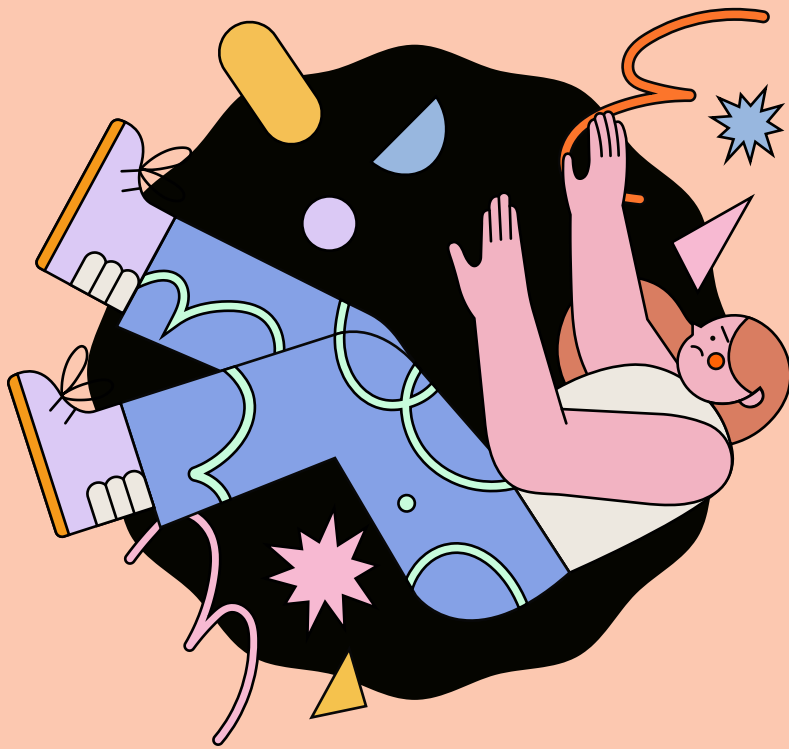

Nicotine and the brain

A report about addiction

DAVID EBERHARD



ephi 

Foreword

Swedish traditions and innovations

In Sweden, we have been using snus for hundreds of years. Snus is now consumed across all the social classes and increasingly by women. A few years ago, a completely new product emerged, like our traditional snus, but without tobacco. It provides the user with a nicotine kick, which is what you are looking for when you use snus, just in the same way you look for effects from caffeine when drinking your morning coffee. Nicotine pouches can be viewed in two ways. Either as the most successful and effective method against smoking since Sweden is very close to being defined as a smoke-free country with only just over 5 percent of the population smoking on a daily basis. Or, one can view this new product, which is a Swedish innovation, as yet another way for the global tobacco industry to make people dependant on something harmful.

This report has been written by a psychiatrist who has spent his entire professional life dealing with people's addictions and with various types of brain-affecting substances. He is very clear about how he views nicotine and its effects on people's bodies and brains. He is also problematizes the concept of addiction. What is addiction really? And is addiction really so dangerous?

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I dare to claim that in Sweden, we could be proud of having moved hundreds of thousands of people away from a very dangerous behaviour like smoking, to something much less harmful.

If you encourage people to behave more healthily by getting them to give up harmful habits and adopt new and better ones, in order to succeed you have to respect the often irrational behaviour of your fellow human beings and the needs for diversion and pleasure.

I dare to claim that in Sweden, we could be proud of having moved hundreds of thousands of people away from a very dangerous behaviour like smoking, to something much less harmful. That is harm reduction in its clearest, neatest form. And instead of being ashamed that we here in the Nordic countries use snus, we should be proud that we have replaced deadly behaviour with something that can be classified as a somewhat bad habit, much like our constant tea breaks (fika) and excessive consumption of coffee.



Marie Söderqvist

Marie Söderqvist

CEO, EPHI

The Meaning of Life

Why do people use substances that they actually don't need in a strictly nutritional sense? What needs do they satisfy? It's an important question that is rarely asked. Instead, the debate is often about trying to limit everything that people do to seek pleasure. Should there be increased focus dedicated to trying to understand what needs people's needs for the little luxuries in life?

