24h-Delayed, Intramuscular Injection Of An Adeno-Associated Viral Vector Encoding Neurotrophin-3 Promotes Sensorimotor Forelimb Recovery In Young Adult And Aged Rats Following Stroke

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Stroke is a leading cause of profound, long-term arm disability which can be partially reversed by rehabilitation in humans and by some experimental therapies in animals. However, there remains an urgent need for therapies that reverse motor and sensory disabilities in an elderly nervous system and that are effective when initiated hours after stroke (because of delays in hospital admission). Neurotrophin-3 (NT3) treatment improves sensorimotor function following spinal cord injury in rats via anatomical plasticity in locomotor networks including the corticospinal tract (CST), serotonergic pathways and circuits between muscle spindles, sensory afferents and motor neurons. Here we show in two randomized, blinded experiments that injections of an adeno-associated viral (AAV) vector encoding human NT3 into disabled arm muscles reversed sensory and motor disability in both adult and aged rats, when treatment was initiated 24 hours after stroke. Recovery correlated with plasticity of spared CST and serotonergic axons in the cord and with transcription of human NT3 in muscle and cord. Magnetic resonance imaging (MRI) showed that recovery was not due to neuroprotection and that infarct volumes in aged groups did not differ either prior to treatment (at 24 hours) or at 8 weeks. This is the first candidate gene therapy able to reverse the sensorimotor disability associated with stroke that works in adult and elderly mammals, even when administered intramuscularly 24 hours after stroke.