88| Cannabis and Driving – With Dr. Tom Marcotte

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NAVIGATING NEUROPSYCHOLOGY

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Speakers: Tom Marcotte, Ryan Van Patten, John Bellone

Intro Music 00:00

Ryan Van Patten 00:17
Welcome, everyone, to Navigating Neuropsychology: A voyage into the depths of the brain and behavior, brought to you by INS. I'm Ryan Van Patten...

John Bellone 00:25

...and I'm John Bellone. Today we have a conversation with Dr. Tom Marcotte about cannabis and driving. Tom is a Professor of Psychiatry at the University of California, San Diego, and co-director of the Center for Medicinal Cannabis Research. He's been a highly productive researcher in this area for many years and we talked to him about his hot off the press JAMA Psychiatry paper on cannabis and driving. This should be a highly influential paper in the coming years, so it's worth knowing about. Plus we as neuropsychologists should be aware of how cannabis might affect a patient's everyday functioning and their safety.

Before we get to the conversation, we wanted to provide a brief background and review of cannabis and cognition. We covered this in full in an episode with Dr. Igor Grant at navneuro.com/51 if you'd like a deeper dive. We'll also give you an overview of the methodology for Tom's study. Keep in mind that although we focus the conversation on his study, we also bring in other literature to inform the discussion of broad issues related to cannabis and driving.

Ryan Van Patten 01:34

It's well known and widely accepted that cannabis intoxication is associated with cognitive inefficiency and impairment, including inattention, working memory, new learning, abstraction, and decision making. As you might expect, people are also interested in whether chronic heavy use of cannabis might lead to long term cognitive decline, independent of acute intoxication. There's good literature on this for other drugs such as alcohol and stimulants, but in the case of cannabis, the literature is more mixed and we aren't quite sure about the answer yet. This uncertainty is due in part to difficulties in studying cannabis over the years given that it's been a DEA Schedule I drug, as well as methodological challenges and study design, such as disentangling the acute from the long term effects in a drug that takes some time to be cleared from the body. There are also issues such as the age that one starts using, the frequency of use, and other variables to consider in these studies.

John Bellone 02:43

For our conversation with Tom, as we mentioned, we'll be talking to him about cannabis and driving broadly and we will zero in on a paper he recently published in JAMA Psychiatry. In terms of study design, Tom and his colleagues recruited 191 regular cannabis users ages 21 to 55, randomized them into three groups, and let them practice and become familiar with a driving simulator set up in the lab. Tom and his group then had the participants smoke as much as they wanted of a

cannabis cigarette that contained either 0.02% THC, this was the placebo group, 5.9% THC or 13.4% THC, and then put them through driving simulations at about 30 minutes, one and a half hours, three and a half hours, and four and a half hours after smoking to measure their driving ability. Prior to each driving session, participants were asked, "How impaired are you to drive?" and, "Would you drive in your current state?" After the sessions they were asked, "How much did the study drug affect your driving?" And, "How well did you drive?" Stay tuned for the results of all of this. We'll go over this methodology again throughout the episode and provide additional details. We'll link to the JAMA paper in our show notes at navneuro.com/88. And without further delay, we give you our conversation with Dr. Tom Marcotte.

Transition Music 04:17

John Bellone 04:27
Right. Tom, welcome to NavNeuro. We're really excited to have you on.

Tom Marcotte 04:30
It's great to be here.

John Bellone 04:31
Can you talk about the differences between marijuana and cannabis, and which terms you prefer to use?

Tom Marcotte 04:38
Sure. Well, obviously, when you talk about cannabis and marijuana people have a general sense of what we're talking about. People tend to think of marijuana more in terms of the plant and something that has THC in it. The part of the plant that gets you high. Cannabis is a broader term and it really refers to the genus of the plant, like cannabis sativa. It's a term that you're seeing much more widely used now because people appreciate that cannabis is much more than just THC. Its CBD, as you know there are many minor cannabinoids. We're actually learning more and more about other aspects of the plant like terpenes that may be beneficial for health. Marijuana also comes with a connotation, because back in the 1800s and early 1900s, it was used as a pejorative term to talk about weed and things that back in the day were seen as criminal. Really, cannabis is much more widely accepted now, although they're used interchangeably. We tend to prefer to call it

cannabis because it covers a much broader range and doesn't come with the historical background that marijuana does.

Ryan Van Patten 05:45

Makes sense to me. I've seen a lot more use of cannabis as a term over time. With that in mind, where in the US is cannabis currently legal? Can you say something about the pace of legalization right now?

Tom Marcotte 05:59

Sure. This is one that in every single interview, I need to hop on the internet [laughs] and see the current state of affairs. As of right now, 30 states have legalized cannabis for medicinal use. Another 12 have actually legalized cannabis with CBD and no THC. 18 states have legalized it for recreational or adult use as well as DC. One reason you need to keep popping on the internet is because some states have passed referendums and then the courts get involved and say that was illegal, and they pull it back. That's where we are right now. Clearly, it's been a major trend over the last five years. One thing that's interesting is it feels like this is a watershed moment - that, my god, this is just happening so quickly. But, actually, if you go back and look, the Pew Research Group has done polls about legalization for decades. Actually starting in about 1990, people started increasingly accepting the legalization of cannabis for at least medicinal purposes. It's really been building over decades. Really in 2010, there was a crossover where it got to the point in this research, in the survey, that 50% of Americans in 2010 felt it should be legal. It's really been a long term trend that just now has hit the tipping point in the last few years.

John Bellone 07:21

Right. We can include a link in the show notes to an up to date map of the US where it's legal for medicinal use, recreational use, etc.

Tom Marcotte 07:31

Sure. I'd be happy to give you a link like that. I tend to go to a national conference on state legislatures that keeps updating it but other places like NORML and stuff do the same thing.

John Bellone 07:42

Awesome. Can you tell us about the acute cognitive effects of cannabis and, in particular, how it might impact driving safety and ability?

