Int. J. Devl Neuroscience 58 (2017) 17–25

Contents lists available at ScienceDirect

International Journal of Developmental Neuroscience

journal homepage: www.elsevier.com/locate/ijdevneu

Measuring neuroplasticity associated with cerebral palsy rehabilitation: An MRI based power analysis

Lee B. Reid [a,b,1], Alex M. Pagnozzi [a,b,*,1], Simona Fiori [c], Roslyn N. Boyd [b], Nicholas Dowson [a], Stephen E. Rose [a]

[a] The Australian e-Health Research Centre, CSIRO, Brisbane, Australia
[b] Queensland Cerebral Palsy and Rehabilitation Research Centre, Faculty of Medicine, The University of Queensland, Brisbane, Australia
[c] Department of Clinical and Experimental Medicine, Università di Pisa, Pisa, Italy

ARTICLE INFO

Article history:
Received 1 December 2016
Received in revised form 23 January 2017
Accepted 23 January 2017
Available online 24 January 2017

Keywords:
Statistical power
Neuroplasticity
Neurorehabilitation
Cerebral palsy
Randomised-controlled-trial power
White-matter
Cortical-thickness
Diffusion MRI
Multimodal MRI
Functional MRI

ABSTRACT

Researchers in the field of child neurology are increasingly looking to supplement clinical trials of motor rehabilitation with neuroimaging in order to better understand the relationship between behavioural training, brain changes, and clinical improvements. Randomised controlled trials are typically accompanied by sample size calculations to detect clinical improvements but, despite the large cost of neuroimaging, not equivalent calculations for concurrently acquired imaging neuroimaging measures of changes in response to intervention. To aid in this regard, a power analysis was conducted for two measures of brain changes that may be indexed in a trial of rehabilitative therapy for cerebral palsy: cortical thickness of the impaired primary sensorimotor cortex, and fractional anisotropy of the impaired, delineated corticospinal tract. Power for measuring fractional anisotropy was assessed for both region-of-interest-seeded and fMRI-seeded diffusion tractography. Taking into account practical limitations, as well as data loss due to behavioural and image-processing issues, estimated required participant numbers were 101, 128 and 59 for cortical thickness, region-of-interest-based tractography, and fMRI-seeded tractography, respectively. These numbers are not adjusted for study attrition. Although these participant numbers may be out of reach of many trials, several options are available to improve statistical power, including careful preparation of participants for scanning using mock simulators, careful consideration of image processing options, and enrolment of as homogeneous a cohort as possible. This work suggests that smaller and moderate sized studies give genuine consideration to harmonising scanning protocols between groups to allow the pooling of data.

1. Introduction

Motor rehabilitation for children with cerebral palsy (CP) is currently hampered by our lack of understanding of how the brain responds to rehabilitative therapy at microscopic and macroscopic scales (Reid et al., 2015). Researchers are increasingly looking to quantify brain reorganisation in clinical trials of motor rehabilitation in order to better understand the relationship between behavioural training, brain changes, and clinical improvements, and/or to index subtle changes which may not be reflected in clinical assessments (Boyd et al., 2013). This information may ultimately inform rehabilitation, for example by elucidating factors that interfere with motor learning, such as maladaptive plasticity, or disrupted network deficits that prevent neuroplastic changes (Reid et al., 2015).

MRI data can be analysed in a variety of ways to acquire metrics of brain changes, including changes in cortical thickness, and changes in diffusion metrics of white matter (Reid et al., 2015). Cortical thickness is a structural measure related to several neurophysiological changes, including variations in neuronal, glial and synaptic density (Zatorre et al., 2012). This measure has been used to quantify structural changes related to plasticity in animal studies (Anderson et al., 2002), and correlated with cognitive performance in several human studies (Dickerson et al., 2009; Narr et al., 2007; Shaw et al., 2006). Diffusion MRI is typically used to

* Corresponding author at: The Australian e-Health Research Centre, CSIRO, Brisbane, Australia.
E-mail addresses: lee.reid@csiro.au (L.B. Reid), alex.pagnozzi@csiro.au (A.M. Pagnozzi), s.fiori@fsm.unipi.it (S. Fiori), r.boyd@uq.edu.au (R.N. Boyd), nicholas.dowson@csiro.au (N. Dowson), stephen.rose@csiro.au (S.E. Rose).
[1] Lee B. Reid and Alex M. Pagnozzi are joint first authors.

http://dx.doi.org/10.1016/j.ijdevneu.2017.01.010
0736-5748/

investigate white-matter microstructure, and metrics such as fractional anisotropy (FA) applied to the corticospinal tract have been found to correlate with a number of clinical scores in CP (Reid et al., 2015; Scheck et al., 2012). A small number of longitudinal studies have demonstrated that motor training can induce changes in cortical thickness and diffusion metrics in animals (Anderson et al., 2002) and in adults who do not have CP (Scholz et al., 2009; Taubert et al., 2010). Speech therapy has also been demonstrated to alter cortical thickness of the left posterior superior temporal gyrus in children with children with CP (Kadis et al., 2014).

