Neurology, Psychiatry and Brain Research 22 (2016) 178–182

Contents lists available at ScienceDirect

Neurology, Psychiatry and Brain Research

journal homepage: www.elsevier.com/locate/npbr

# Effects of neural differentiation maturity status of human induced pluripotent stem cells prior to grafting in a subcortical ischemic stroke model

Matthew B. Jensen*, Lindsey D. Jager, Laura K. Cohen, Susanna S. Kwok, Jin M. Kwon, Crystal A. Hall, Cassandra Heilingoetter

*University of Wisconsin Department of Neurology, 1685 Highland Ave # 7273, Madison 53705-2281, United States*

ARTICLE INFO

*Article history:*
Received 22 February 2015
Received in revised form 19 October 2015
Accepted 17 February 2016
Available online 6 April 2016

*Keywords:*
Neural
Differentiation
Maturity
Human
Induced pluripotent stem cells
Grafting
Subcortical
Ischemic stroke
Rat
Model

ABSTRACT

Neural cell grafting is a promising therapy for stroke, but the optimal differentiation status of the cells prior to grafting is unclear. We grafted cells at different maturity stages (days 28, 42, or 56 of in vitro neural differentiation) into the brains of eight-week-old rats one week after subcortical ischemic stroke, and assessed motor and sensory behavioral recovery over one month. We did not find a difference between the grafted or control groups on behavioral recovery, or on brain tissue outcomes including infarct size, microgliosis, or astrocytosis. Further research is needed into mechanisms of benefit of neural cell grafting for stroke.



## 1. Introduction

Stroke is a major cause of disability, with few effective treatments available to improve recovery (Mozaffarian et al., 2015). Cell transplantation is a promising potential treatment to improve stroke recovery (Bliss, Guzman, Daadi, & Steinberg, 2007). Neural progenitor cells derived from human induced pluripotent stem cells are an attractive candidate cell type for further research (Amabile and Meissner, 2009). One of the initial questions requiring clarification is how the neural differentiation maturity status of the cells prior to grafting affects behavioral and tissue responses of a stroke model. More mature neural cells may be able to more rapidly integrate into host neuronal circuitry to replace lost neurons, but may be less able to survive the grafting process, or less able to secrete beneficial factors. Less mature neural cells may take longer to replace lost neurons, but may better survive the grafting process, or may be more able to secrete beneficial factors present early in development that could aid recovery of the host tissue. We therefore sought to determine the effects of the pregraft neural differentiation maturity status of human induced pluripotent stem cells in a model of ischemic stroke.

## 2. Methods

The full methods are described in the online supplement. The induced pluripotent stem cell line iPS-DF6-9-9T was derived from postnatal human skin fibroblasts (Yu et al., 2009). The cells were expanded as pluripotent cells and differentiated to neural lineages as previously described with modifications (Jensen, Krishnaney-Davison, Cohen, & Zhang, 2012; Jensen, Yan, Krishnaney-Davison, Al Sawaf, & Zhang, 2013). Male 8-week-old Sprague Dawley rats, at an age widely-used for stroke research, were given small deep hemispheric infarcts similar to a human lacunar stroke by intracerebral injection of the vasoconstrictor peptide endothelin-1.

Seven days poststroke, 8 rats per group were randomly assigned to receive intracerebral grafts of approximately 250,000 cells at days 28 (named group W4), 42 (named group W6), or 56 (named group W8) of neural differentiation, or vehicle without cells for the control group (named group C). These time points represented a wide range of neural differentiation in our culture system, as

* Corresponding author.
*E-mail address:* jensen@neurology.wisc.edu (M.B. Jensen).