Tom Marcotte 07:53

Sure. These have been well studied at this point. We know that when people get high, they have reduced attention, they have greater difficulty doing multitasking, and difficulty dividing attention. Of course, a major one is learning and memory. Those both suffer when people are high. We also get distortions in time perception, as well as some perceptual distortions. Now, there are also sort of psychiatric effects. Some people feel reduced anxiety and feel calmer when they're high.

However, some people actually have increasing anxiety and paranoia, particularly if they get particularly high or they use a really high THC content cigarette. The other thing that we should be aware of is that there are also physiological responses. People can get tachycardia and get rapid heart rates and hypotension where blood pressure drops. It's interesting that, as we'll talk a little later, people can self-titrate as to how much they want. Actually, people start experiencing these physiological conditions very quickly in the process of actually smoking. The ability to self-titrate how high you want to get actually can happen pretty quickly, at least with inhaled product.

Ryan Van Patten 09:05

Given that cannabis use leads to temporary cognitive deficits, and it's legal in some US states but not others, have we seen major increases in accident rates like car accidents in states where it's legal compared to those where it's not?

Tom Marcotte 09:18

That is surprisingly difficult research to carry out. So, right now, the data is kind of mixed. It was particularly interesting and [in] the slideshows I used to do a few years ago, I could show you state reports and academic reports that showed an increase in fatal crashes, I could show you reports that show no change, and reports that show reduction. That's for a number of reasons. One is that the data is really hard to come by. People often look at fatalities and that comes from the

Fatality Analysis Reporting System. This is something put out by the National Highway Transportation Safety Administration or NHTSA, that reports all the fatal crashes. The problem is that there is not a standardized way to report such data. Individual police departments and so forth report them to their own system and get them into this database. It's such a state of affairs that actually NHTSA came out a few years ago and said, this is called FARS, this FARS database should not be used for looking at comparisons across drugs and changes over time. And yet many, many people publish on it.

The other challenge in doing this research is that, what do you compare it to? It's not as simple as saying, “Okay, two years ago, we had this number of crashes and now we have this number.” You also have to look at national trends. So, for example, there was an increase in crashes in the states that legalized but when you actually look nationally, unlike a decade long trend, there was actually an increase nationally in the number of crashes. People try to compare two states that are adjacent or states that look similar and that comes with its own limitations. As you can imagine, there's a lot of difference between states. The best we can say right now is we do think there's an increase, maybe not in fatal crashes, and that's hard, because those are fairly rare occurrences. But a study from the National Insurance Institute came out and said there's about a 6% increase in reported collisions in states that legalized. Maybe fender benders and so forth. Even further complicating this is it varies by state. A recent report also came out comparing Colorado and Washington and showed that there was a significant increase in crashes in Colorado. But Colorado looks very different than Washington. It has a lot of tourism, people coming in from other states where it's not legal. It has a lot greater density of dispensaries. Whereas Washington is closer to Canada where it's legal, and so it's not so novel. I think it's pretty clear that there probably is an increase, the magnitude is just not clear. I would say it's probably less than people would have feared. The other reason this could be is that by the time you legalize, often people already have access to cannabis. You may need to go back a few years earlier, to really get a sense of whether there was an increase.

John Bellone 12:16
It's a good point.

Tom Marcotte 12:17
I think the long term goal is to do things like naturalistic studies where you can look at people in real time on the road to understand the effect it has in the real world.

John Bellone 12:25
Or using simulators.

Tom Marcotte 12:27
Yeah.

Ryan Van Patten 12:28

Yeah. Many factors go into a particular state and the number of car accidents that happen in that state. We're trying to isolate this one factor, people using cannabis primarily recreationally, but there's also medical cannabis use. But that is in the context of uncountable other factors that change over time in different states. I think you represented the complexity well, Tom. It's just hard to answer that question from an epidemiological perspective.

Tom Marcotte 12:55

Yeah. You have to look at gasoline prices and miles driven. Epidemiological research is really tough on something like this.

John Bellone 13:04

Epidemiological research is one way to look at it. Of course, you took a different approach and we're very interested in talking with you about your study. You conducted a randomized controlled trial of 191 adults, who are regular drivers, who use cannabis at least four times in the prior month, and who did not use cannabis for 48 hours prior to the study days. Can you tell us more about the study design?

Tom Marcotte 13:29

Sure. This was, as you say, it was a large study. One of the things we are trying to address is that previous studies have been informative, they talk about possible time course of impairment, etc. But they really were limited by sample sizes. I'm pretty honest, when I say some of the seminal studies, a lot of them were using 20 people. They would use 20 people and it's a crossover design, and get people either high or put them on placebo. Crossover designs have problems when you deal with psychoactive substances. People, once you've either had the active product or have placebo, you're pretty good at guessing the next time you're on something. In some of our previous studies, we've shown that people who had cannabis first and then got placebo were always pretty correct in determining that placebo. So, in this one, we opted to do a parallel design. We recruited 190 people and then randomized them to either get a placebo, or 5.4% or a 13.9% cigarette and then have them smoke ad lib.

Another limitation of some of the other studies was they would do a standardized smoking approach. You would say, “Okay, you need to smoke this joint or vaporize and use all the product.” [It] tells us something about dose effects, [but] maybe not as much as we'd want because many of these standardized procedures actually end up still with variability in terms of how much THC actually ends up in the blood.

But we wanted to be more ecologically valid and have people smoke as they would to get high at home. The whole idea here was that these are the people who probably are most likely to go out onto the road. We used regular users and said get as high as you want. I guess the other thing I could add in - so the other issue was many of the earlier studies had all used low potency cannabis. It was 2% or 6% THC. In our study, we went for the highest we could get from NIDA. The only legal source of the drug is the National Institute on Drug Abuse drug supply program. This is the cannabis that's grown in Mississippi. They've been inching their way up to try to get more and more similar to what we see in dispensaries. At the time we started this study, 13.9% was the absolute highest you could get and that was pretty similar to what was being confiscated around that time or a year or two before that. Now, of course, dispensaries have 20 to 25% THC in the plant material. But our thinking was we really wanted to get to the highest [percentage] possible and do two levels to see whether or not when people self-administer whether or not these doses have an effect, because we're all very concerned that with the higher THC levels, there'll be more impaired people on the road.

