The brain's Twitter system: Neuronal extracellular vesicles

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Twitter, a microblogging and social networking service, has become a "go-to'" for conversations, updates, breaking news, and sharing the more mundane aspects of our lives. Tweets, which were lengthened from 140 to 280 characters in 2017, rapidly communicate and disseminate information to a wide audience. Generally, tweets are visible to everyone, though users can mute and block other users from viewing their tweets. Spikes in tweets and tweeting frequency reflect hyper-current events: the last minutes of the Super Bowl, certification of an election, or a new movie release. In fact, social scientists have analyzed tweet frequencies to examine the impact of local and national events. However, few are aware that like celebrities, politicians, influencers, and ordinary citizens, the human brain also tweets.

In this article, we describe the components of the brain's "Twitter" system, how it works, and how it might someday be used to improve the diagnosis and treatment of psychiatric disorders.

Brain tweets

The brain's Twitter system involves extracellular vesicles (EVs), tiny (<1 µm) membrane-bound vesicles that are released from neurons, glia, and other neuronal cells (***Table***, ***page 10***). These EVs cross the blood-brain barrier and facilitate cell-to-cell communication within and among tissues (***Figure 1***, ***page 11***).

First described in the 1980s,[1] EVs are secreted by a diverse array of cells: mast cells reticulocytes, epithelial cells, immune cells, neurons, glia, and oligodendrocytes. Like tweets, EVs rapidly disseminate packets of information throughout the brain and body and direct the molecular activity of recipient cells in both health and disease. These "brain tweets" contain short, circumscribed messages, and the characters are the EV cargos: RNAs, proteins, lipids, and metabolites. Like a Twitter feed, EVs cast a wide communication net across the body, much of which finds its way to the blood. As neuroscientists, we can follow these tweets by isolating tissue-derived EVs in plasma and examining their surface molecules and cargo. By following this Twitter feed, we can tap into important molecular communications and identify "trending" (evolving) pathological processes, and perhaps use the brain Twitter feed to improve diagnosis and treatments. We can pinpoint, in the blood, signals from CNS processes, down to the level of

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Disclosures

Both Drs. Levine and Strawn receive research support from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD, R01HD098757). Dr. Strawn has received research support from the National Institutes of Health (National Institute of Mental Health/National Institute of Environmental Health Sciences/NICHD) and Abbvie. He has received material support from and provided consultation to Myriad Genetics. He also is a consultant to the FDA and receives royalties from the publication of 2 texts (Springer). Dr. Strawn serves as an author for *UpToDate*. Dr. Strawn also receives research support from the Yung Family Foundation.

doi: 10.12788/cp.0257

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Table

Neuronal cells that release extracellular vesicles

Cortical neurons
Hippocampal neurons
Motor neurons
Microglia
Oligodendrocytes
Schwann cells
Astrocytes

Source: Adapted from reference 6

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EVs cross the blood-brain barrier and facilitate cell-to-cell communication within and among tissues

identifying EV cargos from specific brain cell types.

Within the CNS, EVs are secreted by neurons, where they may modulate synaptic plasticity and transfer molecular cargo among neurons. EVs also facilitate communication between neurons and glia, maintain homeostasis, trigger neuroprotective processes, and even regulate synaptic transmission.[2]

What's in a brain tweet?

To discuss what's in a brain tweet, we must first understand how a brain tweet is composed. EVs are pinched off from membranes of intercellular structures (eg, golgi or endoplasmic reticulum) or pinched off directly from cell membranes, where upon release they become EVs. There is a complex cellular machinery that transports what ultimately becomes an EV to the cell membrane.[3] EVs contain unique mixtures of lipids, proteins, and nucleic acids (eg, microRNA [miRNA], mRNA, and noncoding RNA).[4] To date, nearly 10,000 proteins, 11,000 lipids, 3,500 mRNAs, and 3,000 miRNAs have been identified as cargos in extracellular vesicles (***Figure 1, page 11***). Similar to how the release of EVs is dependent on complex intracellular machinery, the packing of these contents into what will become the EV involves a parallel set of complex machinery that is largely directed by endosomal sorting complexes required for transport (ESCRT) proteins.[5] Of interest, when viruses attack cells, they hijack this EV packaging system to package and release new viruses. EVs vary in size, shape, and density; this variation is related to the cell origin, among other things. EVs also differ in their membrane lipid composition and in terms of transmembrane proteins as well as the proteins that facilitate EV binding to target cells (***Figure 2, page 17***).[6] Ultimately, these exosomes are taken up by the recipient cells.

