I’m going to introduce our next speaker, So Doctor Murray Cirilli earned her MD and PhD from the University of Amsterdam, the Netherlands, and is an endocrinologist at the Amsterdam University Medical Center. In 2019 she became the Professor of Medicine, Nutrition and Energy Metabolism at the University of Amsterdam, while she was promoted to Professor of Medicine in the section of Endocrinology. Her research interests lie in the
metabolic consequences of obesity and the role of the brain in weight gain.

Doctor Sohaili,

Thank you Anya and for organizing this great initiative.

So I’m going to talk mostly data in humans and data on the human brain. So, so apparently when there’s a lot of food around, people eat more than they actually need. So the question really is why do we eat beyond homeostatic need?
And I think that answer mostly can be found in the brain. So to very briefly summarize the food intake regulation so that you know you understand more of what we’ve been doing with neuroimaging in humans, I want to just briefly guide you through this very complex regulation and this is very simplified. So there are many signals coming from the body, including the gut peptides, ghrelin that inform the brain about food in the stomach and intestines or no food. But other factors like nutrients,
glucose,

hormones like insulin and leptin

from adipose tissue also inform

different areas in the brain,

as you can see here.

And then all these signals are put

together and then that leads to a

feeding or no feeding response.

To make it even more simple to

be able to study this in humans,

we had to simplify the model even further.

So we defied, and this

is a little artificial,

but the the food intake regulation

systems in a homeostatic part and

a hedonic part or reward part.
Of course there’s a lot of overlap between these areas and there are many neurotransmitters involved. One of the major neurotransmitters in the reward system in the brain is dopamine and one of the neurotransmitters in the homeostatic system, which lies mostly in life settlements in the brain stem is serotonin.

So for the sake of time I’m just going to very briefly touch upon our findings on disturbances in the serotonin system in the brain in people with obesity. And this is by please don’t read this, but this is just to show you.
how difficult it is to study,

NOTE Confidence: 0.966431775

in this case, serotonin,

NOTE Confidence: 0.966431775

serotoninergic regulation of

NOTE Confidence: 0.966431775

food intake by the brain.

NOTE Confidence: 0.966431775

But here you can see we just summarized

NOTE Confidence: 0.966431775

all the literature showing all the

NOTE Confidence: 0.966431775

brain areas and within the brain areas,

NOTE Confidence: 0.966431775

the nuclei that use serotonin for

NOTE Confidence: 0.966431775

signalling to modulate food intake.

NOTE Confidence: 0.966431775

So you can imagine it’s really hard to

NOTE Confidence: 0.966431775

study and therefore we need all the the,

NOTE Confidence: 0.966431775

the animal data.

NOTE Confidence: 0.966431775

So this is just to summarize what we’ve

NOTE Confidence: 0.966431775

been seeing in the serotonergic system.

NOTE Confidence: 0.966431775

And this is small, but it doesn’t matter,

NOTE Confidence: 0.966431775

it’s just one slide.
So when we looked at postmortem hypothalamic tissue in people with a healthy weight and people with ABMI above 25, we found lower expression of serotonin transporters. And to verify that this was not a just postmortem finding, we also validate this with a SPECT scan in vivo where we found lower hypothalamic serotonin transporter binding in people with BMI over 30.