Ryan Van Patten 16:17

Speaking of being on the road, talk about your driving simulator task and, in particular, the composite drive score variable, your primary outcome. Why did you create this composite score rather than keeping the individual variables separate?

Tom Marcotte 16:33

Our simulator is a three monitor system. It's almost 180 degree field of view, a little less than that, 130. It's got a seat that feels like a car seat, gas pedal, steering wheel, etc. It's a fixed base, which means it's not full motion - it doesn't move as you drive. There are fancier systems, there's a very expensive system at the University of Iowa that does full motion. It's not fully clear how much you gain by going to that higher level of fidelity. But I would consider ours a high fidelity system. People who sit down in it, very quickly their brain tells them they're in a car. We've had people look over their shoulder to see if it's safe to pass, and they're looking back and looking at a research assistant staring back at them because the person's back there. [laughs] Your brain just convinces yourself this is real. What we would do is we had people do a 25 minute simulation. We tried to make it as naturalistic as we could. People go through yellow lights, they have to pass cars, there's one or two crash avoidances, fairly limited because I didn't want it to be game-like. Then built into that we have a couple of standardized procedures, which we can talk about a little bit in terms of both car following and how much you swerve in the course of the simulation.

The reason I went to a composite drive score is because, as a neuropsychologist knows, the more measures you put into an outcome, the more stable and reliable it is. One bad performance doesn't all of a sudden call you impaired. Now it comes with some risk, because you may bury some impairments in averaging things out. In the end we did look at individual components as well, but our feeling was a composite drive score gives people one outcome they can look at that represents overall driving performance. It also enabled us to make determinations on classifying impairment that we can talk about later.

John Bellone 18:30
Just to be clear, there were three different doses from my understanding. There were 13.4%, 5.9%, and then 0.02% THC content.

Tom Marcotte 18:40
Yes. The 0.02% is basically placebo. What NIDA does, they take regular cannabis and then try to pull out the THC, but they don't get all of it out.

John Bellone 18:54
Then, like you said, it was a cigarette but they could smoke as much as they wanted of it. Is that right?

Tom Marcotte 18:58
Yeah. For this study, we would get bulk cannabis from NIDA. We taught our research nurse - I don't know that we taught, but our research nurse learned to roll a joint. They were sort of marginal to start with, I think she got praise from later participants that she rolled the nice tight joint. [laughs] But she had her little roller, we'd make them about 700 milligram cigarettes. In the old days, NIDA had 100,000 milligrams, which is a pretty good sized joint. [laughs] We wanted to make sure people had enough if they wanted to smoke the whole joint. On average, they smoked about a little over half of it, and then stopped.

Ryan Van Patten 19:37
One other piece of the methodology that'll come up in a few minutes is that you also asked them about their subjective perceptions of whether they were impaired and if they were safe to drive. Right?

Tom Marcotte 19:51

Yeah, yeah. A major concern is, in the end, we can come out with these interesting scientific findings but each person is going to decide for themselves whether they feel safe to drive. We wanted to do a comparison of objective performance on the simulator versus how people perceived their own level of impairment.

Ryan Van Patten 20:10

Makes sense. Yeah, those findings are interesting. We'll get to them very soon. But let's talk about the primary overall findings first. THC had a negative impact on driving performance not surprisingly, other studies have shown this as well. That's compared to the control group, but the two THC groups did not differ from each other on the driving composite score. What do these results tell us about quantity and dosage effects?

Tom Marcotte 20:35

Yeah, so this was interesting and possibly predictable, but we just didn't know till we got to higher levels. One thing that we learned from earlier studies, these were done by Marilyn Huestis at NIDA, was that people self-titrate. She's done some studies with lower level THC and knew that people use their smoking typography. Smoking typography is how deeply you inhale, how long you hold it in, how much sidestream smoke escapes. We knew there was smoking typography, we didn't know what it looked like when we looked at these higher doses. What we found was that when people were randomized - so we randomized the groups based upon frequency of use. We had split the groups into those who smoked less than four times a week and those who smoked four times or greater a week, just to make sure we had an even distribution in each of the three treatment arms. What we found was that smoking typography played a huge role. So, actually, the 5.9% got a higher blood THC concentration level than the 13.4%. And, obviously, both were higher than placebo. If you look at it, when you look at the amount of the joint that was smoked, about half for each of the two active arms, you would expect about twice the level of THC to get into the system of the person who got 13.4%. That was not at all the case. They found a sweet spot and either they let it go out from the sidestream out of their mouth, or they didn't inhale as deeply. But it really came down to self-titration.

Ryan Van Patten 22:12

They were blinded, too, importantly. They were not explicitly told which THC group they would be in.

Tom Marcotte 22:19
Exactly. That's a great point. Yeah. Just to that point a little bit, we talked a little bit earlier about the issue of crossover designs. Most people who got the active product knew they got the active product. 90 plus percent. In our placebo group, 50% thought they got active treatment. These are regular users. So, anyway, they may not have thought it was very good stuff.

Ryan Van Patten 22:43
[laughs]

Tom Marcotte 22:43
They got the real thing. That the blinding held fairly true.

John Bellone 22:49
Yeah. What was it about the 5.9% [group]? You said the typography was different. Can you talk us through how the typography changed based on the THC difference?

Tom Marcotte 23:00
There were not dramatic differences in how many puffs they took, how much of the joints, they just smoked it differently. As I said earlier, you can tell quickly from your physiological response how much THC you're getting in your system. My assumption is the 5.9% [group] just inhaled deeper and held it longer. Now, to my dismay, we didn't really ask them what they thought of the cannabis and whether - we asked whether or not they liked the high etc. And they did. But we didn't get down to, “Hey, was it harsh on you?” That's something we'll be asking in the future. We don't know whether the 5.9% was better cannabis to smoke than the 13%.

