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Research report

Impaired executive function following ischemic stroke in the rat medial prefrontal cortex

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HIGHLIGHTS

- We describe a rodent model of executive dysfunction.
- Bilateral prefrontal cortical ischemia induces executive dysfunction.
- Mediodorsal thalamic ischemia does not impair executive function in young animals.

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ABSTRACT

Small (lacunar) infarcts frequently arise in frontal and midline thalamic regions in the absence of major stroke. Damage to these areas often leads to impairment of executive function likely as a result of interrupting connections of the prefrontal cortex. Thus, patients experience frontal-like symptoms such as impaired ability to shift ongoing behavior and attention. In contrast, executive dysfunction has not been demonstrated in rodent models of stroke, thereby limiting the development of potential therapies for human executive dysfunction. Male Sprague-Dawley rats ($n=40$) underwent either sham surgery or bilateral endothelin-1 injections in the mediodorsal nucleus of the thalamus or in the medial prefrontal cortex. Executive function was assessed using a rodent attention set shifting test that requires animals to shift attention to stimuli in different stimulus dimensions. Medial prefrontal cortex ischemia impaired attention shift performance between different stimulus dimensions while sparing stimulus discrimination and attention shifts within a stimulus dimension, indicating a selective attention set-shift deficit. Rats with mediodorsal thalamic lacunar damage did not exhibit a cognitive impairment relative to sham controls. The selective attention set shift impairment observed in this study is consistent with clinical data demonstrating selective executive disorders following stroke within specific sub-regions of frontal cortex. These data contribute to the development and validation of a preclinical animal model of executive dysfunction, that can be employed to identify potential therapies for ameloriating cognitive deficits following stroke.

1. Introduction

Vascular disease is the most common cause of frontal lobe and subcortical dementias, and may account for up to 25% of degenerative dementias among middle-aged individuals [1]. Ischemic brain damage in the prefrontal cortex (PFC) caused by progressive atherosclerosis or embolism often lead to impairments in executive function, including problems with planning, behavioral flexibility and attention set shifting ability [2–5]. Cognitive impairment can result from either large or small vessel disease. Unlike large vessel stroke, small vessel disease typically does not include obvious sensory-motor or behavioral symptoms and are thus called

Abbreviations: CD, compound discrimination; ED, extradimensional shift; ID, intradimensional shift; LI, learned irrelevance; MD, mediodorsal thalamus; PFC, prefrontal cortex; REV, reversal; SD, simple discrimination; WCST, Wisconsin Card Sorting Test.

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Table 1
Order of discriminations.

Discrimination	Relevant dimension	Irrelevant dimensions
Simple discrimination (SD)	Odor (patchouli)	
Compound discrimination (CD)	Odor (patchouli)	External texture & digging medium
Intradimensional shift (ID)	Odor (nutmeg)	External texture & digging medium
Reversal 1 (Rev 1)	Odor (lavender)	External texture & digging medium
Extradimensional shift (ED)	External texture (furry)	Odor & digging medium
Reversal 2 (Rev 2)	External texture (flat)	Odor & digging medium (yellow paper)
Learned irrelevance (LI)	External texture (flat)	Odor & digging medium (blue paper)

Examples of stimulus combinations are shown for a rat shifting attention from odor to external texture. The attention set shift test is comprised of seven discriminations where a relevant cue is associated with a hidden reward. The discriminations include simple (SD) and compound discriminations (CD), an interdimensional attention shift (ID) to stimuli within the same dimension as the previous discriminations (e.g. odor), and a reversal (REV1) to the previously unrewarded stimulus of the same dimension. Subsequently, an extradimensional attention shift (ED) is made to a stimulus in a new dimension (e.g. external texture), followed by a second reversal and a test of learned irrelevance.

silent or covert strokes, but they often lead to selective impairments of executive cognitive function [6,7]. Patients with large vessel stroke or small vessel disease frequently exhibit a strikingly similar pattern of impairments in frontal cortex-dependent tasks such as the Trail Making test and the Wisconsin Card Sorting Test (WCST) which respectively assess abilities to shift behavioral tasks and attention [8,9]. Small vessel disease also commonly results in lacunar infarcts in midline thalamic structures within watershed areas that are highly susceptible to hypoperfusion [10]. Thus the predominance of frontal symptoms arising from medial thalamic stroke has been proposed to result from damage to the mediodorsal (MD) thalamic nucleus that provides the major input to PFC, and the subsequent interruption of frontal-subcortical circuits [11,12].