We also studied the response of the energetic system during fasting. So people were either fasting 12
or 24 hours and then we measured hypothalamic serotonin transporter availability using the SPECT scan. And we found that in people with a healthy weight there was an increase in serotonin transporters and this was not the case in people with obesity. So apparently the fasting response in terms of certainrigic fasting response in the brain is different in people with obesity and this might be related to differences in circulating factors like free fatty acids and insulin. And finally we also did a study where we fed people with a healthy weight...
snacks in between meals and they gained like 5 or 6 kilos and they were totally fit leaned man in this case and we were able to replicate the findings in people with obesity. So we think that overfeeding leads to a decrease in serotonin transporters and serotonin signalling and that might contribute to overeating and obesity but moving on to dopamine. So dopamine is a really whole dopamine system is very important in reward learning, reward processing and hedonic part and the motivational part of food intake.
So we are able to image dopamine receptor bind or receptors by using a radio tracer and in this case we used SPECT. In the future we’re probably together with nuclear medicine. We will use PET scan because it has a better sensitivity. But in any case, we found that in people with obesity, these were all women, but there were lower dopamine receptor binding. We don’t know at this point whether there was a lower dopamine receptor expression or more dopamine release. But in any case,
we found lower dopamine receptor binding in people with obesity. So there seems to be something wrong in the dopamine system. So we were wondering is this reversed by weight loss? So the same women with obesity underwent bariatric surgery and six weeks after bariatric surgery where they already were in a negative energy balance for a couple of weeks or six weeks. We found no reversibility, so there was no increase in dopamine receptor binding. We then studied them again about a
year and a half or two years after bretic surgery and there we found that there was a slight but significant increase in dopamine receptor binding. So we think it might be partially reversible. It was still lower as you can see here compared to the lean controls, but BMI was also still higher. But having said that, we of course correlated, We wanted to know what are the determinants of an increase in dopamine receptor binding in these women. And this was not correlated to the decrease in BMI. And actually when we put data together.
from published trials in humans, we found that indeed there is no linear correlation between BMI and dopamine receptor binding using patents, SPECT scans. And it seems to be that there first is an increase followed by a decrease. And this is also what we found in our own studies. This is still unpublished. So we were thinking what other determinants then of lower dopamine receptor binding and we think part of it might be explained by eating patterns and timing of food intake.
And as you know, a lot of people get a lot of calories from snacking. So there was a very elegant study. As you know, there is a lot of interest in intermittent fasting and time restricted eating to lose weight. And this is a very nice study where they looked at total energy expenditure in people that would eat most of their calories in the morning or later in the day during a hypocaloric diet and they found no difference in total energy expenditure. But what they did find is that there were reduced feelings of
hunger in the people that ate most of their calories in the morning. And that fits really nicely with a study that we did earlier in Man with Obesity. So first we looked at their study design they lost the same amount of weight. And while the calories at lunch were the same, So first we looked at the per study design they lost the same amount of weight. And 1st we looked at metabolic...
outcomes and it really didn't matter whether they would eat most of the calories in the morning or evening in terms of improvement in insulin sensitivity in the liver or in muscle. And also liver fat was really decreased in both conditions. But when we then looked at the brain there were some differences. So the man that ate most of the calories in the morning during weight loss had an increase in dopamine transporters. Sorry, a dopamine transporter availability in the street and using SPECT scans while the people,
the man in the dinner group that ate most of the calories at dinner,
they had a decrease and this differential response was significant.
So timing of food intake seems to affect the dopamine system.
And also, this is still unpublished, when we put them in the MRI and scanned them and showed
they pictures of food,
we found that the man that ate most of the calories that during
or later during the day at dinner
that they reacted more strongly to high caloric visual food cues. And we do know that that reaction really predicts weight gain, it predicts the ability to lose weight and it also predicts food intake. So timing of food intake matters. So we were also interested in in nutrient sensing and so how does the brain know that there is food around? Well, that’s by tasting and smelling and seeing food. But there is also an interaction between nutrients in the gut or the gut and the brain and the communication goes through a vagal efferents,
through gut hormones and serotonin and of course also circulating nutrients and hormones. So we wanted to study, is there something wrong in this communication between the gut and the brain in people with obesity. So what we did, we infused directly into the stomach using a nasogastric tube, either glucose or lipid or water control over volume. And it was the same in volume and calories, in people with a healthy weight and also in people with obesity.
And then we did MRIs and SPECT scans, and the people with obesity then underwent a hypocaloric diet intervention and they lost 10% in 12 weeks. And then we rescanned them.

