scanning prefrontal cortex, per se, is fraught with a degree of imprecision. We know where the surface coils are being placed. We're very careful about that. But we're unable, for example, to pick out specific regions within the frontal cortex that might be of particular interest, like you can with PET.

Dr. Hummer: The other question: Has there been any animal work done with nonhuman primates looking at development? It seems that one of the hypotheses is that you'll be able to track the ratio of the monoesters over the diesters as a function of age and development. It would seem to me that it would be critically important to look in an animal model for development to see how those change, and it seems like that could be done.

Dr. Moss: Absolutely. It hasn't been done in our center on nonhuman primates; its been done on the rat model and on humans.

Dr. Hummer: But in humans you can't get brain biopsies or postmortem tissue to actually measure the ratio. I mean that would seem to be critical for calibrating.

Dr. Khalsa: A quick question. A couple of questions actually. What about the process of myelination on maturation affected by multiple exposures to the magnetic field?

Dr. Moss: There is none.

Dr. Khalsa: The second and third questions are related to your technique once again. Some of these radio-opaque dyes tend to be allergenic, and I don't know whether you're going to test the children for hypersensitivity.

Dr. Moss: This technique, really, at this stage of the game, does not involve employing a contrast medium. There is no contrast medium. However, I know you're interested in consequences of drug abuse, and I did have a slide. I think I mentioned to you that in last week's

"Biological Psychiatry" there is an article by a group in San Francisco, I think McKay and colleagues, that shows significant differences in PME and PDE in white matter among chronic cocaine abusers versus normal controls I think it may actually have some utility in some studies that want to look at the brain effects of chronic substance use.

Dr. Devor: Dr. Moss, from the perspective of a molecular biologist who is not obsessed with dopamine receptors, can you see the metabolic mapping techniques as potentially generating candidate genes in the future?

Dr. Moss: Well, as we know more and more about the genetic regulation of the process of maturation, and if we find a dismaturity in one select population that we are studying, then I see some very interesting candidate genes emerging on the horizon. But, I think we're at least 5-10 years away from that point. I guess there's all that work on homeoboxes and matura-tion, and that may be one place to begin looking, but first I'd like to be able to see some demonstration that dismaturation is involved in some of these dysregulated behaviors that are precursors to substance abuse.

Dr. Liu: I'm really intrigued with your synapto--(inaudible)--and how do you translate--(inaudible)--with such densities of synapses?

Dr. Moss: This procedure is very, very new and it involves, instead of using phosphorus as our atom of interest, sodium, sodium 23. The way the procedure is done involves taking advantage of the fact that extracellular fluid is rich in sodium and intracellular fluid is relatively poor in sodium. Through a process of imaging sodium and then a subtractive process, you basically subtract away the water, or the cerebrospinal fluid, in the blood. What you're left with is intracellular synaptic density. And then there are some mathematical ways to convert that information into something a little bit more meaningful in terms of density measures.

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