Everything people do that is not about survival in the strict sense is meaningless. Mere survival just for survival's sake can also be considered devoid of inherent value. Things that make our lives better add value. For instance, sexual relationships that do not lead to offspring have no inherent evolutionary value, but anyone who would legislate today that sex should only occur within marriage with the intent of procreation would rightly be seen as a relic of medieval times. People engage in countless activities that could be deemed unnecessary but that bring us pleasure or pure diversion. Only a fraction of the love people show each other leads to children. Yet, we feel love and desire for many others throughout our lives. Many would argue that the pursuit of such relationships is a fundamental meaning of life.

Most of what people do lacks evolutionary meaning. If you look at it from a purely existential perspective, almost everything becomes meaningless, but for the individual it can be the essence of life itself. This is regardless of how dangerous what you are doing is. The risk of injury in most sports is quite high, at least over time. I love football, but it can somewhat cynically be described as a pointless activity where 22 players kick a ball for 90 minutes with health risks that are far from negligible. Playing football can jokingly summed up as not being a sport – it's a knee injury. And yet it's still a sport that most of us don't see as particularly problematic. Compare this to extreme sports such as riding a bike downhill in rough terrain at full speed just to see who can do it the fastest. The examples of potentially life-threatening things that people do that could be seen as meaningless are almost endless. And yet few would call for them to be banned. Thankfully so, because without all these diversions and challenges, one can with some justification ask what kind of animals we humans really are.

Given that as a collective, we accept an enormous amount of behavior that risks us harming ourselves, it is strange to me that authorities comprising of individuals who are not even affected themselves, in other contexts, call for bans solely because something could lead to an addiction, without considering how harmful this addiction might be. If the purpose of having public health-oriented bans is really

about genuine concern for the citizens, it is difficult to understand why they do not go completely overboard and start intervening in everything from excessive exercising to dictating exactly what foods people should consume. To me, such a society would appear to be hell on earth, but it would at least be logically consistent with the policy that characterises our society's attitude towards nicotine in other contexts. A substance that, as long as it isn't heated up and smoked, seems to be quite harmless, albeit addictive.

If what you are doing does not harm you or anyone else, it is difficult for me to understand why it should be worth prohibiting, regardless of whether that habit is meaningless or not, regardless of whether one can become addicted to it, and regardless of the fact that it is something that, in the strict sense, does not add anything other than one's own subjective pleasure.

The Brain and Addiction and...

We are all governed by our brains. Things that change the brain so that it doesn't function as it should risk harming us. Getting caught up in destructive behavior leads to suffering and, in the worst case, death. Becoming addicted to harmful substances or seeking thrills compulsively such as gambling addiction can destroy a person. But what is an addiction? What happens to the brain when you get trapped in behaviors or substance use? These are important questions you need to ask in order to navigate correctly when trying to help people live a good life with or without the use of various substances.

In standard psychiatric diagnostics, criteria have been set for when people are addicted based on a number of symptoms which indicate that they cannot be without a particular substance or behaviour. The most important and fundamental criterion is that addiction leads to sacrificing of other aspects of life and the use of the substance in greater quantities than intended or for a longer period of time than intended. For it to be particularly destructive, it is also necessary to increase the intake of the substance over time and to feel unwell if you do not take it. Advanced addictions not only lead to neglecting one's daily life but also involve spending a lot of time recovering from the substance's effects or trying to obtain it.¹

The same can certainly be said about different forms of destructive behaviour and how they impact life. Everything from sex, food, gambling to exercise can lead to similar destructive patterns. So something that we all need can in certain

¹ International Classification of Diseases, Eleventh Revision (ICD 11), World Health Organisation (2022).

individuals be used in a way that is neither beneficial for them nor aimed at creating any real added value.

.. The addictive Brain

To understand how an addiction develops, it is important to know a bit about how our brain works at a fundamental level. The brain is so complex that, despite numerous years of researching it, we still have no more than a fairly simplified explanation about how it functions. But there are some things we know a great deal about. The brain consists of a complex network of nerve cells and supporting auxiliary cells, known as grey and white matter. The electrical impulses of nerve cells that arise from different stimuli then communicate with each other via intricate systems of different neurotransmitters and ion channels in their cell membranes. Some of these neurotransmitters play a major role in why we feel the way we do and why we seek different thrills or become addicted to different things.

