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Architecture of cognitive flexibility revealed by lesion mapping

Aron K. Barbey [a,b,c,d,e,f,*], Roberto Colom [g], Jordan Grafman [h]

[a] Decision Neuroscience Laboratory, University of Illinois at Urbana–Champaign, Champaign, IL 61820, USA
[b] Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana–Champaign, Urbana, IL, 61801, USA
[c] Department of Internal Medicine, University of Illinois at Urbana–Champaign, Champaign, IL 61820, USA
[d] Department of Psychology, University of Illinois at Urbana–Champaign, Champaign, IL 61820, USA
[e] Department of Speech and Hearing Science, University of Illinois at Urbana–Champaign, Champaign, IL 61820, USA
[f] Neuroscience Program, University of Illinois at Urbana–Champaign, Champaign, IL 61820, USA
[g] Universidad Autónoma de Madrid, Fundación CIEN/Fundación Reina Sofía, Madrid, Spain
[h] Traumatic Brain Injury Research Laboratory, Rehabilitation Institute of Chicago, Chicago, IL, 60611, USA

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ABSTRACT

Neuroscience has made remarkable progress in understanding the architecture of human intelligence, identifying a distributed network of brain structures that support goal-directed, intelligent behavior. However, the neural foundations of cognitive flexibility and adaptive aspects of intellectual function remain to be well characterized. Here, we report a human lesion study ($n = 149$) that investigates the neural bases of key competencies of cognitive flexibility (i.e., mental flexibility and the fluent generation of new ideas) and systematically examine their contributions to a broad spectrum of cognitive and social processes, including psychometric intelligence (Wechsler Adult Intelligence Scale), emotional intelligence (Mayer, Salovey, Caruso Emotional Intelligence Test), and personality (Neuroticism–Extraversion–Openness Personality Inventory). Latent variable modeling was applied to obtain error-free indices of each factor, followed by voxel-based lesion-symptom mapping to elucidate their neural substrates. Regression analyses revealed that latent scores for psychometric intelligence reliably predict latent scores for cognitive flexibility (adjusted $R^2 = 0.94$). Lesion mapping results further indicated that these convergent processes depend on a shared network of frontal, temporal, and parietal regions, including white matter association tracts, which bind these areas into an integrated system. A targeted analysis of the unique variance explained by cognitive flexibility further revealed selective damage within the right superior temporal gyrus, a region known to support insight and the recognition of novel semantic relations. The observed findings motivate an integrative framework for understanding the neural foundations of adaptive behavior, suggesting that core elements of cognitive flexibility emerge from a distributed network of brain regions that support specific competencies for human intelligence.

Introduction

Cognitive flexibility is a hallmark of human thought, enabling the ability to adapt in the face of environmental change and to generate new ideas that drive innovation and promote growth and discovery (Badre and Wagner, 2006; Hennessey and Amabile, 2010; Leuner and Gould, 2010; Stemme et al., 2005). Despite its central role in human mental life, remarkably little is known about the neural architecture of cognitive flexibility. At its core, cognitive flexibility reflects the adaptability of thought and behavior (Collins and Koechlin, 2012) and promotes the fluent generation of ideas (Costafreda et al., 2006; Gilhooly et al., 2007) and the recognition of novel semantic relations (Jung-Beeman et al., 2004). Cognitive flexibility can be expressed in multiple ways, ranging from the exhibition of genius in the arts and sciences to more mundane acts of adaptive problem solving in everyday life. Given the sheer breadth of conditions under which cognitive flexibility can manifest itself, there is a growing consensus among researchers that it is not a unitary construct (for reviews, see Barron and Harrington, 1981; Batey and Furnham, 2006; Runco, 2004). Rather, the necessary and sufficient conditions for adaptive behavior will vary as a function of task demands and their corresponding cognitive requirements. This perspective has motivated an increasing number of scientists to suggest that cognitive flexibility may depend on multiple information processing systems rather than originate from a unitary cognitive 'module' (Barron and Harrington, 1981; Batey and Furnham, 2006; Runco, 2004).

