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Neuroplasticity: A Potential Target for the Treatment of Depression

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Here’s your host, Dr. Charles Turck.

Dr. Turck:
This is ReachMD, and I’m Dr. Charles Turck. Joining me to discuss neuroplastic changes in depression and explore how this might advance our treatment of depression is Dr. Madhukar Trivedi who’s the Founding Director of the Center for Depression Research and Clinical Care and Chief of the Division of Mood Disorders at the University of Texas Southwestern Medical Center in Dallas, Texas.Dr. Trivedi, welcome to the program.

Dr. Trivedi:
Good to be here.

Dr. Turck:
To begin, Dr. Trivedi, how would you define neuroplasticity, and why is it important for our understanding of depression?

Dr. Trivedi:
I think as our understanding of depression is rapidly improving, we’re now turning our attention to neuroplasticity because neuroplastic changes in the brain have been observed in depression—as well as following treatment for depression.[1-6]And neuroplasticity is the ability of the nervous system to reorganize its structure, function, and connections in response to both internal and external stimuli.[7]

And its key to remember that it’s not only external stimuli that drive neuroplastic changes, but also internal stimuli.8 So what does this have to do with depression? Well, for the longest time, we’ve viewed mood disorders through a bottom-up or top-down approach within the brain.[9]

With a bottom-up approach, we’re dealing with the lower parts of the brain—the amygdala and other limbic regions that rapidly process emotional response to stimuli. Something happens, and we have an immediate emotional response, like fear.[9,10]On the other hand, the top-down approach deals with the higher parts of the brain that are involved in cognition—specifically the prefrontal cortex.[9] So the prefrontal cortex is involved in negative thought patterns that can give rise to symptoms of depression.[11]Neuroplasticity adds another layer to these approaches by focusing on what’s actually changing in the brain.[7] With neuroplasticity, we see rapid creation and elimination of synapses, as well as changes in the connections between areas of the brain.[12]

So this process happens all the time because the brain is constantly changing as a result of experience, stress, emotional processing, learning, and memory.8 So not surprisingly, neuroplasticity also occurs with depression.[13]

Dr. Turck:
Now can you tell us more about these neuroplastic changes that are seen in depression?

Dr. Trivedi:
As I mentioned earlier, neuroplasticity includes changes in structure, function, and connectivity.[7]

In terms of structure, we've known for quite some time that in patients with major depressive disorder, there may be volume reduction in areas of the limbic system—for example, the hippocampus has been observed to reduce in size. There may also be atrophy of the prefrontal cortex.[14]Secondly, changes in the brain function have also been identified as part of neuroplasticity. In neuroimaging studies, we see increased activity in the limbic system and decreased activity in the prefrontal cortex and the hippocampus, which is involved in memory. So this interplay among these areas, with increased and decreased activity, may lead to cognitive and emotional changes seen in depression.[1] And finally, it's not only the structure or the function of the brain that's changing, but also the connectivity amongst the limbic system, the prefrontal cortex, and other areas that can change in neuroplasticity. These changes in connectivity may underlie specific symptoms seen in depression.[2] That's why we should think about neuroplasticity as a dynamic process that reveals itself as symptoms or maladaptive behavior.[13]

Dr. Turck:
So, Dr. Trivedi, you had mentioned specific symptoms of depression associated with neuroplastic changes in connectivity. Can you tell us more about these?

Dr. Trivedi:
So as we know, some of the major symptoms or features of depression include dysphoria, anhedonia, rumination, and disrupted cognitive control.[2]

Dysphoria, or persistent sad mood, appears to be associated with increased connectivity of the ventral limbic affective network.[2]With anhedonia, there is loss of interest or motivation, and people are unable to feel pleasure. And it appears that anhedonia deals with reward processing and is suggested to be associated with decreased connectivity of the frontal-striatal reward network.[2]Then there's rumination, where people constantly dwell on negative thoughts. Rumination seems to be associated with increased connectivity of the default mode network.[2] The default mode network is typically active when you're not focusing on anything in particular and your thoughts are just drifting.[15]And finally, there's disrupted cognitive control, such as the ineffective top-down control over negative thoughts and emotions that we see in depression. This appears to be associated with decreased connectivity of the dorsal cognitive control network.[2]

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Dr. Turck:
And now that you've described the neuroplastic changes seen in depression, can you explain the underlying mechanism for these changes?

Dr. Trivedi:
Thanks to Ron Duman and others, we know that in depression, there's a decrease in neuroprotective factors such as brain-derived neurotrophic factor. This, in turn, leads to atrophy of the neurons and a decrease in the number and function of synapses. The result is an alteration in brain structure, function, and connectivity.[13]I want to point out that changes in brain connectivity can make it harder for people with depression to overcome challenges in their everyday lives.[16,17] For example, when faced with difficulty, they may have a harder time breaking free of rumination than someone with healthy, functional connectivity.[2]

Dr. Turck:
For those just tuning in, you're listening to ReachMD. I'm Dr. Charles Turck, and today I'm speaking with Dr. Madhukar Trivedi about neuroplastic changes in depression.

So now that we have a better understanding of neuroplastic changes seen in the brain in depression. Dr. Trivedi, do we also see neuroplastic changes following treatment for depression?

