Developmental Cognitive Neuroscience 18 (2016) 101–112

Contents lists available at ScienceDirect

Developmental Cognitive Neuroscience

journal homepage: http://www.elsevier.com/locate/dcn

Considerations for MRI study design and implementation in pediatric and clinical populations

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ARTICLE INFO

Article history:
Received 17 July 2015
Received in revised form 3 December 2015
Accepted 10 December 2015
Available online 17 December 2015

Keywords:
Neuroimaging
Development
Neuropsychiatric disorders
Inclusion/exclusion criteria
Mock scanner
Motion artifact
Tourette syndrome

ABSTRACT

Human neuroimaging, specifically magnetic resonance imaging (MRI), is being used with increasing popularity to study brain structure and function in development and disease. When applying these methods to developmental and clinical populations, careful consideration must be taken with regard to study design and implementation. In this article, we discuss two major considerations particularly pertinent to brain research in special populations. First, we discuss considerations for subject selection and characterization, including issues related to comorbid conditions, medication status, and clinical assessment. Second, we discuss methods and considerations for acquisition of adequate, useable MRI data. Given that children and patients may experience anxiety with the scanner environment, preventing participation, and that they have a higher risk of motion artifact, resulting in data loss, successful subject compliance and data acquisition are not trivial tasks. We conclude that, as researchers, we must consider a number of issues when using neuroimaging tools to study children and patients, and we should thoughtfully justify our choices of methods and study design.

1. Introduction

With the rising use of human neuroimaging techniques to answer research questions of developmental and clinical significance, there is increasing need for a comprehensive understanding of strategies for collecting imaging data in special populations. While investigators continue to develop new approaches for acquiring quality data, the field would benefit from further refinements and updated strategies to optimize the cost:benefit ratio of our imaging studies. Here, we discuss two overarching considerations for MRI data acquisition in pediatric and clinical populations: (1) subject selection and characterization, and (2) methods for acquiring adequate, high-quality imaging data. These topics often prompt debate or criticism from reviewers for journals and funding agencies. Thus, it is important that these key issues be well understood.

In this article, we refer often to our own experience collecting data from children with Tourette syndrome (TS), which exemplifies many of the key issues researchers face in acquiring data from pediatric and clinical populations. TS is a neuropsychiatric disorder with childhood onset. Thus, many of the issues that arise in TS research are similar to those in studies of typical development as well as other childhood disorders, such as autism and attention deficit hyperactivity disorder (ADHD). TS is characterized by motor and vocal tics, which are brief, unwanted movements or sounds (Leckman et al., 2006; Black et al., 2014); common tics include exaggerated eye blinking, head jerking, sniffing, and throat clearing. Therefore, special considerations are required with respect to motion during data acquisition, as is the case in studies of child populations in general as well as other movement disorders, including Parkinson disease and dystonia. Also, like many neuropsychiatric disorders, TS has a high comorbidity burden, with particularly high rates of comorbid ADHD and obsessive compulsive disorder (OCD) (Freeman et al., 2000). Moreover, patients can be treated with behavior therapy (e.g., Piacentini et al., 2010) or with a variety of psychoactive medications, including antipsychotics, centrally acting adrenergic agents, and SSRIs (Black et al., 2014; Eddy et al., 2011). Thus, issues that must be considered with respect to comorbid conditions and medication status in studies

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http://dx.doi.org/10.1016/j.dcn.2015.12.005

of TS also apply to research in other clinical populations. Further, while we focus here on MRI data collection in typical and atypical development, the issues discussed apply to studies in a wide range of clinical populations and across the lifespan.

2. Considerations for subject selection and characterization

An important, early step for neuroimaging research is appropriate study sample selection. While sample selection may seem trivial initially (e.g., research aimed at studying TS will include children with a diagnosis of TS), there are important issues to consider when determining study inclusion/exclusion criteria. One might think that the best approach to studying any neuropsychiatric population is to restrict subject selection to a "clean" or "pure" sample with no comorbid conditions or current medications. While there are scenarios in which this approach is appropriate, it is underappreciated that such an approach can raise as many concerns as it solves. Here, we discuss these concerns, offer our opinions, and describe strategies implemented in our own research studies.

