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# Examining the multifactorial nature of a cognitive process using Bayesian brain-behavior modeling

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ABSTRACT

Establishing relationships among brain structures and cognitive functions is a central task in cognitive neuroscience. Existing methods to establish associations among a set of function variables and a set of brain regions, such as dissociation logic and conjunction analysis, are hypothesis-driven. We propose a new data-driven approach to structure–function association analysis. We validated it by analyzing a simulated atrophy study. We applied the proposed method to a study of aging and dementia. We found that the most significant age-related and dementia-related volume reductions were in the hippocampal formation and the supramarginal gyrus, respectively. These findings suggest a multi-component brain-aging model.



## 1. Introduction

A central task in cognitive neuroscience is the establishment of relationships among brain structures and neural activity on the one hand, and cognitive functions or processes on the other. Such relationships are referred to as brain-behavior or structure–function associations. Delineating brain-behavior associations is of fundamental importance to understand the neural bases of cognition. The classic examples of brain-behavior association involve the neural bases of language [1]. Broca and Wernicke examined patients with brain damage, who had difficulty with language as a result (aphasia). Broca reported a lack of language production in patients with damage to the posterior and inferior regions of the left frontal lobe (Broca's area); and Wernicke reported that patients who have damage to the posterior/superior aspect of the left temporal lobe (Wernicke's area) could no longer comprehend language. Putting these two studies together, we have a brain-behavior association involving two brain regions (Broca's area and Wernicke's area) and two cognitive processes (producing language and comprehending language). Broca's area is specialized for producing language, whereas Wernicke's area is specialized for comprehending language.

In this manuscript, we focus on the problem of establishing associations among a set of function variables (denoted by $F$) and a set of brain regions (denoted by $R$). Two examples of such an analysis are dissociation analysis [2–4] and conjunction analysis [5–8]. Both inferential methods have played important roles in cognitive neuroscience.

One of the fundamental approaches to the demonstration of structure–function associations in lesion-based brain studies is to establish associations and dissociations [3,4]. An association pattern is established when damage in brain region A disrupts the performance of task $\alpha$. A dissociation pattern is established when damage in brain region A disrupts the performance of task $\alpha$ but not that of task $\beta$; in this case, region A and task $\beta$ are dissociated. A more firm approach to the demonstration of brain-behavior associations is to establish a double-dissociation model [2]. A double-dissociation pattern is established when damage in brain region A impairs task $\alpha$ but not task $\beta$, whereas damage in region B impairs task $\beta$ but not task $\alpha$. In a double dissociation analysis, investigators model interactions among two function variables, $F_\alpha$ and $F_\beta$, and two brain structures $R_A$ and $R_B$. The observation of double dissociation provides evidence of functionally distinct neural systems, which is central to the delineation of underlying mechanisms.

In conjunction analysis, the central question is "which brain regions are damaged in all tasks?" For example, in a study involving two function variables where $F_\alpha$ represents the language production deficit and $F_\beta$ represents the language comprehension deficit, our goal is to find brain regions that are damaged in patients with language production deficit and language comprehension deficit.

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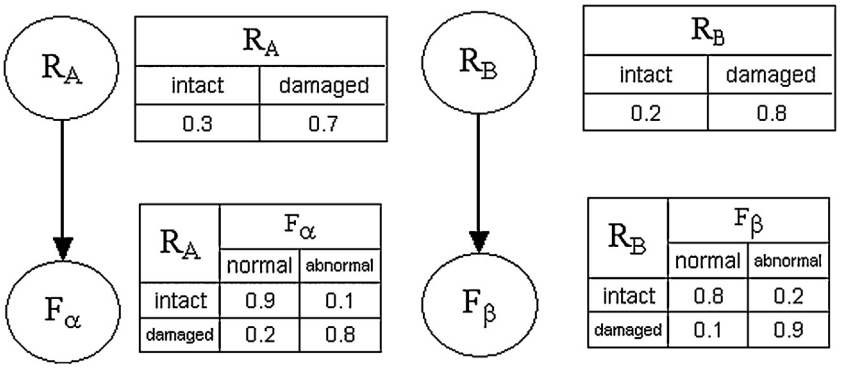


**Fig. 1.** A Bayesian network represents double dissociation in a neuropsychology study.

Existing methods for the elucidation of brain-behavior associations have two major limitations. First, these methods are confirmatory; that is, they are designed to confirm a particular hypothesis, rather than compare models. Davies recognized this limitation when he said "None of this be allowed to suggest that double dissociation rules out the possibility of any kind of alternative explanation" [9]. For example, consider a study with model $M_1$, in which damage in brain region A impairs task $\alpha$ but not task $\beta$, whereas damage in region B impairs task $\beta$ but not $\alpha$. This model may reasonably explain the data observed in this study; however, this analysis ignores the possibility that there exist one or more additional models that offer more-plausible explanations of these data.