Dr. Trivedi:
I think that is one of the most exciting things that we're beginning to see.We know that antidepressant medications help mitigate the neuroplastic changes in depression by increasing gene expression for brain-derived neurotrophic factor. But this is an indirect and delayed effect, which may explain why response to antidepressant medication tends to be delayed.[3]

On a structural level, we've seen changes in hippocampal and amygdala volume with electroconvulsive therapy, along with changes in default mode network connectivity. Transcranial magnetic stimulation usually targets the dorsolateral prefrontal cortex, and it's hypothesized to alter activity in the cognitive control network.[4] With cognitive behavioral therapy, we've observed altered connectivity between the medial prefrontal cortex and anterior cingulate cortex.[5] Some groups have studied exercise as a treatment for depression, and they've seen changes in hippocampal function following consistent exercise.[6]

So these are some of the neuroplastic changes that have been observed following treatment for depression. But we need to remember that these treatments were not originally designed to affect neuroplasticity—these are just post hoc effects that we've seen.

Dr. Turck:
With that in mind, do you think we can develop treatments for depression that are specifically intended to target neuroplastic changes?

Dr. Trivedi:

I think this idea of targeting treatments for the kinds of changes that we want to see in the brain is very fascinating, and it's the subject of current research.[18,19] The short answer is yes, I do think we can target neuroplastic changes in the treatment of depression. Ideally, we would focus on specific functions or domains implicated in depression and seek to produce neuroplastic changes in the associated circuits.[18,19] Not only would we be targeting neuroplasticity, but this could also allow us to be more precise and thoughtful in how we treat patients.

With all the other treatments that we currently have, we basically select the treatment blindly rather than basing it on a really thoughtful hypothesis of what particular neuroplastic changes we want to create in the brain.[20]We might end up going through rounds of trial and error where we throw everything at the patient.20 If we could develop treatments that target specific domains, we might be able to reduce the trial and error.

Dr. Turck:
I'd love to hear more about this. How would we develop a treatment that targets neuroplastic changes?

Dr. Trivedi:
So earlier, I mentioned that neuroplasticity happens because the brain is constantly changing due to emotional processing, learning, and memory.[8] What we could do is devise a task that combines these things, and through this task, we would target specific brain connectivity. In turn, that could address the emotional and cognitive dysfunction seen in depression.[19]And in fact, Brian Iacoviello and Dennis Charney at Mount Sinai have devised such a task.[19]

They wanted to see if they could leverage neuroplasticity to improve top-down emotional control by the prefrontal cortex over the limbic brain regions. To do this, they proposed an exercise that combines cognitive processing, with a working memory task, and emotion processing, from identifying emotions as part of the working memory task.[19] They called this the Emotional Faces Memory Task, or EFMT.[21]EFMT is a modified N-back task.[19] Basically, patients are shown a series of faces, each with an emotional expression such as happy, sad, disgusted, or surprised. For each face, patients are asked whether the emotion is the same as the one N faces back. So for N equals one, patients are asked, "Does this emotion match the previous one?" and for N equals two, the question is, "Does this emotion match the one two faces back?" and so on.[21]

EFMT sounds simple, but it's actually a very fascinating approach. And in a functional MRI study that the Mount Sinai group conducted, they found that EFMT does in fact induce neuroplastic changes in patients with major depressive disorder.[22]They saw increased connectivity from the right dorsolateral prefrontal cortex to the amygdala, as well as decreased connectivity from the left and right dorsal anterior cingulate cortex to the amygdala. What's more, these neuroplastic changes were associated with an improvement in depressive symptoms.[22]

So we now we have proof of concept that we can target neuroplastic changes in the treatment of depression. This is an area of research that's very exciting, and I think it will help produce targeted treatments for depression as we move forward, potentially targeting specific neural circuits for neuroplasticity and neurogenesis.

Dr. Turck:
Exciting, indeed! So, Dr. Trivedi, how could HCPs deliver therapies, such as EFMT and other potential treatments, that target these neuroplastic changes in patients?

Dr. Trivedi:
Actually, we can learn from other forms of treatment like psychotherapy. The COVID pandemic has really taught us that treatment

doesn't always need to be in person—it can be delivered virtually or even via an app.[23,24] So along the same lines, EFMT and other treatments that target neuroplasticity could be delivered digitally.[21] And this would not only be a novel mechanism of action, but also a different way of delivering treatment for depression.I think the digital format has several benefits. One is that it allows patients to receive their treatment remotely, therefore they don't have to drive two hours to then have a 45-minute session with a therapist. And the other thing is that patients can do it on their own time, whenever it fits into their schedule. So I think patients may feel more engaged and in control of their treatment.[25]

But we also need to keep in mind that the digital format has several barriers.[26] If the patient doesn't have a computer, smartphone, or access to the internet, they can't access their treatment digitally.[27] And some patients may not be interested in using technology. They may need to be a little more educated about it, and some will still insist on being treated in person. But I think many patients will find it convenient to have a digital treatment option.[26]

Dr. Turck:
And as we come to the end of today's program, Dr. Trivedi, what key takeaways would you like to leave with our audience?

Dr. Trivedi:
We've seen neuroplastic changes in patients with depression, as well as after treatment for depression. So now, we can explore the potential to develop therapies for depression that produce specific neuroplastic changes in patients. And digital therapeutics are one avenue that can be used to deliver these targeted treatments.

Dr. Turck:
That's a great way to round out our discussion on this subject. And I want to thank my guest, Dr. Madhukar Trivedi, for helping us better understand neuroplastic changes in depression and how they might advance the treatment of depression.

Dr. Trivedi, it was great speaking with you today.

Dr. Trivedi:
Thank you for having me.

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