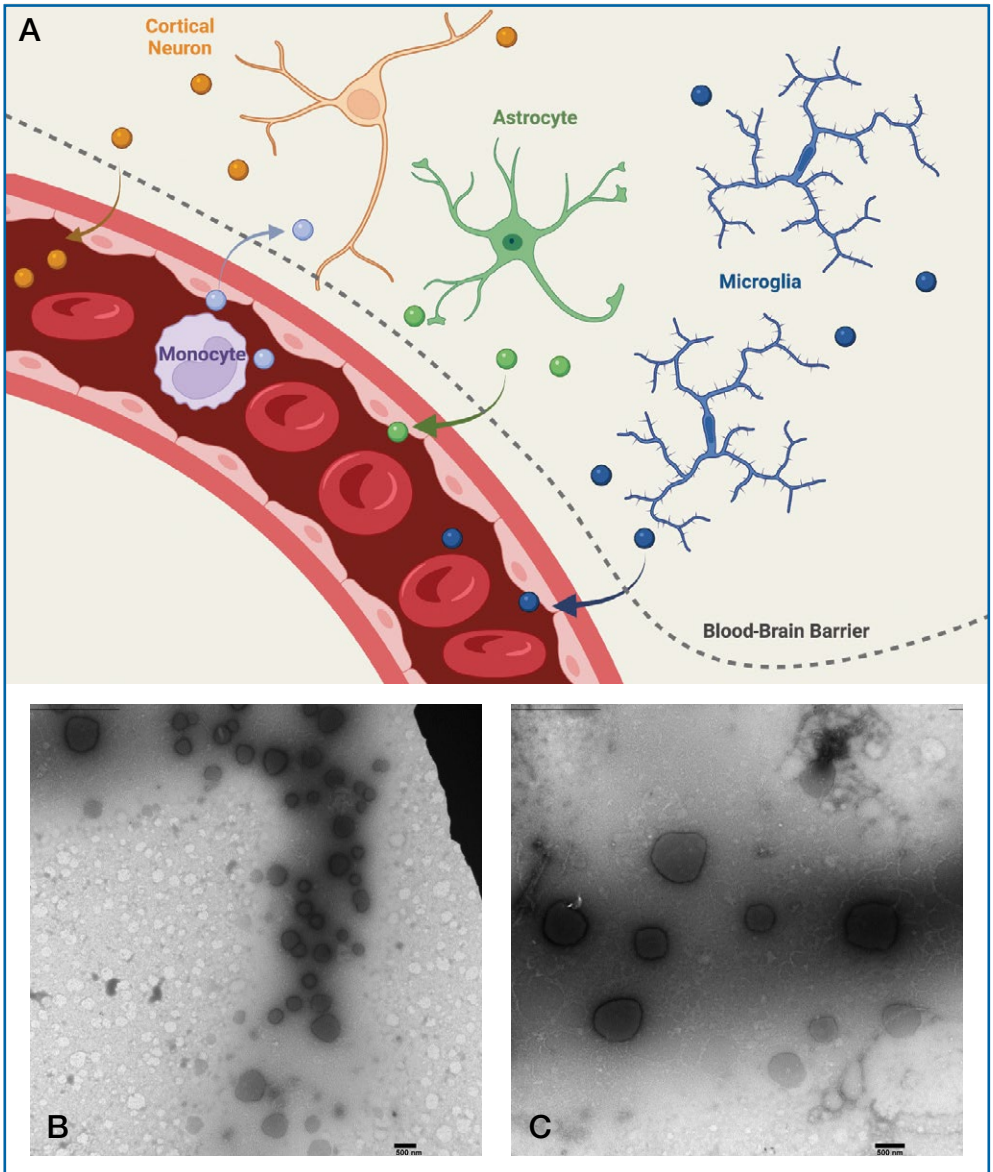
EV-facilitated neuron-to-neuron tweets have been implicated in neuronal growth and differentiation.[7] EV-driven communication between cells also can decrease dendrite growth and can trigger microglia to prune synapses.[8] EVs from glial cells may promote neuronal integrity, directly boost presynaptic glutamate release,[9] or even, through miRNAs, change the expression of glutamate receptors.[10] EVs from astrocytes transport proteins that enable neuronal repair, while EVs from microglia regulate neuronal homeostasis. EV cargos—lipids, proteins, and miRNAs—from neurons modify signal transduction and protein expression in recipient cells. Taken together, data suggest that EVs facilitate anterograde and retrograde transfer of signals across synapses,[7,11] a putative mechanism for driving synaptic plasticity,[12] which is a process implicated in the therapeutic efficacy of psychotropic medications and psychotherapies.