So this is just to show you this is, this is the scan after the intragastric infusion of either lipid or glucose. So there were so glucose gave more like immediate effect to lipid. It took a while, but we saw a decrease in many brain regions, and those included striatal.
00:12:34.820 --> 00:12:37.600 structures and limbic structures.

00:12:37.600 --> 00:12:40.776 So you could say this is the physiological response to food in the stomach.

00:12:40.776 --> 00:12:43.120 When we did the same,

00:12:43.120 --> 00:12:45.080 this whole brain analysis,

00:12:45.080 --> 00:12:47.228 we found no effects whatsoever measurable in people with obesity.

00:12:49.920 --> 00:12:52.520 So somehow the brain doesn’t sense that there’s 500 kilocalories in the stomach.

00:12:52.520 --> 00:12:55.964 When we then zoomed in on specific regions,

00:12:55.964 --> 00:12:58.680 doing a region of interest analysis,

00:13:00.920 --> 00:13:02.600 we found that in glucose and lipid condition,

00:13:05.280 --> 00:13:07.404 there was a decrease in brain activity in the nucleus accumbens,

00:13:08.948 --> 00:13:10.433 which is the ventral striatum,
which is really really important


And this decrease in activity makes sense because if there's food in the stomach,

there's no need to go and search for more food,

there's no need to be motivated to go and eat food.

But this reaction was not present in people with obesity and more importantly this didn't change after these people lost 10% of their body weight.

This was the same in the dorsal stratum.

Then we looked at,
what are the determinants?
And of course we think it’s it’s
it’s got brain communication,
something we cannot easily measure in
people but we can of course in rotor models.
But we found that GOP one seems to predict
some of the response in the dorsal stratum.
So lipid sensing might need GOP
one signalling.
I’m going to go over this because of time.
We also looked at functional connectivity.
Now functional connectivity really is
looking at brain areas that change in
synchrony and we think if they change
in synchrony that they directly or
indirectly communicate with each other.
So this is more brain network response
to intragastric nutrients and overall
We found that lipid had most effects
on functional connectivity between
the accumbens and some brain areas.
Areas well glucose had more effect on
functional connectivity between
the dorsal stratum and and other areas.
Interestingly also areas involved
in memory and cognition functional
done dopamine release using
while glucose was still
able to elicit dopamine release in people with obesity, lipid was not. So there seems to be a reduced dopamine response upon lipid infusion and this really lines up with animal data that was published years ago. So why do we eat beyond homeostatic need? I think we have shown in humans using neuroimaging that there are disrupted dopamine and serotonin systems in the brain, that there is impaired nutrient sensing and obesity, which is not reversible after 10% weight loss. And this might account also for regaining weight even after
00:15:39.044 --> 00:15:40.954 treatment with GOP one agonists.
NOTE Confidence: 0.8037825235

00:15:40.960 --> 00:15:43.571 So maybe we're not restoring food intake
NOTE Confidence: 0.8037825235

00:15:43.571 --> 00:15:45.840 regulation and the last two minutes,
NOTE Confidence: 0.8037825235

00:15:45.840 --> 00:15:48.255 if I may, it's just that my
NOTE Confidence: 0.8037825235

00:15:48.255 --> 00:15:50.400 interest is also a metabolism.
NOTE Confidence: 0.8037825235

00:15:50.400 --> 00:15:52.672 So we are also interested in how the
NOTE Confidence: 0.8037825235

00:15:52.672 --> 00:15:55.120 brain regulates glucose metabolism
NOTE Confidence: 0.8037825235

00:15:55.120 --> 00:15:58.124 and besides dopamine having a huge
NOTE Confidence: 0.8037825235

00:15:58.124 --> 00:16:00.079 role in food intake regulation,
NOTE Confidence: 0.8037825235

00:16:00.080 --> 00:16:04.290 we also were able to show that that dopamine
NOTE Confidence: 0.8037825235

00:16:04.290 --> 00:16:07.320 is able to modulate insulin sensitivity.
NOTE Confidence: 0.8037825235

