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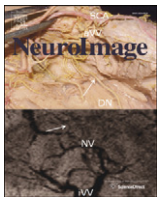

Review

Neuroimaging in aphasia treatment research: Standards for establishing the effects of treatment

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ABSTRACT

The goal of this paper is to discuss experimental design options available for establishing the effects of treatment in studies that aim to examine the neural mechanisms associated with treatment-induced language recovery in aphasia, using functional magnetic resonance imaging (fMRI). We present both group and single-subject experimental or case-series design options for doing this and address advantages and disadvantages of each. We also discuss general components of and requirements for treatment research studies, including operational definitions of variables, criteria for defining behavioral change and treatment efficacy, and reliability of measurement. Important considerations that are unique to neuroimaging-based treatment research are addressed, pertaining to the relation between the selected treatment approach and anticipated changes in language processes/functions and how such changes are hypothesized to map onto the brain.

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Introduction

The goal of this paper is to provide guidelines for designing and implementing treatment studies that aim to examine the neural mechanisms associated with language recovery in aphasia, using functional brain imaging. This research requires measurement of neural changes from pre to post intervention using functional magnetic resonance imaging (fMRI), PET (positron emission tomography) or other methods (e.g. ERPs). In addition, and the focus of the present paper, careful measurement of language and/or cognitive changes from pre- to post-intervention and interpretation of the relationship between the two sets of changes (neural and behavioral) are required. As pointed out in recent reviews, there is variability in regions of the brain recruited by people with aphasia to support language recovery both within and across studies (see Crinion and Leff, 2007; Meinzer et al., 2011, Thompson and den Ouden, 2008). Possible reasons for this may be related to the treatment provided and the experimental designs used to evaluate its efficacy. Although there have been recent methodological advances in the measurement of language behavior in individuals who have suffered a stroke using fMRI (Abutalebi et al., 2009; Bonakdarpour et al., 2007; Fridriksson et al., 2006; Kurland et al., 2004; Marcotte and Ansaldo, 2010; Peck et al., 2004, Rorden et al., 2009), few studies have systematically investigated the effects of rehabilitation on brain mechanisms recruited to support recovery. In this paper, we address a series of questions on the design of treatment studies when treatment effects are assessed both behaviorally and in terms of brain activations, presenting the consensus derived from discussions among experts in neuroimaging and aphasia at the Neuroimaging in Aphasia Treatment Research Workshop, held at Northwestern University in September, 2009. Because the nature of the experimental design, task manipulations and spatio-temporal manifestations of the data are different for fMRI studies and ERP studies, we limit our discussion to fMRI studies in this paper.

The first section of the paper considers different options for designing treatment experiments. Specifically, we discuss group versus single-subject experimental or case-series design options for establishing the effects of treatment and consider their advantages and disadvantages. We examine the general components of and requirements for treatment research studies, including the operational definition of variables, the criteria for defining behavioral change and treatment efficacy, and the reliability of measurement. We also point out unique considerations required in neuroimaging-based treatment research, concerning the relation between the treatment approach selected and the anticipated changes in language processes/functions and hypotheses about how changes in language function are expected to map onto changes in brain function. Other design considerations relevant to relating the effects of treatment directly to changes in brain function are covered in other papers in this series. For example, questions related to the reliability of activation patterns seen on repeated scans, fMRI task selection, and single-subject versus group approaches to analysis of the fMRI data are discussed in Rapp et al. (2013–this volume) and Meinzer et al. (2013–this volume).

Establishing the effects of treatment (internal validity)

The first essential requirement in designing a treatment study to evaluate treatment-induced neural plasticity is that the experiment uses a design that allows the researcher to establish that behavioral changes are a result of treatment (internal validity). There are several experimental approaches for accomplishing this—group approaches that compare the performance of experimental and control groups, and single-subject approaches that compare performance between experimental and control phases in the same participant. Both design types, if implemented properly, rule out the influence of extraneous variables, (e.g., environmental or participant factors), on the language behaviors or processes under study. The philosophy is the same for both: between-group experimental designs compare the performance of groups of individuals (experimental and control groups), whereas, single-subject experimental designs compare the performance of individual participants during experimental and control (baseline) phases. The idea is that similar extraneous variables are at play in both the experimental and control groups or conditions and that the influence of these variables on the behavior(s) under study can be ruled out by comparing patterns of performance between the two groups or conditions (see Thompson, 2006).

In studies examining the neural mechanisms of treatment-induced language recovery, the experimental treatment design employed is not only relevant to establishing the efficacy of treatment, but it also impacts analysis of the neuroimaging data. Between-group treatment design requires averaging the treatment effect in the experimental groups and comparing change over time between the treated and untreated groups. Thus, to estimate the effects of treatment on brain processing, a group approach to analysis of the fMRI data is required. However, the group approach may be confounded because it is possible (and likely) that not all participants in the experimental group will change to the same extent. As pointed out by Meinzer et al. (2013–this volume), group analyses of aphasic neuroimaging data, in general, should be approached with caution because of individual differences in variables such as lesion site and extent, unless the goal of the study is to account for the effects of such variables on either treatment-induced behavioral performance or neural recruitment patterns, which requires large, rather than small sample sizes. Conversely, single-subject/case-series designs require measurement of language change throughout the treatment period, with no data averaging across study participants. The neuroimaging data derived from pre- and post-treatment scans of individual participants then can be examined and evaluated with regard to treatment improvement. However, there is an inherent lack of power to detect changes in activation over time when comparing changes in neural activation in individual study participants. It is therefore, important during the experimental design phase to include a sufficient number of experimental trials in the neuroimaging task. In addition, this practice has drawbacks with regard to external validity, or generalization to other individuals with aphasia. However, this latter problem can be addressed by replication of treatment across participants (see below for further discussion of single-subject experimental designs with regard to replication across study participants).

Independent of experimental design, it is important to conduct a power analysis and sample size estimation to justify the inclusion of a particular sample size and interpretation of a particular effect size. Particularly for neuroimaging treatment studies that are inherently clinical in nature, justifying the sample size and benchmarks for effect size can be very beneficial in evaluating what constitutes a clinically (or theoretically) important effect.

Establishing experimental control between groups

Between-group designs require at least two groups of participants, an experimental group that receives the (experimental) treatment, and a control group that either does not receive treatment or is provided with an alternative treatment or placebo. At the beginning of the study, both experimental and control participants are tested on one or all dependent measures, both behavioral and neuroimaging, and at the end of the study these measures are repeated. Performance on each measure is averaged across participants in each group at each time point and a treatment effect is established when the experimental group shows significantly greater pre- to post-treatment changes than the control group. One requirement of between group experimental designs is that study participants be randomly selected from a population of people (e.g., those with aphasia or a particular aphasia profile). When random selection is not accomplished, an unwarranted extrapolation from the sample to the study population may occur, creating a problem of sample bias. Notably, when studying disorders