

DISCUSSION

Audience and Panel Members: William Iacono, George Uhl, David Comings, Ralph Tarter, and Dan Hummer

Dr. Iacono: I'd like to make a few comments. One is that Dr. Lukas was talking about the coolest paradigm that we're using in this research, and it's actually a variant of Hare's countdown procedure. We have a slightly different type of presentation, but we tell the children in the study that it's a test of their cool, how well they can handle the anticipation of an aversive stimulus.

Also, Dr. Lukas mentioned that the use of psychophysiological measures tends to eliminate some problems with subjective responsiveness inherent to other kinds of measures. Although that's true, it's also the case that these techniques involve psychology as well as physiology. It's very important to pay attention to the relevant psychological methodological issues that might affect the outcome of this research, just as it is important to pay attention to the quality of physiological recording.

A lot of effort goes into this type of research to refine a paradigm and to get it to the point where you can generate reproducible results. That's difficult to do in psychophysiology just as it is in many other areas of research.

Let me say a little about the actual study that we're doing. It's a study of twins who are at risk for developing substance use disorders. Dr. Lykken talked a little bit about it this morning, as did Dr. Lukas. It's an epidemio-logical investigation in which twins are identified from birth records. These are the twins born in the State of Minnesota. We're very effective at finding the twins. We find over 90 percent of them at age 11 and age 17. We send them questionnaires that include questions about the drug and alcohol use of family members as well as other questions about mental health and criminal activity. We make sure we overselect families who belong to risk groups defined by parental antisocial behavior and drug and alcohol use. Because there are more twins in any given year than we can possibly bring in, we randomly select from the remaining twins. We bring the twins and their parents who come from all over Minnesota into our laboratory for a full day's assessment, putting them up in a hotel if necessary. We have a large number of assessments and diagnostic interviews, some of which are repeated annually through phone and mail

contacts, and an extensive reassessment is carried out every 3 years in our lab. The project includes over 1,000 pairs of twins and their families, studied for about 10 years.

Dr. Uhl: This is a bit of a naive question. You have access to the birth records and so on. So, do you have any sense that perinatal issues that can lead to these changes (I think long-lasting changes) in things like evoked responses, and so on, are contributing to some of the concordances in the genetic studies with physiologic measures basically? It seems like that's an area that could covary again in the correlational substitutions with such measures as small for gestational age, prematurity, and so on. These may link directly to the perinatal issues that can have subsequent evoked response reflections that will last 6 months.

Dr. Iacono: Yes, it's an interesting question. As it turns out, the records we have are the birth certificates. We don't have hospital records, but we do interview the mother about the twins' births. That's as close as we get to covering this issue.

Dr. Comings: I think you mentioned this morning that there have been two studies now. One in our lab and one in Opel's lab that showed that the latency in the P300 is highly correlated to the D2/A1 allele pool. To me, it would be a shame for you to do all this work and then not, some-where down the line, do some genetic correlates with it.

Dr. Iacono: Well, I was wondering, since your talk this morning, how hard would it be for us to add something like that?

Dr. Comings: All you have to do is draw blood and find somebody that will do it for you.

Dr. Iacono: We've already got the blood.

Dr. Comings: We'd be happy to talk about it.

Dr. Tarter: I was surprised that you didn't mention anything about the use of visual tracking and eye-movement measurements, particularly since we've had a lot of discussion today about attention deficit disorder as a potential risk factor and some discussion centered around ERPs. Can you comment on the potential value—and I'm speaking again naively to this group—of looking at those kinds of variables as markers of frontal lobe development or functional

maturation, those processes that are supposed to be subserved by the frontal lobes such as eye movement, visual tracking studies?

Dr. Iacono: Yes. In the first place, I do schizophrenia research that includes eye-tracking studies. We have looked at schizophrenics' smooth pursuit eye-tracking and related it to performance on neuropsychological tasks, and we get a fairly strong correlation between the inability to generate smooth pursuit eye movements and various indices of frontal lobe dysfunction in adult schizophrenics. That particular finding has also been reported in other labs using less extensive neuropsychological assessments than the one we use. So, it does seem to be the case that the inability to do pursuit tracking might be related to some kind of frontal lobe problem.

In the twin study we're talking about here, we are assessing smooth pursuit eye tracking. I was a little timid about including that in my presentation because I'm less certain what the relationship of pursuit eye-tracking dysfunction might be to substance use disorders. And we've also found a strong developmental effect in our assessment of smooth tracking. For example, the 11-year-old twins in this study are about as good at smooth tracking as the typical person with schizophrenia. On the other hand, the 17-year-olds are among the best trackers that I've ever assessed. And I've assessed, up until now, over 500 people ranging in age up to about 70. If you plot eye-tracking proficiency versus age, the 11-year-olds are at about the same level as people who are 70 in terms of eye-tracking proficiency. There's a peak in proficiency—maybe at ages 16, 17, or 18—and then a gradual dropoff toward around age 40 or 50; the dropoff then starts to accelerate. So, there's something developmental going on with pursuit eye tracking, at least early in life, in these kids that we need to get a better handle on before we look at this as a way of assessing frontal lobe functioning.

People aren't born with the ability to produce smooth pursuit eye movements, and children mature at different rates. It could be the case that some individuals never get to the point of having full frontal lobe maturation and never really develop the ability to produce smooth eye movements, whereas others mature and eventually reach a point where they can produce them. In a study like this in which we carry out multiple assessments over time, I hope we'll be able to get an answer to this question of how development relates to smooth eye-tracking performance.

Dr. Tarter: Do you have any preliminary data around correlations with noncognitive variables such as impulse control and hyperactivity?

Dr. Iacono: It would be wonderful if I did, but I don't.

Dr. Hummer: I'd just like to say that we've seen the same kind of correlations in children and smooth pursuit eye tracking that you're reporting, with adult levels reaching around 15-17. And the other thing we've seen is children with ADHD, on and off Ritalin, using the delayed response task. This is a task in which a person has to inhibit eye movements until the target actually disappears, so it's a way of looking at ability to inhibit responses. This task has been extensively studied in nonhuman primates to understand the prefrontal cortex. What we find is that the kids with ADHD are normal in all other aspects of their eye movements, including smooth pursuit, but they have difficulty inhibiting premature responses during—only during—a delayed response task, which I think gets to your question about some of the frontal lobe kinds of deficits. We're preparing to look at that in children of alcoholics and other risk groups.

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