Several different factors are required for us to get stuck in behavioural patterns or end up in difficult states that make us depressed or anxious. These are often called multifactorial conditions. Therefore, it is common – something that for me, who has worked in psychiatry and addiction all my adult life, can almost be considered a certainty – to see that people who feel mentally unwell and suffer from various psychiatric syndromes are more likely than others to use different substances in a destructive way.

The neurotransmitter that in many studies seems to be perhaps the most important cause of addiction is dopamine. Dopamine is released when we feel good, for example when we eat well, receive a cherished gift we have wanted to receive for a long time or engage in sex. When the dopamine system doesn't function properly, we can suffer from various different diseases or syndromes. In Parkinson's disease, dopamine is deficient in the nerve cells that control our motor skills, but also in parts that control desire and joy, which is why the disease often causes depression and an emotional impact that is even worse than the physical tremours and stiffness that characterize it.

In ADHD, several parts of the dopamine system are affected, resulting in hyperactivity, impulsivity and difficulty focusing. People with ADHD are also more prone to addiction than others, probably partly because they themselves discover that by adding substances that in one way or another stimulate the dopamine system, they feel better, at least for the moment.

The problem with adding something that stimulates the release of dopamine is that

the brain doesn't have to "produce" it on its own. Eventually, it stops doing so unless an external factor kicks the system into gear. You end up in a situation where the substance no longer gives you a kick but is instead needed to achieve "normal state". It's called allostasis, and it's a reason why people keep using things that no longer give them the initial satisfaction they used to get. The brain has changed slightly and it becomes difficult to stop². The brain then remembers the substance even after stopping with it. So even for a smoker who has been cigarette-free for many years and lives a good life without cigarettes, the risk of relapse is very high if for example, after so many years, they believe they can easily have a cigarette at a party and can control it. So, of course, there are memories even at the neurotransmitter level, memories we do not control consciously.

All of that sounds very dire when you describe it in dry terms when it concerns our most important organ. It changes fundamentally and for a very long time, perhaps forever. But what is it all about?

Is addiction inherently dangerous?

Caffeine is an addictive substance. If you usually drink coffee every morning or several times a day, you don't feel good if you don't get your cup of coffee. You may get headaches, feel negatively affected in your ability to think, and generally low. So, in the long-term drinking a beverage that, strictly speaking, does not provide nutrition nor any real physiological benefit for people – the brain has been restructured in exactly the same way I have described. However, we accept coffee nowadays (in the past it was forbidden and considered destructive) because it is not harmful and adds value for the person drinking it. But there is probably no substance that does not have fierce opponents, including caffeine. In the United States, there are a number of outspoken organizations that are dedicated to fighting the harmful effects of caffeine, despite the fact that today it is something that virtually every adult drinks on a daily basis. That it can lead to intoxication if you ingest too much is very well known and something that most of us coffee drinkers have experienced at some point, but despite that, these organizations are so considered so strange that they can be seen as fanatics. An overwhelming majority of people consider it entirely unrealised to want to prohibit coffee.

² Koob, G. & Volkow, N., (2016) Neurobiology of addiction: A neurocircuitry analysis. *Lancet Psychiatry* 2016 Aug 3(8):760-773

But for some reason, a lot of people seem to want to ban the comparably dangerous substance nicotine^{3 4}.

The Plastic Brain

Addiction is a rather broad concept. And what causes people to use different substances varies enormously, both between individuals and between different substances. In fact, this does not only apply to substances, it applies to everything. And just like addition, what we are exposed to leaves traces in our brain. In the same way as when we become addicted to various substances, people tend to get "stuck" in other habitual completely harmless (or at least not fatal) behavior. Even when you are in the habit of walking the same route to work every morning, molecular traces appear in the brain that for many people make it more difficult to choose another path. Just as molecular traces emerge from the substances we introduce into our bodies and that reach our brain. In other words, ingrained routines create similar phenomena. In fact, whatever we do, whatever we learn, absolutely everything we think and feel affects our brain down to its smallest components. Because the brain is plastic – that is, it is changed by what it is exposed to. And thankfully so because if that weren't the case, we actually wouldn't be able to learn anything at all.