Ryan Van Patten 23:46
That's fascinating. I don't know that a lot of people are aware of the topography of smoking like that, but it makes sense and the self-titration as well.

Tom Marcotte 23:54
One of the potential limitations, and we've had reviewers comment on this, was it wasn't a control dosing study. What can you say about it? As I mentioned a little earlier, there are studies that use standardized control dosing and if you look at blood THC concentrations right after they smoke, there's a lot of variability. Even if

you tell people to inhale, hold it in for five seconds, exhale, people still manage to moderate how much actually gets into their blood.

John Bellone 24:24
Right, so it's more like a placebo versus a high.

Tom Marcotte 24:29
Yeah. We ultimately joined it together because if you look at the two THC groups, they achieved the same level of driving reduction. I mean, it almost overlaps from 30 minutes to an hour and a half. So, again, people - I don't know if a “sweet spot” is the right term because people were also getting impaired, but they found the exact same spot in terms of level of highness and the effect. For analysis, we then pulled it together and just said THC versus placebo.

John Bellone 25:00
I guess that has interesting implications. Because if someone gets a lower THC cannabis, they might think that they're safer than someone who gets a relatively high dose.

Ryan Van Patten 25:11
But they would self-titrate most likely.

Tom Marcotte 25:15
One thing that was an interesting part of our study - I know we can talk about this later, but we can just talk about now, was the issue of tolerance. What we found was that - so what I did is we looked at quantity by frequency over the last six months. We did a self report, “How often do you smoke? How much do you smoke or do you use?” Then I divided those into three groups, the highest quartile, the lowest quartile, and then the middle 50%. The notion here was to say, “Okay, if we take the heaviest users and the lightest users do they differ in certain respects on both THC concentration on driving performance?” What we found, maybe not surprisingly, was that the heavier users ended up getting a significantly higher blood THC concentration immediately after smoking. They got a lot more in. All these groups were told to smoke as you would at home to get high. The lower level users had a significant lower level of THC in their system. But what was interesting is when we looked at the simulator performance, they did not significantly differ. It argues for tolerance in that the heavy users could get a lot more THC in their system and perform just as well as the lighter users. What it also points out, though,

is that when you tell people to smoke as you would to get high, the heavier users got more into their system and ended up doing just as poorly as the light users. Behavioral tolerance is real, it exists. If you get a fixed dose, you do better than someone who's not a regular user. On the other hand, if you're seeking a certain level of highness, you offset that tolerance by ingesting more and can be just as potentially impaired on the road.

Ryan Van Patten 26:58

Right. Some people might use tolerance, the idea that, “Yeah, I do this all the time. I'm used to it. I know how I'm doing when I'm high and I can tell.” They might use that as a justification for being safe. They might think that they're safe driving soon after having smoked, and that may not be the case based on your data.

Tom Marcotte 27:17

Exactly. Now, part of those could be true. They may know what it's like to be high, they may be more cautious. They may make some behavioral changes. In our study, they did not. They perform just the same as the other group. But, yeah, obviously, what we don't answer is what about the really naive user who then smokes and becomes dangerous on the road?

Ryan Van Patten 27:39

In a minute, we'll talk about the subjective perceptions part, which is very important, but specifically the blood THC concentration data that we're discussing now, what implications does that have for law enforcement of impaired driving on the road?

Tom Marcotte 27:54

A very strong push over the years has been to develop per se laws. So, understandably, people would love to have something like there is for alcohol where, at a certain level, we know most people might be impaired and unsafe to go on the road. So, early on, there was a strong push to develop those and some states have done that - Colorado and Washington. Canada has implemented some per se laws. However, many groups including NHTSA, AAA, and our study shows that there's really no scientific rationale or justification for per se laws. That the relationship between THC in your blood and impairment is very marginal. What we found was there was almost a flatline - if you do a correlation between blood THC levels and driving performance, they were not at all correlated. The issue here is that it's not how much THC is in your blood, it's how much is in your brain because very quickly, it disperses throughout your body. So when people like law enforcement draw blood to try to determine whether or not you're impaired due to

THC levels, it just doesn't work. The other complication is that it takes like an hour and a half to usually get a blood draw out in the field. THC within about the first hour is 90% out of your blood. It just disperses so quickly. One thing that's important to understand about THC is something called counter-clockwise hysteresis. This is how THC distributes in your body. You get this nice linear relationship between blood alcohol level and driving impairment. With THC, when you smoke, it shoots up really high in your blood. But, as I said, within that first hour it disperses and it's very low. You can have very high levels and be impaired if you get someone really early on. But you can also have low levels and still be impaired because it has left your blood. After an hour it's low but you're not a safe driver. Then the other complications with blood concentrations is that if you're a regular user, it hangs around in your blood. If you're, say, a medicinal user, and you haven't smoked in 12 hours or 24 hours, you still can have low THC levels in your blood. You can have low levels and be impaired and you can have low levels and not be impaired. It just doesn't work to look at blood levels.

John Bellone 30:34
Do you have any advice for policing for cannabis use and driving?

Tom Marcotte 30:40
Well, don't use blood.