#Targets and #neuron

Adding a hashtag to a tweet links it to other tweets, just as membrane features of EVs direct how EVs link to target cells. When these EVs bind to target cells, they fuse and release their cargo into the target cell (***Figure 2, page 17***). These directed cargo—whether mRNA, proteins, or other molecules—can direct the recipient cell to modify its firing rate (in the case of neurons), alter transmitter release, and increase or decrease expression of various genes. The targeting process is complex, and our understanding of this process is evolving. Briefly, integrin, lipid composition, glycans (eg, polysaccharides), and tetraspanin

Figure 1

Extracellular vesicles



A. Extracellular vesicles (EVs) facilitate communication between cells within the CNS and between the CNS and periphery, and easily traverse the blood-brain barrier (dotted line). EVs are an emerging biomarker of CNS processes that clinicians may access through routine phlebotomy. EVs are shown as small spheres in the extracellular space and are the same color as their cell of origin.
B. and C. Photomicrographs of EVs from an adolescent female.

Source: Image created with BioRender.com

components of EVs influence their affinity for specific target cells.[13] Recently, we have been able to read these hashtags and isolate cell-specific, neuron-derived EVs. Immunoadsorption techniques that leverage antibodies against L1 cell adhesion molecule protein (L1CAM(+)), primarily expressed in neurons, can identify neuronally-derived EVs (***Figure 3, page 18***). The specific EVs contain cargos of

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When EVs bind to target cells, they fuse and release their cargo into the target cell

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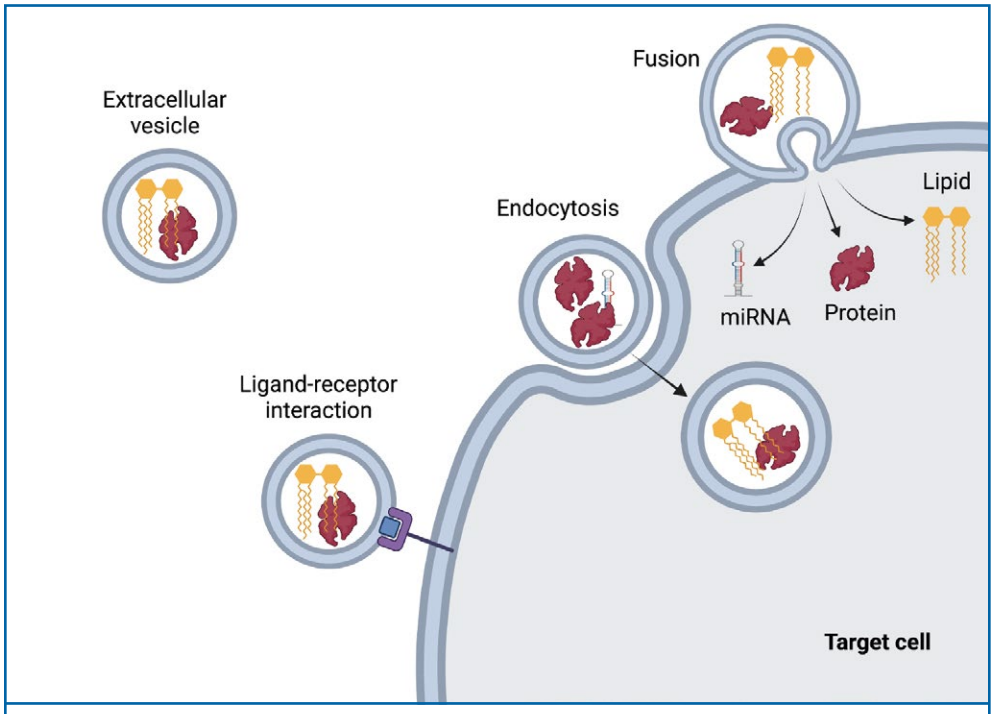
Figure 2

