Neurobiology of Learning and Memory 139 (2017) 69–75

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

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

Transcranial infrared laser stimulation improves rule-based, but not information-integration, category learning in humans

Nathaniel J. Blanco [a,b], Celeste L. Saucedo [a], F. Gonzalez-Lima [a,*]

[a] Department of Psychology and Institute for Neuroscience, University of Texas at Austin, TX 78712, USA
[b] Department of Psychology, The Ohio State University, Columbus, OH 43210, USA

ARTICLE INFO

Article history:
Received 3 July 2016
Revised 13 December 2016
Accepted 24 December 2016
Available online 27 December 2016

Keywords:
Photobiomodulation
Low-level laser therapy
Cognitive enhancement
Transcranial laser stimulation
Category learning
Neuromodulation

ABSTRACT

This is the first randomized, controlled study comparing the cognitive effects of transcranial laser stimulation on category learning tasks. Transcranial infrared laser stimulation is a new non-invasive form of brain stimulation that shows promise for wide-ranging experimental and neuropsychological applications. It involves using infrared laser to enhance cerebral oxygenation and energy metabolism through upregulation of the respiratory enzyme cytochrome oxidase, the primary infrared photon acceptor in cells. Previous research found that transcranial infrared laser stimulation aimed at the prefrontal cortex can improve sustained attention, short-term memory, and executive function. In this study, we directly investigated the influence of transcranial infrared laser stimulation on two neurobiologically dissociable systems of category learning: a prefrontal cortex mediated reflective system that learns categories using explicit rules, and a striatally mediated reflexive learning system that forms gradual stimulus-response associations. Participants (n = 118) received either active infrared laser to the lateral prefrontal cortex or sham (placebo) stimulation, and then learned one of two category structures—a rule-based structure optimally learned by the reflective system, or an information-integration structure optimally learned by the reflexive system. We found that prefrontal rule-based learning was substantially improved following transcranial infrared laser stimulation as compared to placebo (treatment X block interaction: $F(1, 298) = 5.117$, $p = 0.024$), while information-integration learning did not show significant group differences (treatment X block interaction: $F(1, 288) = 1.633$, $p = 0.202$). These results highlight the exciting potential of transcranial infrared laser stimulation for cognitive enhancement and provide insight into the neurobiological underpinnings of category learning.

1. Introduction

Mounting evidence demonstrates the promising potential of using near-infrared light for a variety of psychological and neurological applications (Gonzalez-Lima & Barrett, 2014; Naeser et al., 2014). This approach is also called low-level laser/light therapy (LLLT) or photobiomodulation (Chung et al., 2012). It consists of using directional low-power and high-fluence monochromatic or quasimonochromatic light from lasers or light-emitting diodes (LEDs) in the red-to-near-infrared wavelengths to modulate biological functions (Rojas & Gonzalez-Lima, 2011). Photobiomodulation can modify neuronal function in a non-thermal manner in cell cultures, animal models, and clinical conditions (Cassano, Petrie, Hamblin, Henderson, & Iosifescu, 2016; Eells et al., 2004; Schiffer et al., 2009; Wong-Riley et al., 2005). It has been shown to produce a wide range of biological effects including the enhancement of cellular metabolic energy (ATP production) and gene expression (Rojas & Gonzalez-Lima, 2013). The primary mechanism of action of photobiomodulation is the photonic activation of cytochrome oxidase (Karu, Pyatibrat, Kolyakov, & Afanasyeva, 2005; Rojas & Gonzalez-Lima, 2011; Rojas, Lee, John, & Gonzalez-Lima, 2008; Wong-Riley et al., 2005), which is the mitochondrial enzyme that catalyzes oxygen consumption in cellular respiration for metabolic energy production (Wong-Riley et al., 2005), and the primary cellular photoacceptor of red-to-near-infrared light energy (Karu et al., 2005). In animal studies, there is evidence that both the enzyme activity and the protein levels of cytochrome oxidase are increased by photobiomodulation (Hayworth et al., 2010; Rojas et al., 2008). In human studies, broad-band near-infrared spectroscopy (Wang, Tian, Soni, Gonzalez-Lima, & Liu, 2016) has demonstrated that the 1064 nm laser used in the present study

* Corresponding author at: The University of Texas at Austin, 108 E. Dean Keeton Stop A8000, Austin, TX 78712, USA.

E-mail addresses: nathanblanco@gmail.com (N.J. Blanco), celestesaucedo@utexas.edu (C.L. Saucedo), gonzalezlima@utexas.edu (F. Gonzalez-Lima).

http://dx.doi.org/10.1016/j.nlm.2016.12.016
1074-7427/

affects cytochrome oxidase enzyme activity, as shown by increased oxidized cytochrome oxidase during and shortly after light stimulation. This primary action on cytochrome oxidase is then followed by increased hemoglobin oxygenation.

1.1. Transcranial photobiomodulation

Previous work has shown that non-invasive transcranial photobiomodulation can increase cytochrome oxidase activity in the rat brain (Rojas et al., 2008), which can provide neuroprotection and improve behavioral performance (Rojas & Gonzalez-Lima, 2011, 2013). In particular, Rojas, Bruchey, and Gonzalez-Lima (2012) demonstrated that transcranial photobiomodulation can improve prefrontal cortex oxygen consumption and metabolic energy, and thereby increase prefrontal cortex-based memory functions in rats. These findings in animals suggest that the oxygen metabolism of cortical tissue exposed transcranially to photobiomodulation is enhanced, and that this can result in enhancement of cognitive function.