John Bellone 30:41
[laughs]

Tom Marcotte 30:41
I think we actually saw - our study was funded by the state of California. Some legislators, including Tom Lackey, who's a former CHP officer in Lancaster, supported putting in a study, say, if California is going to legalize it, let's at least learn what the effect is on driving. Many of those legislators were really interested in per se laws. And, to their credit, they looked at the data and they changed their mind and realize per se laws are just not the way to go. Right now, the best we can do is officer observation of how you're driving. They can do the field sobriety test to get a little sense of whether or not you're showing impairment when they talk to you and so forth. The other thing people are looking at are oral fluid tests where you can do a swab in the cheek and that can determine whether or not you have THC, at least in your oral cavity. That'll tell you a little bit about whether you've recently used. The problem is, as an example, in our study, we told people to refrain for 24 hours. They would come in, they do this oral swab, if it is above 5 nanograms, we'd

cancel the visit. But we ended up doing a fair number of cancellations very early on. We realized that the oral fluid test, at least in our case, was catching people who swore up and down they had not used for over 24 hours. We then extended that - you had commented that we used a 48 hour abstinence period. Part of it, we didn't want carryover effects, but part of it was we needed to go that far out to get a negative oral swab. After that no one ended up testing positive.

John Bellone 32:17
I see. Can you tell us more about your results on how driving was affected, both the composite score and maybe specific aspects of driving that were affected?

Tom Marcotte 32:30
Sure. I made the composite score out of the most sensitive measures that are used in driving research. This is something called standard deviation of lateral position or swerving, how much standard deviation or variability do you have in your lane position. We have people doing that tasked with divided attention tasks. They're looking at the monitors and looking at the roadway, but when a phone rings, they need to look away from the roadway and respond on an iPad and identify different stimuli. That they have to take their eyes off the road, but also maintain safety. We looked at swerving, how much their speed changed and variability, how accurate they were on that task. Then the other task we did was something called far car following where a lead car speeds up and slows down and you just need to speed up or slow down with that car. We put these into the composite drive scores. What we found was there was a significant medium sized effect size between the THC and placebo groups. It was about 0.5 at both 30 minutes and then an hour and a half or 90 minutes. We had a gap because we had to feed people lunch, unfortunately, but a lot was probably happening then. Then at three and a half hours, actually, that difference had gone to where it's no longer statistically significant between the two groups. There was still an effect size of about 0.29, so there's still some people who are showing the effects. Then by four and a half hours, they were right back to the exact same level. We saw that in the composite drive score. We'll talk a little bit about perceptions, but at the 90 minute mark, people were more likely to leave the roadway. They would cross over to the right shoulder of the road. I think that's because this divided attention task was an iPad off to the right. They tended to look off to the right and they would spend more time on the shoulder of the road. They may not crash, so that did not happen, but they were showing less attention to the three facets between speed, divided attention, and lane position.

John Bellone 34:28
Can you tell us your thoughts about that time course and how it might map onto a real world driving?

Tom Marcotte 34:34
It was really interesting. We asked people whether they were safe to drive and whether they'd go on the road. The majority of people said, “No, [they] would not go on the road at 30 minutes.” At an hour and a half, they were increasingly saying, “Yes, I would drive.” They were saying, “Yes, I'm feeling less impaired.” They thought they drove well. The objective data says otherwise. The objective data says that their 30 minute and 90 minute performance was basically the same. It was the same effect size. People are detecting that initial impairment, but then as time goes on, who knows what the mechanism is, but perhaps comparing how they are now to how they were an hour earlier, and they're feeling it's gotten better. Really an area of concern is this 90 minute point where people may have some good concordance early on that, "I'm a little stoned, I shouldn't drive." But then they start feeling this worn off but at least our data indicates that is not. That's at least my thought as to why perhaps we saw this leaving the roadway and going over the right shoulder, which we didn't see a difference at 30 minutes because people were being less attentive. They thought they were a better driver, and in fact, they weren't. They were more likely to leave the roadway.

Ryan Van Patten 35:58
Yeah. As you mentioned, to be clear, at the three and a half hour mark the groups were not statistically significant, technically, I think the p value is 0.067, something like that. So statisticians can debate that. The effect size was like 0.29. Those are non-negligible differences, arguably.

Tom Marcotte 36:17
Yeah. Another important point to comment on is that even at 30 minutes, there was a lot of overlap between the placebo group and the THC group. We've had discussions with reviewers on this, but when people hear there's a medium effect size - getting stoned makes you a worse driver. That's all true. But when you get down to the individuals, which is what we care about often as neuropsychologists, actually, there's a lot of variability. Even though, conceptually, we know that we have two distributions and there's always some overlap, when we look at mean comparisons that often gets lost in the shuffle. We created an impairment score, and using that at 30 minutes about half the people would have been called impaired under THC, but then half would not. They would have been more or less in the

distribution than the THC group. Somewhat akin to if we gave you a glass of wine or some alcohol, some people would use it to a certain level where they feel a little buzz, but maybe not significantly impaired.

Ryan Van Patten 37:27

Right. Do we know anything about individual differences in the resiliency against THC? Those people who had it in their system, but we're safe to drive? Or is that a future direction?

Tom Marcotte 37:39

Unfortunately, that's a future direction. I mean, we look through all the parameters we could think of and we're unable to identify what really differentiates those people who got THC and were impaired and those people who were not. It wasn't THC level and THC concentration. Obviously, it wasn't the dose of the cigarette. Sex did not play a major factor. So there's still a lot of unknowns.

Ryan Van Patten 38:05

Then, stepping back, if somebody asks your advice, like, not putting you on the spot that this is the final word on this issue. But if someone asks, “How long should I wait to drive after smoking?” You know, the three and a half hour data are mixed. What's your general thought?

Tom Marcotte 38:24

Yeah, that's a tough one. It always comes down to individual differences. It's just at a group level, I would say by four hours, you're probably fairly safe. But that's at a group level. It does not mean it's very true for you.