That it sometimes changes in some individuals in a way that perhaps not everyone in society understands the point of, or perhaps even the person who is affected is completely incomprehensible to, is part of normal human life. When one is head over heels in love with some unattainable "goddess" or "he-man", the brain has changed so that it "only sees" the object of the infatuation and can only see its merits, no matter how little the object of love cares about the lovestruck person. It's not constructive, but it's not harmful either.

Dependency or substitute

One thing that is obvious, if you, like me, have worked your entire adult life in psychiatry, is the significant overrepresentation of people with psychiatric problems who smoke. Of course, as a benevolent outsider, one can argue that we are dealing with a substance that "affects" those who have it the hardest. But if you flip that coin, the globally renowned Canadian physician Gabor Matés' thesis actually becomes

³ Ismail M et al (2022) A cross-over study of postprandial effects from moist snuff and red wine on metabolic rate, appetite-related hormones and glucose. *Drug Alcohol Depend* 2022 Jul 1;238: 109479

⁴ Clarke E, et al (2019) Snus: a compelling harm reduction alternative to cigarettes *Harm Reduct J*. 2019 Nov 27; 16(1):62

important⁵. I don't agree with everything Maté says. Intellectuals who achieve some kind of rock star status, as he has been given, tend to go against a paradigm, but to prove their point, they go straight into its antithesis. So does Gabor Maté, who claims that during his many years of clinical career as an addiction specialist, he has never met a patient who is addicted to something that does not have a serious psychological trauma in their background. That is not the case. I have met several heroin addicts and alcoholics who actually lived normal lives with a normal upbringing until they got hooked on the drug.

Considering that there are about 1.2 billion smokers in the world, I can't help but wonder if they really all have trauma that they process with cigarettes. Regardless of this, it must be considered clear that more people with psychiatric problems smoke than in groups that do not have such problems.

What makes the concept of addiction difficult is that it is extremely easy to say that a person is addicted to something that is obviously harmful to the user's health or leads to destructive behavior. But at the same time, it's hard to draw the line because somewhere along the way, it becomes vague. Injecting illegal heroin in a doorway with dirty needles because you otherwise get severe withdrawal is easy to explain as an addiction to the substance. To gamble away all your money seemingly for no other ulterior reason can be explained by addiction. A successful person who develops a daily alcohol consumption that causes him or her to end up homeless on a park bench may be due to the fact that the substance is not only addictive but inherently destructive. The reason why this affects some people is multifactorial. There are many different underlying factors. And it can vary from person to person, but some of us have a genetic vulnerability⁶. This, in its turn, is not simple. There are several different genes involved. Likewise, some substances have more potential to actually restructure our brain so that we create an "addictive brain" than others. And beyond that, there is everything from trauma to mental illnesses and the psycho-social environment we live in, both here and now and back in time. So it's easy to define the destructive drinking, injecting, or behavior as an addiction, but at the same time difficult to pinpoint exactly what causes it.

When you broaden the concept to include things that are not necessarily harmful, it becomes even more complicated. You may be using a substance that is dangerous but does not cause the same physical withdrawal. The concept then remains rele-

⁵ Gabor Maté (born 1944) is a Canadian physician who focused on trauma as a cause of numerous psychiatric and addictive medical conditions

⁶ Clay S et al (2008) A review of addiction. *Postgrad Med* 2008 Jul 31; 120(2):E01-7

vant, albeit even more difficult to define. The more you move away from obviously harmful but still define it as addiction, the more diffuse the concept becomes. Is an exerciser who runs one or two hours a day "addicted" to his running? Is the person who has two cups of coffee in the morning before work "addicted" to caffeine? Is someone who takes a few pouches of snus a day "addicted"? Or are these essentially harmless activities better classified as "habits"? Somewhere along the way there's a shift.

The concept of addiction is inherently vague. The entire psychiatric diagnosis and how to define the concept of addiction is really based on how addictions work with regard to two highly physically addictive substances. And as it happens, these substances are alcohol and opiates (such as heroin and morphine). For almost all other substances that are defined as "addictive", most of the criteria set by psychiatry do not apply. It is almost never seen that nicotine provides a significant tolerance over time. Withdrawal is fairly short-lived and even mild compared to other substances.

