Available online at www.sciencedirect.com

ScienceDirect

Journal homepage: www.elsevier.com/locate/cortex

Behavioural neurology

Neuropsychiatric effects of neurodegeneration of the medial versus lateral ventral prefrontal cortex in humans

Edward D. Huey [a,b,c,d,*], *Seonjoo Lee* [d,e], *Adam M. Brickman* [a,c,f], *Masood Manoochehri* [a,c], *Erica Griffith* [a,f], *D.P. Devanand* [b,d], *Yaakov Stern* [a,c,f] *and Jordan Grafman* [g,h]

[a] *Taub Institute and Gertrude H. Sergievsky Center, Columbia University Medical Center, New York, NY, USA*
[b] *Division of Geriatric Psychiatry, Department of Psychiatry, Columbia University, College of Physicians and Surgeons and New York State Psychiatric Institute, New York, NY, USA*
[c] *Department of Neurology, Columbia University, College of Physicians and Surgeons, New York, NY, USA*
[d] *Department of Psychiatry, Columbia University, College of Physicians and Surgeons and New York State Psychiatric Institute, Columbia University, New York, NY, USA*
[e] *Department of Biostatistics, Columbia University, College of Physicians and Surgeons, New York, NY, USA*
[f] *Cognitive Neuroscience Division, Department of Neurology, Columbia University, College of Physicians and Surgeons, New York, NY, USA*
[g] *Brain Injury Research Program, Rehabilitation Institute of Chicago, Chicago, IL, USA*
[h] *Northwestern University, Chicago, IL, USA*

ARTICLE INFO

Article history:
Received 26 March 2015
Reviewed 4 May 2015
Revised 23 June 2015
Accepted 4 August 2015
Published online 15 August 2015

Keywords:
Neurodegeneration
Prefrontal cortex
Neuropsychiatry
Lesion studies

ABSTRACT

Animal evidence suggests that a brain network involving the medial and rostral ventral prefrontal cortex (PFC) is central for threat response and arousal and a network involving the lateral and caudal PFC plays an important role in reward learning and behavioral control. In this study, we contrasted the neuropsychiatric effects of degeneration of the medial versus lateral PFC in 43 patients with Frontotemporal dementia (FTD) and 11 patients with Corticobasal Syndrome (CBS) using MRI, the Neuropsychiatric Inventory (NPI), and the Sorting, Tower, Twenty Questions, and Fluency tests of the Delis-Kaplan Executive Function System (D-KEFS). Deviations in MRI grey matter volume from 86 age-matched healthy control subjects were determined for the patients using FreeSurfer. Multivariate regression was used to determine which brain areas were associated with specific neuropsychiatric and cognitive symptoms. Decreased grey matter volume of the right medial ventral PFC was associated with increased anxiety and apathy, decreased volume of the right lateral ventral PFC with apathy and inappropriate repetitive behaviors, and of the left lateral ventral PFC with poor performance on the sorting and Twenty Questions task in patients with FTD and CBS. Similar to in animal studies, damage to the medial OFC appears to be associated with a

* *Corresponding author*. Taub Institute and Gertrude H. Sergievsky Center, Columbia University Medical Center, 630 W 168th St, P&S Box 16, New York, NY, 10032, USA.
E-mail address: edh2126@cumc.columbia.edu (E.D. Huey).
http://dx.doi.org/10.1016/j.cortex.2015.08.002

disruption of arousal, and damage to the lateral OFC appears to be associated with deficits in trial-and-error learning and behavioral dysregulation. Studies of brain dysfunction in humans are valuable to bridge animal and human neuropsychiatric research.

1. Introduction

Tracing and lesion studies in animals suggests that the medial and lateral ventral prefrontal cortex (PFC) are components of distinct networks with related, but separable, functions (Carmichael & Price, 1995, 1996; Drevets, Price, & Furey, 2008; Haber, Lynd, Klein, & Groenewegen, 1990; Murray, Wise, & Drevets, 2011; Nakano, 2000; Price & Drevets, 2011; Saleem, Miller, & Price, 2014). In this study, we examine the neuropsychiatric and cognitive effects of neurodegeneration of the medial versus lateral ventral PFC in patients with neurodegenerative illness targeting the frontal lobes. The goal of this study is to test whether dysfunction of these brain regions results in neuropsychiatric and cognitive symptoms in humans that are similar to those found in animals.