I guess another thing I might comment on of particular interest to neuropsychologists is how do we determine someone's impaired? One of the challenges here is this is an experimental procedure. It's not as simple as, unfortunately, someone went on the road and crashed and we know that's a bad outcome. In this case, we have continuous data. People really care about, well, how many people were impaired? Especially if you get out to the lay and policy makers, talking about effect sizes is not much use. What we did with this composite drive score was to determine a cut point based upon the performance of the placebo group. This is one approach that's been used by Bob Heaton, who's at our research center for many years. He uses a cut point of 15 percentile, in a healthy group. In our case, we used a placebo group and then said, “Okay, if you use that cut point, how many people would be called impaired in the THC group?” So, yeah,

there's controversy. “Hey, is that too liberal or conservative? You're having 15% false positives, in essence, if you're calling it that group.” What we did, and part of this was in response to one of the reviewers, was we did an analysis that looked - first of all, we chose a priori the 15% cut point because Bob Heaton has shown in some of his norms manuals and some HIV work that it's really a good cut point for detecting mild impairment. Based upon some comments from reviewers, we looked at 5%, 10%, 15%. And actually that held very true. Again, that's the maximal differentiation when you're looking for mild effects was by setting an a priori 15% cut point in the healthy group, you get the greatest differentiation between those who might be showing some impairment. What we found was when we have 15% impairment in placebo, we had 45% impairment in the active THC group. It's somewhat arbitrary, but it's trying to get to the point that people care about individuals, care about what percent impairment rate there is. This is at least one attempt to show that, again, you'll have people who are definitely not doing well, but then there are some people who are not doing too bad.

John Bellone 40:57
It's important to have that comparison group because it could be the case that everyone's just terrible at driving. [laughs]

Tom Marcotte 41:03

Absolutely. That's a great point. What we did for our study, going back, is we'd have people come in and do an hour long training so it felt natural to them. Then on the testing day everyone had a baseline before they smoked. The crazy drivers, the bad drivers, they're compared to themselves. We're looking to change scores from that baseline.

Ryan Van Patten 41:26
Yeah, that's a great design.

John Bellone 41:28
I know you talked a little bit about some of the limitations of this study. But any other major limitations that you wanted to talk about?

Tom Marcotte 41:36

Well, I think one of the strengths is that we did ad lib. People got to the level of highness they wanted. One of the limitations is if we think about what law enforcement's more likely to encounter, it's probably people who get really high. We

didn't have people who really got really stoned so we could really see those effects. I think there are many, many studies to be done. I think ours was important to say, “Hey, if you take regular users, they get to that level of highness they want, how do they do?” That answers one question. It's one study that answers that question. But what does it look like when people really get to higher levels? That's something we couldn't address. And, of course we had a very specific population of regular cannabis users. Perhaps the highest risk are those people who are naive or are infrequent users who just really don't modulate it very well in terms of how high they get.

John Bellone 42:28
Right. You would hope that they wouldn't be on the road right after smoking.

Tom Marcotte 42:31
Yeah, I would hope not. Yeah.

John Bellone 42:32
Right. Yeah, just for our listeners, in case it wasn't clear ad lib, ad libitum just means smoke as much as you as you would like to smoke. Your study was based on smoking cannabis, I'm curious if we have any data on the effects or time course of ingesting cannabis and driving safety.

Tom Marcotte 42:55
We don't have any from our group as of now. But there have been studies done with edibles. As many people may know, when you take an edible, it's a much longer time course because it has to go through digestion and first pass metabolism through the liver. In smoking or vaporizing, you get the immediate THC into the blood. With edibles, usually, the effects start about an hour in. And, again, in our study, we found about three to five hours it's wearing off. When people take edibles, it usually lasts six to eight hours, the effect. It's a very different mechanism. When people inhale, they get THC into their system. When people take an edible, that THC actually gets converted into 11 hydroxy which is a different psychoactive part of THC. You can look at those 11 hydroxy levels when people get stoned. People have done some of the studies and the impairment matches on to that timeframe. There have been a few studies that have done brownies, some have done Dronabinol, which is a legal form of THC approved by the FDA. The real challenge here is that we really can't so far do anything with all of the modes of administration that many people use. I mentioned vaporization, that's not vaping. That's when you actually take the plant material and heat it up to non-combustion and then vaporize

the product. Vaping is using oils where it's a very high THC level that you get a very quick hit of THC. As of right now, there is no FDA - when you do studies with human subjects, you need to not only have access to the product, you need the FDA to approve it so that you can put it into humans. As of right now, we can't do studies of vaping which is probably one of the most popular ways of ingesting THC or consuming it. We can't do wax material - so people do dabbing where they put sort of a wax onto a heated, they call the nail, and get a big dose of THC. We can't do drinks etc. All the other methods of administration are still yet to be examined in terms of impairment and driving.

John Bellone 45:05
I'm curious how difficult it was for you to manage this study. You said NIDA had to send the cannabis. What's the process look like for doing a study like this?

Tom Marcotte 45:14
It takes about a year to year and a half to get through all of the regulatory processes. We were lucky because - so our center, so these studies by the way were done at the Center for Medicinal Cannabis Research here at UC San Diego. We were founded in the year 2000. We've done a lot of studies, really more on the medicinal side, looking at spasticity and neuropathic pain. We had a lot of experience with the regulatory agencies. But even then [laughs], experience can only move an aircraft carrier so quickly, and it takes a year to a year and a half to get these studies done. You go through and you get the funding approval, you use the usual IRB approvals, but then you need to get approval from the FDA. That involves a fairly comprehensive submission to get an IND, usually some back and forth with the FDA. Then also, in the state of California, [you] need to go through something called the Research Advisory Panel of California, who monitors and deals with Schedule I research in the state of California. That's a whole nother review system to go through. Then you have to harmonize all of these. And then once you get all that together, you go out to NIDA, you get approval that they will ship something to you but you also have to have a DEA review. The DEA has to do a site visit to determine that there's minimal risk of diversion. You have to have a DEA license, and then ultimately get the cannabis from NIDA.

John Bellone 46:43
[laughs] Quite the process.