Rat Park

Yet people relapse time and time again. The question is why. When it comes to smoking, many actually manage to quit in the end. But the road there is paved with many failed attempts.

To understand this, Gabor Maté's theories come into their own better than for alcohol and heroin. He points out serious methodological flaws in how the conditions for addiction are set up. In addition to what has been observed about how alcohol and opiates function, addiction diagnosis is based on how laboratory animals react when they are exposed to various substances. There are several classic examples such as experiments that show how lab rats, for example, became cocaine addicts until they die because they chose substances instead of food and water. Perhaps not surprisingly, similar experiments for alcohol, heroin and even sugar led to similar effects. Getting a lab rat to become addicted to nicotine, on the other hand, proved much more difficult and required dedicated scientists who initially essentially force-feed the rats with the substance. Even into the poor meagre environment these rats have been forced into, they are not particularly prone to use nicotine.

And if you move the rats to a more stimulating environment, the results for most so-called addictive substances seem to be completely different. The Canadian psychologist Bruce Alexander⁷ made more intricate experiments already in the

⁷ Bruce K. Alexander (född 1939). Kanadensisk psykolog verksam vid Simon Fraser University

1970s where he built a large amusement park for the lab rats and tried to get them to become addicted to morphine, a substance that in cages would have been extremely easy to get the animals to addicted to in such a way that they actually died from forfeiting nutrition to get a substance kick instead.

But in Bruce Alexander's "Rat Park," the rats didn't even become significantly addicted to morphine to that high levels⁸. Alexander's experiments were criticized, however, as one of his followers failed to replicate them. Since then, no similar experiments have been conducted. Nevertheless, it's hard to ignore how our psychosocial environment affects the risk of addiction. And given that it is extremely difficult to get rats to become addicted to nicotine, even in the poorest lab environments, it is of course even more interesting to think about what is really the reason why someone gets addicted of such a substance. Why is there such a high overrepresentation of smokers among psychiatric patients? The most natural explanation is hardly that it is the substance itself that is the problem. If you want to try to help people with mental health issues to quit smoking, the first step is to ask why they smoke more than others. If a particular group tends to behave different or use a substance more than others, it is probably due to something related to the group's specific circumstances rather than the behaviour or substance itself.

Instead, we should think what smoking provides for people who, for various reasons, do not feel mentally well. It is easy to imagine that it fulfils many different functions, sometimes contradictory ones. In schizophrenia, for example, it has been shown that nicotine can improve cognitive abilities⁹. A deeply depressed person may smoke forty cigarettes a day because they believe they "do not deserve to take care of their health because they are so worthless anyway." Some people drink themselves to death for that very reason. For many others, a cigarette acts as a distraction manoeuvre. It helps you focus on other things than your bad mood or state of mind. It provides a break, just like when I was young and almost everything would be rounded off with a cigarette. You had to digest the food, have a cigarette with your coffee, round off the last lesson. And of course, there are also clear social aspects to almost all types of addiction, not least having a cigarette. But above all, one should not overlook the fact that depressed people also need external stimuli. If you can't get it any other way because you simply don't have the energy to exercise, meet people or because you're completely isolated and have no social interaction at all.

⁸ Alexander B et al (1981) Effects of early and later colony housing and on oral ingestion of morphine in rats. *Pharmacology Biochemistry and Behaviour* 15(4):571-576:

⁹ Tregelias J et al (2019) Alpha 7 Nicotinic Receptors as Therapeutic Targets in Schizophrenia. *Nicotine Tob. Res.* 2019 Mar 21(3): 349-356

To get people who, for various reasons, are in a psychosocial environment or in such a mental state that the only stimulus they can give themselves is a cigarette, to change the undeniably very harmful smoking, to an almost harmless way of ingesting nicotine saves lives.

Why should I stop?

It is difficult to define what addiction is even when it comes to harmful substances and behaviors. When it comes to other – i.e. largely harmless – ways of ingesting nicotine, the issue becomes even more complex. An important criterion in the current concept of addiction is that you have tried to quit several times but have relapsed even though you know that the substance is harmful to your health. But why should you stop when you don't feel in any way harmed by the substance or if the negative effects are so mild that the positive stimulation you experience from the substance outweighs the downsides? Of course, nicotine products cost money and in many cases, the use is unnecessary, but for many people there are more important things to "get to grips with" than quitting smoke-free nicotine. So, when that feeling of discomfort, which undeniably comes a few days after quitting nicotine, hardly motivates people very much. Of course, reoffending is easier than if it's a matter of life and death. In that case, it's even harder to say what is addiction and what is habitual behavior. Or actually just a free choice, to do what you actually want to do.