00:16:07.320 --> 00:16:10.368 When we increase dopamine in people in this
NOTE Confidence: 0.8037825235

00:16:10.368 --> 00:16:13.717 case they had deep brain stimulation for OCD,
NOTE Confidence: 0.8037825235

00:16:13.720 --> 00:16:16.096 so obsessive compulsive disorder
NOTE Confidence: 0.8037825235

00:16:16.096 --> 00:16:18.729 in an area near the striatum.
NOTE Confidence: 0.8037825235

00:16:18.729 --> 00:16:20.710 And we know that when we turn
the stimulator on there is a, there is dopamine release.
So we studied these, these patients with the stimulator on or off and what we found is that when we turned the DBS on, there was an improvement in insulin sensitivity. We were also thinking, if we deplete dopamine, we should see a reduction in insulin sensitivity. And that is indeed what we found in humans when we blocked dopamine.
00:16:50.081 --> 00:16:51.997 synthesis blocking tyrosine hydroxylase.
NOTE Confidence: 0.8037825235
00:16:52.000 --> 00:16:55.000 We found that not at the hepatic level,
NOTE Confidence: 0.8037825235
00:16:55.000 --> 00:16:57.125 but we found a decrease
NOTE Confidence: 0.8037825235
00:16:57.125 --> 00:16:58.400 in insulin sensitivity,
NOTE Confidence: 0.8037825235
00:16:58.400 --> 00:17:00.840 showing that dopamine in the
NOTE Confidence: 0.8037825235
00:17:00.840 --> 00:17:02.792 brain also regulates insulin
NOTE Confidence: 0.8037825235
00:17:02.792 --> 00:17:06.720 sensitivity in the body in humans.
NOTE Confidence: 0.8037825235
00:17:06.720 --> 00:17:11.676 So I think that beyond gut peptides,
NOTE Confidence: 0.8037825235
00:17:11.676 --> 00:17:14.910 the striatal dopamine system in the
NOTE Confidence: 0.8037825235
00:17:14.999 --> 00:17:18.118 brain really is a target for future
NOTE Confidence: 0.8037825235
00:17:18.118 --> 00:17:20.613 new medication reducing food intake
NOTE Confidence: 0.8037825235
00:17:20.613 --> 00:17:22.680 and improving metabolic health.
NOTE Confidence: 0.8037825235
00:17:22.680 --> 00:17:25.056 And I think working on and
NOTE Confidence: 0.8037825235
00:17:25.056 --> 00:17:26.640 understanding why nutrient sensing
NOTE Confidence: 0.8037825235
00:17:26.706 --> 00:17:28.844 is so disturbed and whether we can
NOTE Confidence: 0.8037825235
00:17:28.844 --> 00:17:31.414 restore that in the long term with the
new medication is really essential.

So I want to thank all these people and yourself.

Thank you for that.

We have time maybe for one or two very quick questions. Yes, Diana.

Never mind. Do you want to just say it?

I’ll repeat it, I’ll repeat it. For the current response in the nutrient setting, the dopamine system, would you advocate for something like a ketogenic diet or a little carbohydrate diet to kind of maintain or reset the system?
Well, that’s an interesting thought. We don’t know.

We do know that fatty acids modulate the response in the serotonin in people with a healthy weight. So that whether I think that the ketones and fatty acids that enter the brain that’s more you know that’s a different route than the vagal afferens in the gut. Whether caloric restriction or intermittent fasting to increase ketones and fatty acids will improve food intake, we don’t know. But in animal models with prolonged intermittent
fasting where animals or would only eat for a few hours a day, they do see all kinds of improvements in body weight and in memory function etcetera. So who knows? Yeah, yes. One more quick question. Well, that’s a really difficult question because mental health in people with obesity of course has many. You know the etiology of that is very complex and I don’t know whether in humans we can distangle these different factors.
Given the effects of obesity on the serotonin system,
I can imagine that that might make them more prone to depression,
but I'm not sure. Yeah, great.
Thank you very much. And we are going to move into our second networking break.