Tom Marcotte 46:45

Yeah. One thing that's an exciting development, we'll have to see how it plays out, is the DEA just approved additional manufacturers for cannabis beyond Nida. NIDA has kind of done okay in this business, I'm not sure they want to be in the business. Originally, they were growing for research on the negative aspects and it actually all started with confiscation originally from arrest. But the DEA finally approved additional manufacturers who are committed to trying to do greater varieties or chemovars of cannabis, trying to get products that more closely mimic real world - things like vape oils, etc. They've gotten approval to do that. The challenge, though, comes down to okay, once they do that product, how will the FDA review these? If they come up with a vape oil, what kind of research does the FDA require for safety? As you know, for pharmaceuticals, you're talking a lot of money and a lot of years with animal studies. The hope is that that's not what happens here. But it's undetermined right now.

John Bellone 47:50

Yeah. Wow. It's so fascinating how much of a process it is. Do you know if this is a similar process for other substances, Schedule I agents?

Tom Marcotte 48:00

I do not. But one of the challenges is that cannabis is so variable. There's so many different methods of administration, there's so many different plant materials, etc. Whereas if you want to do research on other Schedule I substances, usually you go to one or two sources that give it to you. In our medicinal studies, we've sometimes gone to study places that do synthetic CBD. Now CBD is descheduled so it's much easier to do that research.

John Bellone 48:42

We've been talking about recreational cannabis for most of this conversation, that's what your study was focused on. But more and more over time, people are using cannabis for medical purposes and you referenced that a few times. Is there any reason to believe that using cannabis medically might have different implications for driving compared to recreational use?

Tom Marcotte 49:03

They're actually probably are. People, and certainly when I would do presentations over the last few years, especially if I went to law enforcement or to different government agencies, they sort of made a scoffing comment to medicinal cannabis because it was always just perceived as a way to get pot - to get your card, etc. As

you say, there's much greater appreciation that there are medicinal benefits. Epidiolex is something that's an FDA approved, plant derived CBD that's used in childhood seizures. We have studies going on in autism. There's a much greater appreciation of medicinal benefits. A couple reasons why it could be different and THC actually shows a lot of benefits. In our early studies, when we looked at spasticity and neuropathic pain, improvement was seen. Those were only THC products, because that's all NIDA had. THC actually is beneficial. What you want to do is not get someone stoned when they use it. They want to just get relief from the symptoms.

A couple of reasons why medicinal cannabis use might be different is that A) if you're treating a condition that itself affects driving performance, maybe you're a better driver. We have some early small studies looking at the spasticity in neuropathic pain showing that, in general, people did worse when they smoke cannabis on the driving performance. But on certain aspects, they actually, I wouldn't say they were doing better, but they were doing less worse. At this point, maybe the dose was too high because it was still affecting their driving performance. But if someone has less neuropathic pain or has reduced spasticity maybe using cannabis makes them better on the road. The other issue is we talked about this tolerance and people sort of compensating by ingesting more. If, in fact, you start using a standard dose as a medicinal patient, and you stick with that dose, you will develop a tolerance broadly. But you're not offsetting that by ingesting more. That tolerance may be more evidenced in driving. You're not seeing the impairment that maybe you saw when you first started using cannabis. Now you're a month or two into it, that tolerance may have taken effect and now your driving is not so affected as long as you're not increasing the doses.

Ryan Van Patten 51:17

Right. What you said about medical cannabis and driving mirrors what we see in terms of cognitive functioning more broadly, not surprisingly, because driving and cognition are related. But again, if somebody has a condition, you mentioned neuropathic pain and spasticity, that itself can negatively affect cognitive functioning, which is related to your ability to drive. Then treating that and improving that symptom could improve cognition and driving. Although, at the same time, it's complicated. THC itself has a negative effect on cognitive functioning. I just want to draw a parallel between cognition and driving based on what you said.

Tom Marcotte 51:58

Sure. One of the frustrating challenges when we did some of our early submissions was we'd have reviewers say, “Well, cannabis will never become a viable option for patients because it's impairing.” And, you know, these were in conditions like MS where people are taking gabapentin and all these things that clinicians know have profound effects. But because they were FDA approved pharmaceuticals, people just, I mean, clinicians don't look the other way, but sort of. People need it. They use the drug but because cannabis started off as an illicit drug, it has this aura about it that people pay extra attention to it's impairing effects when, in fact, compared to some of the approved medications, it's probably less.

Ryan Van Patten 52:44

Benzodiazepines, anticholinergics, the list goes on where there are cognitive side effects that can be problematic.

Tom Marcotte 52:51

Absolutely.

Ryan Van Patten 52:53

There's some controversy over the issue of residual cognitive effects in cannabis users. We've been talking about acute effects a few hours after smoking a cigarette, for example. But the controversy is about effects not when acutely intoxicated. Do heavy cannabis users show cognitive impairment or driving impairment three days or a week after the last time they smoked? What do we know about this issue with respect to driving?

Tom Marcotte 53:22

It's a really interesting question. I know you had Dr. Grant on earlier who talked a little bit about this. That was a while ago. In some studies with the really heavy users, they see worse performance primarily in learning and memory lasting up to 30 days or something like that. It's a very small effect size for the most part. There aren't these continuing impairments. Usually those resolve within 30 days. One of the challenges in doing our kind of research is because in our studies we administer cannabis, we always tend to use cannabis users. It's hard to determine whether or not there's any effect compared to a non-user. There have been a couple of interesting studies that came out in the last year, one by Staci Gruber's group, I think it's Harvard, who did a small study and found that cannabis users when they were not acutely smoking did worse than non-users. Interestingly, what they also did was look at the onset of use. She has a particular interest, I think, in

youth cannabis use and found that people who'd started before age 16 actually drove that outcome. Then when she examined things like impulsiveness that also explained a great deal of the variance. It's one of the challenges of doing this research, we really don't know. Is it the residual effects or is it premorbid? Is it something that either people were like this before they started at age 16 or because they started at a young age, it affected their brain function. That's really hard to parcel out. There was also another small study that came out that found the opposite. That non-users actually did worse than the cannabis users. It's unanswered. We're taking a look at our 191 individuals because we all have a pre-smoking performance. We're in the process of finalizing analysis and writing it up. But, in essence, what we're finding is we are not seeing a dose effect. When I talked about those three groups, that the heaviest users, the lightest users, we are not seeing that the heaviest users when they've been abstinent, on average, our group was probably abstinent for five or six days, when they've been abstinent, at least on our driving simulator and our specific variables, we are not seeing worse performance. We're not seeing indicators of residual effects. But it's still a really important question that we can't directly answer because we don't have a non-using group but it is an interesting one. For public safety, if people know, "Hey, I'm a heavy user. I haven't used in a few days, I'm fine." You know, is that true? It's still undetermined.