Power analyses are relied on to plan clinical-trial enrolment numbers, but are usually based on expected behavioural improvements, rather than secondary image-derived measures of neuroplasticity potentially conducted as a part of these trials. Clinical trials based on these behavioural changes alone may be underpowered for detecting changes with neuroimaging, because neuroimaging and clinical changes may have substantially different effect sizes and variance. Underpowered trials are wasteful in terms of time and resources but, to the best of the authors' knowledge, no literature is readily available for ensuring rehabilitative trials are sufficiently powered with respect to neuroimaging. The present work aims to address this gap by providing participant numbers required to detect secondary-outcome changes in both cortical thickness and tractography-derived diffusion metrics in white matter, which may occur as a result of primary therapeutic intervention. Required n values for a variety of effect sizes are presented. These effect sizes are based on published literature and brain changes measured in a longitudinal motor-learning study of healthy adults (Reid et al., 2016c; Sale et al., 2016). Population-appropriate variances were calculated by applying methods from this study to images from children with unilateral CP. This work pertains specifically to studies wishing to detect the amplitude of structural and/or microstructural measures in specific motor-related regions. It should be noted that alternative analysis methods which investigate the 'typicality' of imaging findings (Friston et al., 1999a,b), originally developed for functional MRI analyses, have distinctly different form of hypothesis to most randomised controlled trials of neurorehabilitation, and so are considered out of scope for the present manuscript.

2. Methods

Participant numbers were calculated for a theoretical longitudinal study in which MR imaging took place immediately prior to, and immediately following, several weeks or months of treatment. It was assumed that such a study would utilise a paired parametric test (e.g. *t*-test) for differences in cortical thickness, or differences in FA of the delineated corticospinal tract using ROI-seeded or functional MRI (fMRI) seeded diffusion tractography. The general power analysis equation is described below before the description of values and sources of its parameters for each imaging metric.

2.1. Statistical analyses

The power analyses were performed using the 'pwr' package in R statistical software (The R Development Core Team, 2008). This test computes the sample size required to achieve a certain statistical power threshold (which is defined as one minus probability of a false negative finding), of a one-sided, paired *t*-test for a predefined effect size. Statistical power was varied between three thresholds; 0.8, 0.9 and 0.95, which represent a 20%, 10% and 5% chance of a false negative finding, respectively. A standard alpha value of 0.05 was used for all analyses. The longitudinal effect size for the power analysis was computed using the Cohen's d formula as follows:

$$effect \quad size = \frac{\mu_{post} - \mu_{pre}}{sqrt\left(\sigma^2_{measurement} + \sigma^2_{response}\right)}$$

where μ_{pre} and μ_{post} are the mean MRI measures from pre-treatment and post-treatment time points respectively. The variations of this formula includes two sources of variance; the measurement error ($\sigma^2_{measurement}$) and the variance in the longitudinal response to therapy ($\sigma^2_{response}$). Variance in response to treatment was set at 10% of the mean change, based on the variance in behavioural improvements reported in rehabilitative trials for CP (Eliasson et al., 2005; Gordon et al., 2011). These measurement and response to therapy variances are provided in Supplementary Table 1, while participant numbers for 5% and 15% variances in response are provided in Supplementary Fig. 2. Therefore, assuming a null hypothesis of no longitudinal change ($\mu_0 = 0$), the calculation of the sample size n using the software package can be approximated with the following equation:

$$n = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2}{effect\ \ size^2}$$

where $z_{1-\frac{\alpha}{2}}$ represents a standardised z-distribution of the test statistic at the $\alpha = 0.05$ cut-off for significance, and $z_{1-\beta}$ represents the same standardised distribution at the $\left(1-\beta\right)$ power threshold (Chow, 2011). For each imaging modality, mean change in MRI measures and measurement error were based on quantitative data, as described below.

2.2. Cortical thickness

Power was calculated for a hypothetical analysis that measured change in cortical thickness in the primary sensorimotor cortex of the impaired hemisphere. An ROI-based approach was assumed, as altered neural development in CP can invalidate assumptions of structure-function homogeneity across the cohort or hamper the accurate registration of anatomy, which would affect approaches such as voxel-based morphometry. A variety of expected cortical thickness increases were explored; these were based on published studies (Anderson et al., 2002; Iscan et al., 2015; Pagnozzi et al., 2016a) of this cortical thickness in different circumstances (Table 1). Based on this literature, an increase of 8% was considered to be a balanced estimate of change for effective therapies conducted over a 6-month time frame (See Table 1).

An outline of the cortical thickness pipeline is shown in Fig. 1, and is described in detail below. An estimate of variance due to measurement error was obtained from five children with unilateral cerebral palsy (UCP) (4 male; mean age 13.2 y; age-range 9–15.8 y; 4 GMFCS II; 1 GMFCS I; 3 right-sided hemiplegia), enrolled in the control arm of the Mitii clinical trial (Boyd et al., 2013). The pathology present in this cohort was fairly homogeneous with respect to injury type and location (Supplementary Fig. 1). These children underwent two MRI scans 20 weeks apart. As no intervention took place between these two scans, differences in measures of cortical thickness between the two scans is indicative of measurement error. This data is referred to herein as the 'UCP-dataset'. Ethics approval for the aforementioned trial was granted by the University of Queensland Human Research Ethics Committee and the Royal Children's Hospital Brisbane. Written informed consent was obtained from each participant's legal guardian.

Cortical thickness analyses utilised T1 MPR volumes (TR/TE: 1900/2.32 ms; 0.9 mm isotropic; Siemens Tim Trio 3T) that underwent N4 bias field correction (Tustison et al., 2010), intensity normalisation and skull stripping. For longitudinal analyses, it is