Extracellular vesicle communication mechanisms



Extracellular vesicles interact with target cells to deliver their multiple small molecular cargos (eg, microRNA, proteins, and lipids) through multiple mechanisms, including endocytosis, ligand-receptor interactions, and direct fusion.

Source: Image created with BioRender.com

neuronal origin and provide a "window" into molecular processes in the brain by way of the blood (or other peripheral fluids). In following the neuronal tweets, we can follow molecular measures of important brain molecules in biofluids outside the CNS, including saliva and potentially urine (***Figure 1B*** and ***1C, page 11***). In following these specific neuronal Twitter feeds, we can gain critical insights into specific brain processes.

EVs in psychiatric disorders

EVs are implicated in neuroinflammation,[14] neurogenesis, synaptic plasticity, and epigenetic regulation—all processes that are involved in the pathophysiology of psychiatric disorders. Postmortem research suggests that EVs in the brain carry proinflammatory molecules from microglia, as well as secretions of regulatory miRNA that are responsible for synaptic plasticity and dendritic growth in depression, bipolar disorder, schizophrenia, and addiction. In addition, second-generation antipsychotics change the composition of EV cargos in the brain, altering their RNA, protein, and lipid content, often reflecting profound changes in gene expression in various cells in the CNS. In our lab, we have identified several molecules in plasma EVs, both lipids and miRNA, that can potentially predict the response to treatment of pediatric anxiety with selective serotonin reuptake inhibitors as well as opiate addiction.[15]

Further, given our increasing understanding of the way in which EV cargo reflects neuronal physiology as well as the potential pathophysiologic states of cells

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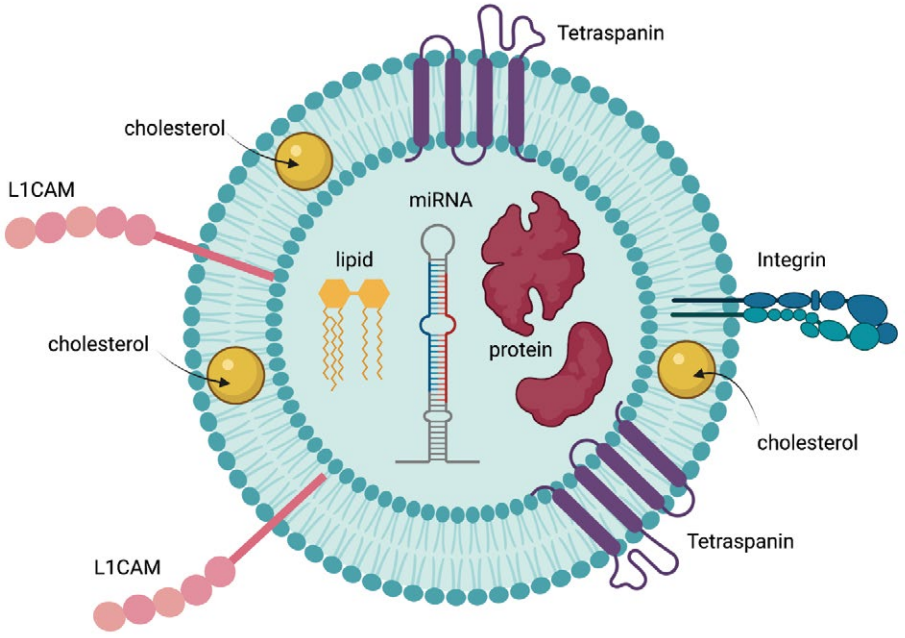
EVs are implicated in neuroinflammation, neurogenesis, synaptic plasticity, and epigenetic regulation

Figure 3

Extracellular vesicle cargos



Extracellular vesicles contain multiple small molecular cargos, including microRNA, proteins, and lipids. Additionally, their surface contains multiple elements that facilitate docking to target cells (eg, L1CAM) as well as molecular machinery to facilitate targeting.