Bad habit or lifesaver?

Just as the unfortunate lovesick person, due to a changed perception of another individual, sees everything through rose-coloured glasses and hardly engages in anything that can be considered necessary or particularly constructive, one can argue that the habit of using nicotine (or for that matter coffee, tea, Coke Zero or sugar-free chewing gum) does not create any real added value either. At least not for those who don't use the substance themselves. But the question is, whose responsibility it is to put an end to other people's "bad habits?" And who decides what a "bad habit" is? Nicotine as it is used in Scandinavia, under the lip, that is not burned and thus inhaled into your lungs along with tar and hundreds of other dangerous combustion products increases blood pressure slightly, just as coffee does, but otherwise minimal effects on the health¹⁰. At worst, it's just an unnecessary, but harmless "bad habit". At best, something that adds satisfaction for an individual.

¹⁰ Ismail M., et al (2022) A cross-over study of postprandial effects from moist snuff and red wine on metabolic rate, appetite-related hormones and glucose, *Drug Alcohol Depend.* DOI:10.1016/j.drugalcoddep.2022.109479

The global trend is to use political means to limit free will for people to do what they want with their lives, as long as it does not harm others, is problematic in itself since it is simply not scientifically supported¹¹. But to make it more difficult for people to use an almost harmless substance under the pretext that it is "addictive" is even more troubling. There is no scientific basis to support doing this. Instead, it is likely to be a matter of completely different motives. At best, decision-makers simply lack knowledge about what an addiction is and how much less harmful smoke-free nicotine is compared to tobacco smoke. They need to receive accurate information to make better decisions in the future. At worst, however, it is a question of sheer meddling and a moralising attitude towards other people's behaviours and meaningless choices. Whatever the reason for the resistance that exists, it must change. By legislatively equating life-threatening smoking with smoke-free nicotine you prevent the shift from cigarettes to a more harmless alternative. Such a policy thus perpetuates smoking. This results in policies that harm the most vulnerable, those who have the greatest difficulty in quitting smoking.

Nicotine as an addictive substance

It's the tar that kills, not nicotine. It was already the case in the 1970s. And this has since been proven over and over again. Nicotine is not dangerous in the doses that you get from normal use of nicotine and tobacco products. It has been known since the Renaissance that it is the dose that determines whether something is toxic or not. However, the strong addictive potential of nicotine is indisputable, even if the exact causes and definition of addiction are not entirely clear.

The logic behind all prohibition, where all forms of nicotine are compared to smoking, is probably due to the fact that people have a tendency to get hooked on nicotine use "unnecessarily". The rationale for the argument is that it is good to combat something that people do not need in the strict sense. In a perfect world, it would probably be best if nobody had ever started using nicotine, because it is indeed unnecessary to use something that you could have done without if you had not been introduced to it in the first place. Like sweets, for example, or coffee. These are also things people use which can hardly be considered to be particularly beneficial to our survival.

But does everything have to contribute evolutionary value? It's not much fun to live without stimulation, whether it's good food or other things like caffeine or nicotine doesn't really matter.

¹¹ Nutt D et al. (2010). Drug harms in the UK: a multicriteria decision analysis. *Lancet* 201; 376: 1558-65

The Unnecessary Coffee

Smoke-free nicotine should be considered in the same way as coffee. Firstly, because it concerns comparable (non)harmful substances with a certain potential for addiction. Secondly – and this is more important – if the message that smoke-free tobacco is almost harmless was more widely known there would be an increased willingness among people to replace lethal cigarettes with almost harmless alternatives, instead of them being discouraged. A change that would prevent millions of people from dying prematurely if it were to become globally accepted. And therein lies the actual difference between caffeine and nicotine. People drink coffee "unnecessarily" but for every smoker who switches to smoke-free nicotine, we save lives.

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