John Bellone 56:00
Before we start wrapping up, are there any other big picture takeaways from your study for clinicians and neuropsychologists in general?

Tom Marcotte 56:09
I think we've touched upon all of them.

Ryan Van Patten 56:13
This is obviously all relevant to neuropsychologists who see people who may be using cannabis, which is becoming more and more common. Driving is relevant to us in terms of our recommendations, in terms of how we talk to the patient. Patients might ask us about this research. Driving is an important instrumental activity of daily living. There are a lot of ways in which this is pertinent to clinical evaluations.

Tom Marcotte 56:40
Yeah, I completely agree. I guess one thing, this would not fit into the conclusion section or whatever. But one thing that's been interesting about doing this research is - so at our center, we also do methamphetamine research and so forth. Quite

often frequency of use matches well onto impairment and overall exposure, obviously. But what's really been interesting over the years as we've done more and more cannabis research, is taking the notion of an illicit drug and what happens when you flip it over to be something more acceptable. What comes to mind is when we think of frequency of use and heavy use, we could think, “Oh, a daily user. That's a pretty heavy user.” Well, now if you switch that over to alcohol and someone has a glass of wine once a day at dinner. They drink every day. Would you fit that person as a heavy user? Increasingly, you hear people - I mean, it was interesting, I was at a conference a few years ago with government officials and they did a study and one of the persons noted that he was surprised to find out how many CEOs blah, blah, blah, had part of a joint at the end of the day just to calm down. It's been an interesting twist to really understand what constitutes a heavy user. That's why in our study we did quantity times frequency because it certainly is the case if you’re a daily user, you tend to use more, but that's not going to always be the case. I think the more it becomes acceptable in society, you may have people who use a little bit daily and maybe they are a very different group than obviously the very heavy users.

John Bellone 58:14
Yeah, it's a good point. We had a couple of bonus questions for you before we end this conversation here. If you could improve one thing about the field of neuropsychology, what would that be?

Tom Marcotte 58:24
My answer is something that is profoundly unsexy. [laughs]

Ryan Van Patten 58:27
[laughs]

Tom Marcotte 58:28
The issue here is replication. All of our careers are built on novelty and what is new. I think that advances all fields, including neuropsychology, tremendously. It also just kneecaps us just to some degree too because all of us are doing our own thing. Being able to compare across studies and have confidence in findings because it so depends on your sample and what outcomes, I think slows us down as well. I don't have a solution to that. But I think the more that we can collaborate with fellow neuropsychologists and try to use some common methods - we all may have our own little tweak, but the more we can do that, the more we build a bolus of research that really helps move the field forward.

Ryan Van Patten 59:18

I love that answer. We haven't gotten that from anyone yet as I recall. That's a great answer for psychology and science more broadly. There's the replication crisis in psychology that has been widely talked about and certainly it applies to neuropsychology as well. I've thought about this quite a bit and I've imagined that the level that I would want to attack this would be the journal level. Like encouraging more replication papers and making that destigmatized, so to speak. It's not, like you said, it's not sexy. It is not considered to be a high impact paper if you have a replication study, if it'll get published at all. I wish that we focused more on good methodologies, on solidifying ideas we already have, and journals would accept replication studies if they're well done, and review them without such a bias toward novelty.

Tom Marcotte 1:00:11

That's a great statement. I guess what I would add to that are academic review panels as well, right? There's also - all these have our effects on our careers to do that.

Ryan Van Patten 1:00:25

Yeah. The incentive structure pushes us to not do replication work - to do novel. Novel grant writing, novel manuscript submission, etc.

Tom Marcotte 1:00:35

Exactly.

Ryan Van Patten 1:00:36

Great answer. The other bonus question is, what is one bit of advice you wish someone told you when you were training, or maybe someone did tell you that really made a positive difference? With this question we're hoping for an actionable step that trainees could take to improve their experience.

Tom Marcotte 1:00:54

I guess my answer to that is, I guess more reflecting on how fortunate I was. [laughs] People may not fall into the situation I did, but I would encourage them to seek it out. That is to be truly part of a multidisciplinary effort. That's always not easy to do. But when I started my training - I'm at UCSD in part of the HIV neurobehavioral research program. We are comprised of neurologists, psychiatrists, people who do imaging, people do neuropathology, infectious disease

experts. The more that I think trainees and early career psychologists can reach out to these other disciplines, I think the more you can advance your knowledge, advance your career. I'm now 25 years into that and I think the more it keeps it exciting and interesting, and you keep learning newer and newer things, and in particular things that neuropsychology might be able to contribute to. I would encourage reaching out, if you're just in a small group that's just a psychologist, and you just see each other to do what you can to get exposure to these other disciplines.

Ryan Van Patten 1:02:02
Well, that's great. Thank you so much for the time, Tom. We really appreciate it.

Tom Marcotte 1:02:06
I'm glad I could join you. Thank you.

Transition Music 1:02:08

Ryan Van Patten 1:02:12
Well, that does it for our conversation with Tom Marcotte. Upcoming content in NavNeuro includes working memory, autism, culturally informed neuropsychological evaluations, neuropsych interventions following acquired brain injury, case presentations, and a Neuropsych Bite with Tom Marcotte on driving simulators. As always, thanks so much for listening, and join us next time as we continue to navigate the brain and behavior.

Exit Music 1:02:44

John Bellone 1:03:08
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Ryan Van Patten 1:03:19

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