Source: Image created with BioRender.com

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The study of CNS-derived EVs in blood may allow us to gain access to brain molecular signatures that predate clinical changes

(including neurons), studying EVs' molecular content can identify molecular messages—in blood—that are derived from the neurons in the brain. Having the tools to examine molecular brain regulators or other markers of disease progression (eg, beta amyloid) or brain health (eg, brain-derived neurotrophic factor) may advance our understanding and treatment of psychiatric disorders and create opportunities for precision medicine driven by biological rather than ethnologic and phenomenological markers. Whereas in the not-too-distant past molecular processes in the brain were only accessible through invasive measures—such as brain biopsy or through a lumbar puncture—studying CNS-derived EVs in blood offers us an opportunity to gain access to brain molecular signatures with relative ease. Often, these molecular signatures predate clinical changes by years or months, allowing us the prospects of potentially identifying and treating CNS disorders early on, possibly even before the onset of symptoms.

Therapeutic use of the Twitter feed

EV may be used to alter brain receptor structures in a targeted way to facilitate treatment of various psychiatric disorders. One example is a proof-of-concept study in mice in which administration of artificially manufactured EVs led to a decrease of opioid receptor mu.[16] This was done by constructing EVs that carry neuron-specific rabies viral glycoprotein (RVG) peptide on the membrane surface to deliver mu opioid receptor small interfering RNA into the brain. This resulted in downregulation of mu opioid receptor and a decrease in morphine relapse.[16]

Additional ways in which EVs can be used therapeutically is via targeted drug

delivery CNS methods. EVs may represent the next generation of treatment by allowing not only medication transport into the CNS,[17] but also by facilitating directed CNS transport. What if we could use a molecular hashtag to send a dopaminergic agent to the substantia nigra of a patient with Parkinson disease but avoid sending that same treatment to the limbic cortex, where it might produce perceptual disturbances or hallucinations? In the future, EVs may help clinicians access the CNS, which is traditionally restricted by the blood brain barrier, and make it easier to achieve CNS concentrations of medications[13] while decreasing medication exposure in other parts of the body. The therapeutic potential of EVs for medication delivery and regenerative medicine is awe-inspiring. Several studies have modified EVs to improve their therapeutic properties and to target delivery to specific cells[13] by leveraging EV surface markers.[18]

Future directions for EVs

A better understanding of neuron-derived EVs may eventually help us abandon nosology-based diagnostic criteria and adopt molecular-based diagnostic approaches in psychiatry. It may allow us to consider a molecular synaptic etiology of psychiatric disorders, and diagnose patients based on synaptic pathology utilizing "neuron-derived EV liquid biopsies." Such a shift would align psychiatry with other medical fields in which diagnosis and treatment are often based on biopsies and blood tests. Because proteins in EVs often exist in their native states, intact with their post-translational modifications, they provide a window into testing their actual in vivo functioning. EVs have an immense potential to revolutionize psychiatric diagnosis, facilitate precision treatment, predict response, and discover much-needed novel therapeutics.

Related Resources

- Vesiclepedia. www.microvesicles.org/

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EVs may eventually allow medication transport into the CNS and facilitate directed CNS transport

Bottom Line

Much like a tweet, extracellular vesicles (EVs) encode short messages that are transmitted efficiently throughout the CNS and body. They may represent a reservoir for CNS-specific biomarkers that can be isolated from plasma to guide psychiatric diagnosis and treatment. EVs represent a new frontier in the molecular study of psychiatric illness.

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Clinical Point

EVs have immense potential to revolutionize psychiatric diagnosis and facilitate precision treatment