2.1. What is the ultimate goal of your research?

Investigators must consider the ultimate purpose of their research program. When designing an experiment, researchers regularly evaluate aspects of study design (including subject inclusion/exclusion criteria) with respect to the particular experimental question at hand. We argue that in addition to considerations related to the specific experiment, investigators ought to reflect on the overall motivation behind that study and the eventual goal in the context of the greater research program. In other words, what does the "Significance" or "Impact" section of the grant supporting the work claim? Is the aim of the work to understand the neural correlates of a particular disorder as a whole rather than a single symptom? Is the overarching objective to inform future discovery of better treatment targets or clinical care? In our own studies and often in other laboratories, the answer to these questions is "yes." In such cases, results that are generalizable to most individuals with the disorder are most desirable. Indeed, there is research aimed at understanding and/or targeting one specific symptom (e.g., tics, impulsivity) of a complex disorder (e.g., TS, ADHD). For these studies, it may be more appropriate to take a restricted approach to subject inclusion in order to isolate the symptom under study. Yet, researchers must understand the important distinction between studying the mechanisms of a specific *symptom* and studying the mechanisms of a *disorder*. Typically, a disorder is characterized by many types of symptoms—thus, the appellation "syndrome". TS, for example, while defined by the involvement of motor/vocal tics, most often presents clinically with any one of a number of cognitive and behavioral symptoms (Freeman et al., 2000; Martino et al., 2013). Therefore, any study of TS must consider whether the goal is to investigate tics in isolation or the clinical presentation typical of the majority of patients. If only a small percentage of individuals with the disorder have no other known neuropsychiatric problems, as is the case with TS, research limited to understanding that small fraction of individuals may have limited applicability, at least initially. Even a study focused on the neural mechanisms of tics (or treating tics) in isolation with a clear justification for studying a pure and unmedicated sample is but a first step toward understanding TS as a whole. Such a study will require follow-up research to test whether or not the findings generalize to those patients with more typical clinical presentation of the disorder (i.e., with comorbid conditions, medication history). Moreover, if the translational significance of the research is to inform future discovery of treatments, researchers ought to consider whether the population studied includes those individuals who are most likely to seek clinical care (Gilbert and Buncher, 2005). Thus, when the ultimate goal is to understand or treat the complex disorder, we argue that ignoring those patients with the most typical clinical presentations will limit the clinical applicability of the research, impeding its ultimate purpose. In other words, we prefer to collect an ecologically valid sample for most neuroimaging (and non-neuroimaging) studies. There are two approaches one can take to achieve such ecological validity: (1) first study a pure sample, and then conduct follow up research to test the generalizability of the results, or (2) study a larger heterogeneous sample, and conduct subgroup analyses to test the specificity of the results. Some may opt for the former option, but we opt for the latter. Either way, an ecologically valid sample will ultimately need to be studied in order to obtain truly translational results.

We recognize that ecological validity may not be entirely feasible for some neuroimaging research. For example, many MRI studies in autism spectrum disorders (ASD) include only patients with high-functioning ASD. Lower functioning ASD patients may not be able to lie inside the scanner without sedation or may not be able to understand or comply with task instructions. Therefore, it is not practical to include these lower functioning children with ASD in an fMRI study of working memory, for example. In such cases, it is defensible to exclude subjects who could not practically participate, but limitations in generalizability must be acknowledged. When feasibility is not a limiting factor, however, we recommend striving for ecological validity. In our own studies, we aim to place the burden of heterogeneity on the analysis, not on narrowly focused recruitment, allowing for data collection that best captures the real-world population. Often, this strategy will necessitate large sample sizes in order to capture the heterogeneity, i.e., including both treated and untreated patients, and those with and without diagnosed comorbid conditions. In the following subsections, we discuss the less commonly considered issues with respect to comorbid conditions and medication status that have informed our decisions for subject selection, leading to our preference for ecologically valid samples in most of our neuroimaging studies.

2.2. Considering comorbid conditions

Comorbidities are quite common, and for some disorders the presence of comorbid conditions is the rule rather than the exception. TS is a prime example, as only 10% of individuals with TS have no other known comorbidities (Freeman et al., 2000). The most common comorbid conditions are ADHD and anxiety, most frequently OCD. In fact, 50–60% of children with TS also have ADHD and 30–40% also have OCD, and so TS, OCD, and ADHD are often discussed as an interconnected triad (Kurlan, 2010). Therefore, if one is interested in studying TS as a condition, these common comorbidities must be considered. Selecting only those TS patients with no comorbid conditions will be logistically difficult from a recruitment standpoint and will usually limit the generalizability of the results. TS is not alone in this regard; mood disorders, anxiety, and sleep disturbances often co-occur (Vazquez et al., 2014; Chorney et al., 2008), ADHD is frequently comorbid with conduct disorder, oppositional defiant disorder, dyslexia, and learning disabilities (Pliszka, 1998; Germano et al., 2010), and substance abuse is highly comorbid with mood and anxiety disorders (Conway et al., 2006). Thus, these principles apply to many studies of neuropsychiatric disorders.

Reviewers of grants and research manuscripts often request that inclusion and exclusion criteria result in "clean" or "pure" samples of patient populations, meaning excluding all comorbid conditions. It has become easy to make such a request reflexively, and colleagues often support it as reasonable. We argue that the issue is more complicated, and requires careful consideration of the consequences and limitations that arise when using pure vs.