Commentary

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# A Note on Traditional Anterograde and Retrograde Tract Tracing

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## Description

Despite numerous efforts to study brain and basal ganglia functional anatomy, the most recent breakthroughs occurred with the development of various powerful neuronographic methods, which were introduced in the late twentieth century and allowed to describe the close interrelation between the core structures of the basal ganglia and to lay the groundwork for current ideas on the circuits.

In animal investigations, degeneration and tract-tracing approaches are two of the most prevalent ways. In the past, highly localised lesions that led to Wallerian degeneration, along with stains that selectively coloured degenerating neuronal cell bodies and axons, were useful for tracing brain circuits. However, degeneration approaches are hampered by the lack of precision in determining the specific location of axonal terminals, as well as the fact that not all neurons degenerate following a lesion. Taking these restrictions into account, the second part of the twentieth century saw a methodological breakthrough based on tracer axonal transport. Chemical tracers and dyes are absorbed into macromolecules by the neuronal cell bodies and subsequently delivered to the end of the axons, allowing anterograde tract-tracing to identify axon terminations. Retrograde tracing is another often used tract-tracing approach, in which a molecular marker (e.g., horseradish peroxidase enzyme) is injected into the area of axonal terminations and transferred back to the cell body by retrograde axonal transport, exposing the neural pathway's origin. Regardless of the transport direction, time must be allowed for the tracer to reach its target before proceeding with tracer detection using fluorescent light or immunohistochemistry. Despite the amazing results of experimental tract-tracing in animals, the sluggish rate of diffusion prevented this technique from being successfully applied in the post-mortem human brain. Furthermore, due to distinct possible sources of false-positive and false-negative outcomes, both anterograde and retrograde tract-tracing have limits. In fact, tracer injections may travel beyond the target or involve neighbouring channels; it's also possible that retrograde tracers get taken up by passing fibres, resulting in false-positive results. Additionally, caution should be exercised when employing Biotinylated Dextran Amine (BDA) for anterograde tracing due to the possibility of retrograde trafficking and subsequent anterograde translocation into neuronal collaterals.

On the other hand, false-negative results may come from the inability to identify all neurons in a population in any specific study. Another source of false-negative results is the inability to detect colocalization of markers, particularly when neural structures are small, due to either inadequate antibody penetration or disproportional antigen concentration. Despite tract-historical tracing's significance and actual benefits, these limitations prompted the creation of new, more precise tracing approaches.

### Neuronal tracing by neurotropic viruses

Neurotropic viruses, in addition to traditional tracers, have the ability to utilise the interconnectedness of brain circuits; viral replication increases the signal at each step of the process, and viral tracers can also cross multisynaptic pathways. These characteristics allow for a more specific identification of anatomical connections as well as the differentiation of direct and indirect projections. Despite the fact that various neurotropic viruses exist, only two major types, the herpes and rabies viruses, have historically been used to trace neuronal circuits in experiments. While such viruses range significantly, they all have the same envelope shape and the ability to infect neurons and proliferate throughout the nervous system. The herpes simplex virus type 1 (HSV 1) was utilised for the first time in rodents to trace neuronal connections across at least two synapses, laying the way for further development of viral tracing in non-human primates. HSV 1 causes rapid neuronal degeneration and can spread to glial and other neuronal cells, which are important drawbacks. As a result, attempts to limit local spread only allow for the tracing of second-order neurons. Rabies viruses, on the other hand, do not cause neuronal degeneration and can detect neural connections across an infinite number of synapses. The poor pace of viral transport, as well as their fast-lethal effects on the experimental animal, which dies from the infection after a short time, are important limitations in employing viruses to mark multisynaptic connections. As a result, and because labelling first-order neurons takes at least two days, higher-order neurons are only labelled after 12 hours or more. As a result, tracing a neural network with seven synapses, for example, could take up to a week.

Despite all of the limitations described above, viral transneuronal tracing remains the gold standard method for mapping axonal connections in animals. When it comes to the human brain, however, such invasive surveillance methods are difficult to apply.