Recent research suggests that transcranial photobiomodulation in humans may have a broad range of neurological and cognitive applications. Transcranial photobiomodulation has been shown to improve *in vivo* oxygenation in the prefrontal cortex (Tian, Hase, Gonzalez-Lima, & Liu, 2016) and neurological outcome after ischemic stroke (Lampl et al., 2007) and mild traumatic brain injury (Naeser et al., 2014). Transcranial stimulation of the forehead with 1064 nm laser induces hemodynamic effects within minutes, as demonstrated by increased hemoglobin oxygenation in the human prefrontal cortex (Tian et al., 2016), which may be responsible for the cognitive benefits reported here.

Transcranial photobiomodulation also shows exciting potential as a form of *cognitive enhancement* in healthy populations. Barrett and Gonzalez-Lima (2013) found beneficial effects of transcranial infrared laser stimulation (TILS; a novel, non-invasive form of photobiomodulation) on both sustained attention and short-term memory retrieval. These effects of TILS were found to be comparable to the cognitive enhancing effects of vigorous aerobic exercise (Hwang, Castelli, & Gonzalez-Lima, 2016). In another study, we also found improved performance on the Wisconsin Card Sorting Task (Heaton, Chelune, Talley, Kay, & Curtiss, 1993), a gold-standard neuropsychological measure of executive function, in healthy young participants (Blanco, Maddox, & Gonzalez-Lima, 2015).

Research has suggested that TILS can enhance cognition, but to date its effects have only been investigated on a small range of cognitive abilities. Whether or not it can benefit other types of cognitive tasks has yet to be explored. The goal of the current study is to extend this investigation by examining the effects of TILS on category learning—a critical cognitive process involved in every aspect of our daily lives.

1.2. Category learning

The ability to categorize is a fundamental aspect of human cognition. Effectively learning new categories and accurately classifying things into known categories are both crucial to day-to-day functioning. Categorization allows us to generalize knowledge to new objects we encounter in the world and make effective inferences about them.

In the category learning literature an important distinction is made between different types of category structures. Two types of category structures have been studied extensively: *Rule-based* and *Information-integration* (Maddox & Ashby, 2004). The optimal strategy that maximizes categorization accuracy in Rule-based category learning structures involves developing and testing explicit hypotheses that can be described verbally (Shepard, Hovland, & Jenkins, 1961). In contrast, the optimal classification strategy in Information-integration category structures is not explicit and cannot be easily described verbally. Instead, information from two or more stimulus dimensions must be integrated at some predecisional stage.

A wealth of evidence implicates two dissociable neural learning systems that mediate optimal learning in each of these two types of category structures: a *reflective* system (optimal for rule-based structures) that explicitly tests hypotheses and is under conscious control (Ashby, Alfonso-Reese, Turken, & Waldron, 1998; Ashby & Ennis, 2006; Nomura et al., 2007), and a *reflexive* system (optimal for information-integration structures) that incrementally learns stimulus-response relationships and is not under conscious control (Ashby & Waldron, 1999).

While both systems rely on a network of brain regions, the reflective system has been shown to be highly reliant on processing in the prefrontal cortex (Filoteo, Maddox, Ing, Zizak, & Song, 2005; Filoteo, Maddox, Salmon, & Song, 2005; Filoteo, Maddox, Simmons et al., 2005; Lombardi et al., 1999; Monchi, Petrides, Petre, Worsley, & Dagher, 2001; Nomura et al., 2007; Schnyer et al., 2009; Seger & Cincotta, 2005), particularly the dorsolateral prefrontal cortex (DLPFC). In contrast, the reflexive learning system relies mainly on processing in the striatum (Aron et al., 2004; Filoteo, Maddox, Ing et al., 2005; Maddox & Filoteo, 2001, 2005; Nomura et al., 2007; Poldrack et al., 2001; Seger, 2008; Seger & Cincotta, 2005).

1.3. Goals and predictions for the current study

The goal of the current study was to test the effects of TILS on category learning. Participants received a single TILS treatment to the right forehead, targeting right lateral prefrontal cortex, and then engaged in one of two category learning tasks: Rule-based or Information-integration. Right PFC was targeted for consistency with our previous study (Blanco et al., 2015), where we found TILS-related enhancements in Wisconsin Card Sorting Task performance, though to our knowledge the literature does not indicate differences in activation or function by hemisphere in category learning. Considering the results of our previous study (Blanco et al., 2015), and the abundant evidence implicating lateral prefrontal cortex in rule-based category learning, one straightforward prediction is that TILS will improve learning in the Rule-based condition.

Predictions for the Information-integration condition were less straightforward, however. One possibility is that TILS would have no effect on learning in the Information-integration condition. It is also possible that performance could be impaired by TILS in the Information-integration condition. Some theories of category learning, most notably the *competition between verbal and implicit systems* theory (COVIS; Ashby et al., 1998), posit that the reflective and reflexive systems compete during learning for control of responses. So boosting the prefrontal, reflective system with TILS may cause participants to rely too heavily on explicit rules instead of adopting the optimal reflexive strategy, thus slowing learning. For this reason, in addition to investigating the potential for TILS to enhance category learning ability, our study provides valuable insight into the interaction between the two systems during learning.

2. Material and methods

2.1. Participants

There were 118 undergraduate students (mean age: 19 (SD = 1.91); age range: 17–35; 60 female, 58 male) who participated in the experiment for partial course credit at the University of Texas at Austin. Participants who reported active neurological