Covert stroke occurs five times more frequently than clinically evident overt strokes [6] and cerebral infarctions resulting from covert stroke have been found in 23–33% of unaware, apparently healthy middle-aged adults [7,11]. While the symptoms of covert stroke may initially be subtle, covert stroke greatly increases the risk of subsequent overt stroke and often leads to the development of vascular dementia [6] which is characterized by impairments in attention and executive function [12,13].

In view of the very high incidence and long-term costs associated with stroke related cognitive impairment it would be useful to develop an animal model of executive dysfunction arising from ischemic damage in either the PFC or MD since cognition is often not assessed in preclinical stroke studies [14,15].

To address these concerns, this study used an animal model of attention set shifting to investigate the cognitive effects of ischemic infarcts within the rodent mediodorsal thalamic nuclei or medial prefrontal cortex, an area that makes analogous connections to the human dorsolateral prefrontal cortex. Consistent with human findings, we hypothesized that ischemic damage in either the MPFC or MD would selectively impair the ability to shift attention between different feature sets of stimuli while sparing other aspects of attention and learning.

2. Materials and methods

2.1. Subjects

Forty, 3–5 month old male Sprague-Dawley rats (Charles River Laboratories, Montreal, Quebec, Canada) weighing ~450–600 g at time of behavioral testing were used in this experiment. Animals were housed on a reverse 12 h light/dark cycle with food and water ad libitum. Behavioral assessments were conducted during the dark phase. All procedures adhered to guidelines established by the Canadian Council on Animal Care and received prior approval from the Institutional Animal Care Committee of Memorial University.

2.2. Surgery

After socialization and habituation to the testing environment, ischemia was induced under isoflurane anesthesia (4.0% induction, 2.0% maintenance in 100% O_2). Animals were placed in a stereotaxic frame, with a flat head angle, and bilateral injections of the vasoconstrictive peptide, endothelin-1 (ET-1), were infused into the MD ($n = 14$) or the PFC ($n = 13$). The PFC encompasses prelimbic, infralimbic and anterior cingulate cortex, which receive afferents from MD [8] and has been implicated in attention set shifting ability in rodents [16,17]. Sham animals underwent similar surgical procedures with burr holes drilled in corresponding frontal or thalamic coordinates ($n = 13$). Temperature was maintained at ~37 °C throughout surgery using a self-regulating heating blanket (Harvard Apparatus, Holliston, MA, USA).

In the PFC, four sites were infused with 0.8 μL ET-1 at the following coordinates [16]: anterior–posterior (AP) +3.5 mm from bregma, medio-lateral (ML) ±0.6 mm, dorso-ventral (DV) −5.2 mm; AP +2.5 mm, ML ±0.6 mm, DV −5.0 mm. Ischemia was induced in the MD by bilateral infusions of 0.25 μL ET-1 at coordinates AP −2.8 mm, ML ±0.7 mm, DV −5.8 mm. Functional assessments commenced 10 days following recovery from surgery by an experimenter blinded to experimental condition.

2.3. Behavioral training

Rats were mildly food restricted to 90% of their free-feeding weight and trained to make a series of discriminations between stimuli by finding a hidden 1/3 Honey Nut Cheerio© (General Mills, Mississauga, ON, Canada) food reward buried in one of two 10 cm diameter ceramic pots in which the location was consistently paired with one of two different stimuli (see below). Criterion for successful discrimination consisted of the rat digging with its paws or nose in the pot containing the buried reward on six consecutive trials. Three subjects were excluded for failure to complete this criterion.

The attention set shift test was administered the following day and consisted of seven discriminations (Table 1) [18]: (1) a simple discrimination (SD) where rats were rewarded for responding to a stimulus feature of one of the two pots (e.g. a patchouli odor) using simplified pots with features added only in one relevant stimulus dimension (e.g. odors); (2) a compound discrimination (CD) where the reward was paired with the same stimulus feature in complex pots where two additional, irrelevant, stimulus dimensions were added (e.g. different digging media and external textures); (3) an interdimensional shift (ID), where a new set of pots were presented (Table 2) and the rat was required to locate the reward paired with one of two features in the same sensory dimension as the previous tests (e.g. a nutmeg *odor*); (4) a reversal (REV1), where the other, previously unrewarded feature in the same sensory dimension was