The medial PFC (MPFC) network involves the more medial and rostral ventral PFC including human BA 10, medial 11, 14, 24, 25, and 32 (Carmichael & Price, 1995, 1996; Haber, et al., 1990; Price & Drevets, 2011). It appears in animals to be preferentially involved in a network that responds to fear and threat (Price & Drevets, 2011). This network includes cochlear – pontine – spinal loops controlling rapid simple startle responses (Lee, Lopez, Meloni, & Davis, 1996), the periaqueductal gray (PAG), which helps to coordinate somatic reactions to fear including the quiescence response in which the animal becomes quiet and withdrawn in response to injury (Bandler, Keay, Floyd, & Price, 2000), and the amygdala (LeDoux, 2007; Price, 2005). There is a large animal literature linking both the amygdala and medial PFC with fear conditioning and extinction [see (Etkin, Egner, & Kalisch, 2011; Marek, Strobel, Bredy, & Sah, 2013) for reviews of this topic]. Lesions of these regions interfere with fear conditioning and extinction in animals (Etkin, et al., 2011; Marek, et al., 2013).

The lateral PFC (LPFC) network involves the more lateral and caudal ventral PFC including human BA lateral 11, 13l, 13m, 13b, 47l, 47m, and 47r (Carmichael & Price, 1995, 1996; Haber, et al., 1990; Price & Drevets, 2011). It receives extensive sensory and limbic inputs in addition to input from areas involved in reward processing including the ventral tegmental area (VTA), nucleus accumbens, and ventral striatum (Carmichael & Price, 1995, 1996). The LPFC network plays important roles in olfactory and gustatory processing and reward and reinforcement learning in primates (Kringelbach & Rolls, 2004; Price, 2005). The LPFC network has been associated with assessing the rewarding or punishing nature of stimuli (Saleem, et al., 2014). Lesions of the lateral ventral PFC in monkeys results in impaired reward learning, but preserved fear conditioning (Kazama, Davis, & Bachevalier, 2014).

We cannot perform brain lesions in humans as we do with animals. However, certain neurodegenerative illnesses in humans result in degeneration and atrophy of the frontal lobes, including Frontotemporal dementia (FTD) and corticobasal syndrome (CBS). The study of these patients can be used as a model for the effects of frontal dysfunction in humans. FTD primarily affects the PFC and the anterior temporal lobes (Seeley et al., 2008), while CBS affects the posterior frontal lobes, anterior temporal lobes, and the basal ganglia (Boeve, 2005). Both illnesses present with neuropsychiatric symptoms and cognitive deficits. Together, these illnesses affect the entire frontal lobes and provide a means to investigate the effects of frontal dysfunction in humans.

Based on findings in animals that the MPFC network is more associated with arousal/threat response, we hypothesize that damage to the MPFC network structures in patients with FTD and CBS will be selectively associated with dysregulation of arousal with excessive arousal (manifesting as anxiety), or decreased arousal (manifesting as apathy) in our subjects. Based on animal findings that the LPFC network is more associated with reward processing, we hypothesize that damage to LPFC network structures will be selectively associated with a decrease in the performance of previously rewarding behaviors (manifesting as apathy), impairment in behavioral regulation (manifesting as inappropriate repetitive behaviors), and deficits in reversal learning (manifesting as poor performance on a sorting task) in patients with FTD and CBS. To test these hypotheses, we administered to caregivers a questionnaire designed to elicit their observations of neuropsychiatric symptoms, the UCLA Neuropsychiatric Inventory (NPI), and we evaluated patients with a sorting test. We performed structural MRI scans on the patients and determined their deviations in grey matter volume from a sample of age matched control subjects.

There are data from previous studies on the neuroanatomical associations of neuropsychiatric symptoms in patients with neurodegenerative illness and brain injury to support these hypotheses. In one such study in patients with neurodegenerative disease, apathy was associated with atrophy in the right ventromedial PFC and aberrant motor behavior with the right dorsal anterior cingulate cortex extending laterally to the supplemental motor area (Rosen et al., 2005). Other studies have linked degeneration of the ventromedial PFC with apathy in patients with Alzheimer's disease (Benoit et al., 2002; Craig et al., 1996; Migneco et al., 2001) and FTD (Peters et al., 2006), and also with the lateral PFC in FTD (Zamboni, Huey, Krueger, Nichelli, & Grafman, 2008) (note, however, that 15 of the patients in this study were included in the current study as well). In studies of brain injury resulting in focal lesions, apathy has been associated with medial and lateral PFC lesions (Knutson et al., 2014), and anxiety with damage to structures involved in the MPFC network (Knutson et al., 2013). Apathy has been associated