Parallel developments in cognitive neuroscience support this emergent perspective (for reviews, see Arden et al., 2010; Dietrich and Kanso, 2010). Dietrich and Kanso (2010) reviewed the neuroscience literature on cognitive flexibility and creative problem solving, examining studies that assessed: (1) divergent thinking (i.e., the ability to generate multiple solutions to open-ended problems); (2) cognition

* Corresponding author at: Decision Neuroscience Laboratory, Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana–Champaign, Champaign, IL 61820, USA.
E-mail addresses: barbey@illinois.edu (A.K. Barbey), jgrafman@ric.org (J. Grafman).
URL: http://www.DecisionNeuroscienceLab.org/ (A.K. Barbey).

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of art and music; and (3) insight (i.e., the recognition of novel semantic relations). Rather than identifying a unitary brain module that implements these aspects of adaptive behavior and creative problem solving, Dietrich and Kanso (2010) observed a highly variable pattern of brain activity; identifying, for example, only diffuse recruitment of the prefrontal cortex across studies. Arden et al. (2010) reached a similar conclusion after reviewing the neuroscience literature on adaptive problem solving, having found no consistent pattern of brain activation across different experimental tasks and methods.

The inconsistent pattern of findings across studies raises fundamental questions about the usefulness of the theoretical constructs motivating the search for the neural bases of adaptive behavior and creative problem solving. Arden et al. (2010) point to the absence of task specificity as a major contributor to the heterogeneity of findings and suggest that a psychometric approach for characterizing the cognitive foundations of adaptive behavior is needed. This critique underscores the need for a coherent methodology to study specific and dissociable mental processes that underlie cognitive flexibility.

The lack of convergence within the literature on adaptive behavior and creative problem solving resonates to studies that have assessed the relationship between cognitive flexibility and other mental processes, such as general intelligence. Kim (2005), for example, conducted a meta-analysis of 21 studies of adaptive problem solving and intelligence, and found that performance across these domains was only weakly correlated (0.17; Kim, 2005). Nusbaum and Silvia (2011), however, challenged this conclusion, reporting a latent correlation of 0.42 between adaptive problem solving and fluid intelligence (Nusbaum and Silvia, 2011). In addition to advocating a psychometric approach, these authors emphasized the importance of investigating cognitive flexibility in a broader light, recommending that future research assess social and emotional processes that may play a central role in adaptive behavior.

Research on the neural bases of cognitive flexibility would therefore benefit from a more precise characterization of its cognitive foundations, applying a psychometric approach to identify key competencies of adaptive behavior and their relation to a broad spectrum of cognitive, emotional, and social processes. The application of lesion methods to map the information processing architecture of cognitive flexibility would further advance our understanding of the core mechanisms that give rise to adaptive behavior (Barbey et al., 2012c; Gläscher et al., 2010; Woolgar et al., 2010). Neuropsychological patients with focal brain lesions provide a valuable opportunity to study the neural mechanisms of cognitive flexibility, supporting the investigation of lesion-deficit associations that elucidate the necessity of specific brain structures. Although the neural foundations of cognitive flexibility remain to be assessed using lesion methods, the broader neuropsychological patient literature has provided significant insight into the neural bases of higher cognitive functions, such as general intelligence (Barbey et al., 2012c; Basso et al., 1973; Bechara et al., 1994; Black, 1976; Blair and Cipolotti, 2000; Bugg et al., 2006; Burgess and Shallice, 1996; Duncan et al., 1995; Eslinger and Damasio, 1985; Gläscher et al., 2009, 2010; Isingrini and Vazou, 1997; Kane and Engle, 2002; Parkin and Java, 1999; Roca et al., 2010; Shallice and Burgess, 1991) and working memory (Barbey et al., 2011; Barbey et al., 2012d; Baldo and Dronkers, 2006; D'Esposito and Postle, 1999; D'Esposito et al., 2006; Muller et al., 2002; Tsuchida and Fellows, 2009; Volle et al., 2008). These studies, however, share one or more of the following features: diffuse (rather than focal) brain lesions, lack of comparison subjects carefully matched for pre- and post-injury performance measures, exclusive use of neuropsychological tests without an assessment of cognitive flexibility, and lack of latent variable modeling to derive error-free indices of the psychological constructs of interest. As a consequence, there has been no comprehensive evaluation of cognitive flexibility in a relatively large sample of patients with focal brain damage, and across a broad range of tasks and stimulus material.