http://dx.doi.org/10.1016/j.npbr.2016.02.001
0941-9500/

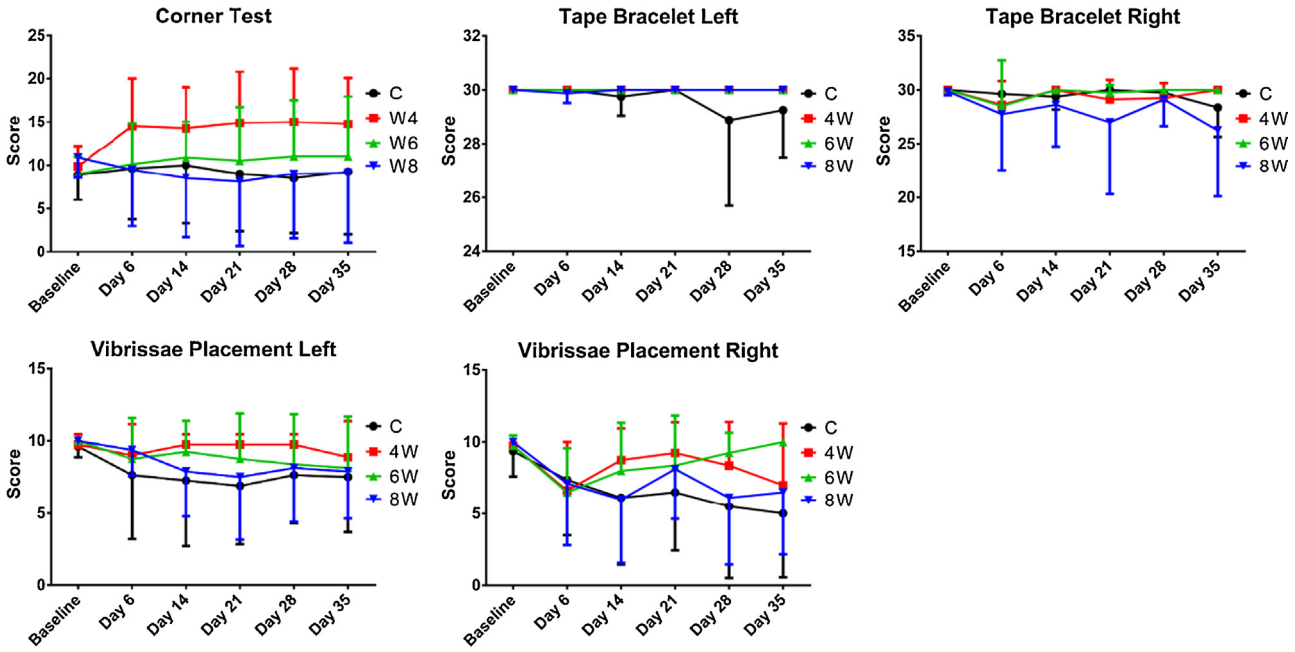


**Fig. 1.** There were no significant differences between groups for the sensory behavioral tests.

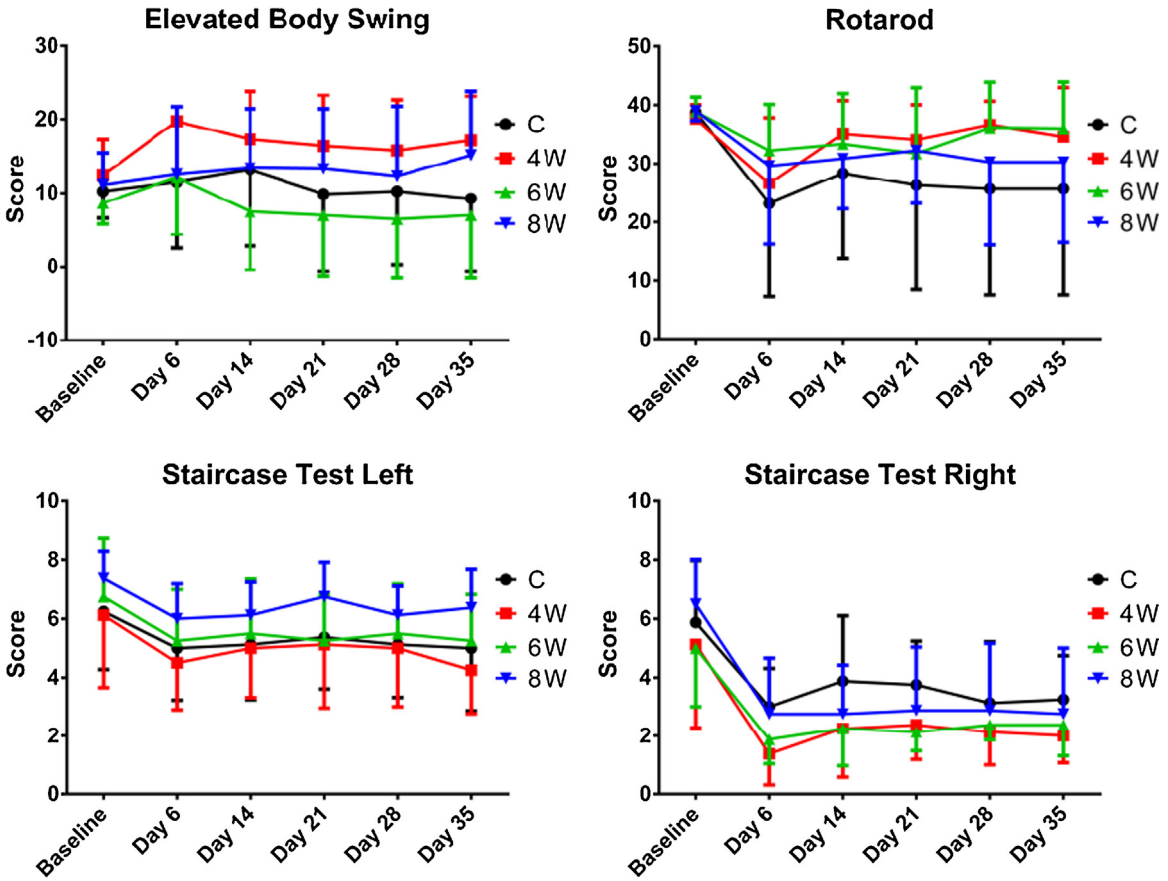


**Fig. 2.** There were no significant differences between groups for the motor behavioral tests.