The second major limitation of existing methods is their focus on functional specialization. Functional specialization and functional integration are two fundamental principles of brain functional organization [10]. Functional specialization posits that a brain region is specialized for some aspect of a cognitive process, whereas functional integration emphasizes interactions among brain regions. Existing approaches do not consider regional interactions and therefore cannot detect functional-integration patterns.

We propose a new method, Bayesian brain-behavior modeling (BBM), for the delineation of brain-behavior associations. BBM directly models the joint-probability distribution among brain regions and task variables, and directly addresses the two major limitations of existing methods for brain-behavior associations. First, BBM has a model-comparison mechanism: from a set of candidate theories (the model space), BBM searches for the model that is most consistent with the observed data. Second, BBM generates a network model, which provides a natural framework within which to explore functional integration: brain regions are modeled as nodes, and interactions are modeled as edges between nodes.

As a data-driven approach, BBM accepts, but does not require, the specification of a prior model. BBM can reveal arbitrary interactions among brain regions and function variables, not limited to the dissociation pattern or conjunction pattern.

## 2. Methods

The overarching goal of BBM is to delineate structure–function associations. Let $R_A$ denote a feature associated with brain region A, such as the presence of activation in a functional MR (fMR) experiment, or the presence of a lesion or morphological feature manifest on structural MR. Let $F_\alpha$ denote the functional assessment of a process $\alpha$ (e.g., performance on a particular task); $F_\alpha$ could also represent the presence or absence of a disorder, such as Alzheimer's disease. In this framework, we model a structure–function association as an association between $\{R_A\}$ and $\{F_\alpha\}$.

### 2.1. Background: Bayesian networks

BBM is based on Bayesian network (BN) models [11]. A Bayesian network is a probabilistic graphical model that specifies a joint probability distribution over a set of variables $V = \{X_1, X_2, \ldots, X_n\}$. A Bayesian network $B$ consists of two components: a structure $S$, and parameters $\Theta$; i.e., $B = (S, \Theta)$. The structure of the Bayesian network describes the probabilistic associations among the variables, and is represented as a directed acyclic graph. Nodes in this graph represent variables of interest, such as brain regions or clinical variables. A directed edge in this graph from a variable $X_i$ to $X_j$, written as $X_i \rightarrow X_j$, indicates that the variables $X_i$ and $X_j$ are associated, that $X_i$ is a parent node of $X_j$, and that $X_j$ is a child node of $X_i$. Each variable in a Bayesian network is associated with a conditional-probability distribution $Pr(X_i|pa(X_i))$, where $pa(X_i)$ represents the parent set of $X_i$. A discrete Bayesian network can represent any joint distribution over these discrete variables [11].

Fig. 1 shows a simple example of a Bayesian network. There are four variables in this Bayesian network: two brain regions ($R_A$ and $R_B$) and two function variables ($F_\alpha$ and $F_\beta$). This Bayesian network represents a scenario in which $F_\alpha$ is probabilistically determined by the state of region $R_A$, and $F_\beta$ is probabilistically determined by that of $R_B$; therefore, in this network, $pa(F_\alpha) = \{R_A\}$ and $pa(F_\beta) = \{R_B\}$.

When variables are categorical, $Pr(X_i|pa(X_i))$ can be represented as a conditional probability table. Let $\theta_{ijk} = Pr(X_i = k|pa(X_i) = j)$ be the conditional probability of $X_i$ assuming state $k$ given that its parents, $pa(X_i)$, assume joint state $j$. If $X_i$ does not have parents, then $\theta_{ijk}$ is the marginal probability distribution of $X_i$. $\Theta = \{\theta_{ijk}\}$ represents the parameters of a Bayesian network, from which the joint distribution over all variables can be computed. In Fig. 1, the conditional probability $Pr(F_\alpha = \text{abnormal}|R_A = \text{damaged}) = 0.8$ means that the probability of a subject's having abnormal $F_\alpha$ is 0.8 when region $R_A$ is damaged.

A critical notion in Bayesian network modeling is that of a *Markov blanket*. In probabilistic terms, the Markov blanket of node $X$, denoted by $mb(X)$, is the minimum set of variables that renders $X$ conditionally independent of all other variables in the Bayesian network. In the context of predicting the state of $X$ based on knowledge of a subset of the variables in a Bayesian network, we achieve greatest accuracy when we know the states of the Markov blanket of $X$. That is, nodes in the Markov blanket of $X$ are jointly most predictive of $X$.

One of the advantages of the Bayesian network representation is its powerful inferential capability [11]. The inference task is to find the posterior distribution of a set of outcome variables, given values for evidence variables. For example, in Fig. 1, we may be interested in the posterior probability that $F_\alpha$ is abnormal, given that $R_A$ is damaged. In this query, the outcome variable is $F_\alpha$, and the evidence variable is $R_A$. Standard BN inference algorithms [12] can efficiently calculate such queries.