Motivated by these considerations, we studied the neural bases of cognitive flexibility in a large sample of patients with focal brain injuries ($n = 149$). We applied latent variable modeling to characterize the psychometric properties of cognitive flexibility and we then assessed cognitive flexibility with respect to a broad spectrum of cognitive and social processes, including psychometric intelligence (Wechsler Adult Intelligence Scale), emotional intelligence (Mayer, Salovey, Caruso Emotional Intelligence Test), and personality traits (Neuroticism–Extroversion–Openness Personality Inventory). Finally, we applied voxel-based lesion-symptom mapping to elucidate the information processing architecture of cognitive flexibility, identifying core brain mechanisms that contribute to adaptive aspects of intellectual function.

Materials and methods

Participant data

Participants were drawn from the Phase 3 Vietnam Head Injury Study (VHIS) registry, which includes American male veterans who suffered brain damage from penetrating head injuries in the Vietnam War ($n = 149$). All subjects gave informed written consent. Phase 3 testing occurred between April 2003 and November 2006. Demographic and background data for the VHIS are reported in Supplemental Table 1 (see also Barbey et al., 2011, 2012c; Koenigs et al., 2009; Raymont et al., 2010). No effects on test performance were observed in the VHIS sample on the basis of demographic variables (e.g., age, years of education, lesion size). It is important to note that all individuals in the VHIS sample are males and therefore conclusions drawn from this study are restricted to an adult male population.

Lesion analysis

CT data were acquired during the Phase 3 testing period. Axial CT scans without contrast were acquired at the Bethesda Naval Hospital on a GE Medical Systems Light Speed Plus CT scanner in helical mode (150 slices per subject, field of view covering head only). Images were reconstructed with an in-plane voxel size of 0.4×0.4 mm, overlapping slice thickness of 2.5 mm, and a 1 mm slice interval. Lesion location and volume were determined from CT images using the Analysis of Brain Lesion software (Makale et al., 2002; Solomon et al., 2007) contained in MEDx v3.44 (Medical Numerics) with enhancements to support the Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002). Lesion volume was calculated by manual tracing of the lesion in all relevant slices of the CT image then summing the traced areas and multiplying by slice thickness. A trained neurologist performed the manual tracing, which was then reviewed by an observer who was blind to the results of the neuropsychological testing. Inter-rater reliability analysis demonstrated reliable consensus among neurologists (Barbey et al., 2011, 2012a, 2012b, 2012c, 2012d, 2013). As part of this process, the CT image of each subject's brain was spatially normalized to a CT template brain image. This template was created by spatial normalization of a neurologically healthy individual's CT brain scan to MNI space (Collins et al., 1994) using the Automated Image Registration program (Woods et al., 1993). For each subject, a lesion mask image in MNI space was saved for voxel-based lesion-symptom mapping (Bates et al., 2003). This method applies a *t*-test to compare, for each voxel, scores from patients with a lesion at that voxel contrasted against those without a lesion at that voxel. The reported findings were thresholded using a False Discovery Rate correction of $q < 0.05$. To ensure sufficient statistical power for detecting a lesion-deficit correlation, our analysis only included voxels for which 4 or more patients had a lesion. The lesion overlap map for the entire VHIS patient sample is illustrated in Supplemental Fig. 1.