

## ECNP Interview, Ellen Leibenluft and chronic irritability in youth

Ellen Leibenluft, M.D., is Senior Investigator and Chief of the Section on Mood Dysregulation and Neuroscience at the Intramural Research Program at the National Institute of Mental Health near Washington DC. Tom Parkhill caught up with her via Zoom.

**Dr Leibenluft, thanks for talking to me. I can see you sitting outside on your porch, and I can hear birdsong. It looks like a beautiful spring morning. How has covid affected your work?**

Like many folks, I've been working from home for over a year. I guess I've gotten pretty used to it, and I'm privileged to have an environment at home where I can be productive. As regards the clinic, we are only just now beginning to see patients. Scanning, for example, has really not been possible. For collecting data about symptoms and for our CBT trial, we have shifted to virtual platforms. So we are able to get data, but it's slow. It's opening up more now, but there's still a natural reluctance, both from parents and children, to come to the clinic.

**What led you into psychiatry, and into this field?**

I was a psychology major, psychology and the brain have always interested me. I decided to go to medical school and become a psychiatrist because I was especially interested in the biological and neuroscience aspects. That got me very interested in research. What led me to studying irritability? I began my career working on rapid cycling bipolar disorder in adults, and then I was moved into a behavioural paediatrics research group. This was in the early 2000s. I realised that there was a lot of new research going on in paediatric bipolar disorder in the US, and there was a developing focus on irritability, especially on kids who were having very severe temper outbursts. Some thought leaders were saying that kids with severe temper outbursts should be diagnosed with bipolar disorder, but it was controversial. So we decided to study the question. The answer came out as "no"; we and others found that children who are very irritable are not at increased risk of developing manic episodes as they get older. It's very difficult to call severe irritability in children bipolar disorder, if that irritability isn't associated with the later development of manic episodes.

Irritability is one of the most commonly presenting complaints in children, but there has been relatively little work from a neuroscience perspective, relatively little imaging, relatively little known about the brain. Kids who are irritable have difficulty tolerating frustration. So it's important to identify what happens in the brains of children who are prone to irritability when they get frustrated, compared to what happens in the brains of children who can better tolerate frustration. And then it's really important to figure out the implications of that for treatment.

Irritability often travels with other problems, most commonly anxiety and ADHD (in kids), and it has been noted in some trials related to this. In clinical trials for these conditions, sometimes irritability has been measured as a secondary outcome. There is a large literature about the effectiveness of parent training for irritability in pre-schoolers, some studies about treating irritability in adolescents with conduct disorder, and some trials for oppositional defiant disorder which is characterised by irritability. But there has been relatively little direct focus on irritability as a treatment target. And there's really not much in school-age kids whose major problem is severe irritability.

### **What is the age of onset, generally?**

For frustration tolerance, there's a normative developmental trajectory where it's high in pre-schoolers then tends to go down. But what about non-normative anger and frustration? People have been very reluctant to identify irritability in the very young because of the risk of "pathologising" normal behaviour. But there's some good research that indicates that you might be able to identify non-normative irritability in pre-schoolers. There's heterogeneity, of course: some kids are highly irritable relative to their peers in pre-school, and then the irritability decreases. Others tend to maintain high levels. An important area of research is to try to predict these different trajectories.

### **And you say it's very common....?**

Irritability has not been well captured by DSM diagnosis, so it's hard to put a prevalence on this. There was a new diagnosis included in the DSM-5, Disruptive Mood Dysregulation Disorder (DMDD), and this has been quite controversial. In many studies the rates found have been low, possibly because many of these are post-hoc analyses of data sets where the questionnaires were not designed to assess irritability in detail. Also, it may be that the criteria for DMDD were set too high; again, there was a real concern about pathologising normal behaviour, so thresholds were conservatively set. A major problem is that the thresholds for DMDD were set somewhat arbitrarily. There are some newer epidemiological studies designed specifically to assess irritability in kids. One recent study found that empirically derived thresholds for DMDD yielded higher prevalences than the current DSM criteria. (Laporte...Salum et al, J Am Acad Child Adolesc Psychiatry, 2021).

### **You say that a lot of irritability diagnosis is linked to anxiety or ADHD. How do parents feel about this, do they come along with preconceptions?**

Parents most often come along recognising ADHD and irritability – severe irritability is hard to miss. ADHD, particularly if it includes hyperactivity, can also be obvious. But the parents may or may not know about the anxiety. It depends on the child, on how old he or she is and how able to express their distress, and so on. It's not uncommon for kids to be brought in for irritability or ADHD, and the parents to be less aware of the anxiety.

### **And irritability changes over time.**

Absolutely. There's a lot of heterogeneity. As I mentioned, for some children their irritability diminishes over time. However, there's population evidence that irritability in childhood has lasting consequences in educational attainment and income. It's important to note that while children with high irritability are not at increased risk of bipolar disorder as they grow older, they are at increased risk of anxiety and unipolar depression.

**I imagine that some irritable kids will grow into irritable adults. Have you been working on irritable adults?**

We have not – that's a very neglected area. There are reasons for this. Children are brought in by their parents, but who brings in an irritable adult? Of course, some do come in by themselves, but there has been less focus on adults. Some of our early work was based on longitudinal studies that had already been completed. They had assessed irritability because of Oppositional Defiant Disorder: this diagnosis exists in kids, and the symptoms for ODD focus on irritability, as well as oppositionality (note that the name emphasises the oppositionality). But ODD is not an adult diagnosis, so there's less systematic assessment. Irritability in adults is a criterion for some diagnoses; for example, Intermittent Explosive Disorder or PTSD. And there has been some focus on irritability in Major Depression – anger attacks, for example. As a child you can meet the criteria for MDD by exhibiting sadness, anhedonia, or irritability, but in adults we only recognise sadness and anhedonia, and it's not clear whether that distinction is valid.

There is an important body of research on suicide and irritability in both children and adults. Some studies show that irritability in children is a risk for later suicidal behaviour. And we now have some studies, in large treatment trials for adult depression, showing that the response of irritability to antidepressants impacts on suicide risk. So they are linked, and this is becoming a new focus. For example, does ketamine have anti-irritability effects, and is that linked to its possible anti-suicide effects?

**Are there other treatments in development?**

As I mentioned, there are studies looking at the effect of ketamine on irritability in adults. In children, CBT for anxiety uses exposure techniques. Melissa Brotman in our group is working on CBT exposure techniques targeted at frustration.

**What are the priorities now?**

There has been an upsurge in research in irritability in kids, and that's something we need to grow. I would say that there's a real need for a greater focus on irritability in adults. We need more of a longitudinal focus; we have a somewhat artificial boundary between childhood and adults, and we need more of a lifespan perspective – for example, we know there are issues with irritability in dementia. There are a couple of clinical situations where irritability is quite common, but which have not been focused on; PTSD, for example,

trauma in general, dementia, autism – irritability is very important in autism. We need a lifetime perspective.