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Commentary

The practical constraints of developing new therapies for hemi-spatial neglect in the US and UK

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Abstract. Hemi-spatial neglect is a disabling, neuropsychological impairment that restricts the ability to attend to incoming information on one side space. Most frequently associated with a lesion to the right hemisphere, the disorder is strongly predictive of general functional recovery from stroke. Although the standard therapy is of limited effectiveness, pilot studies indicate that more effective treatments may follow. Interest in these new potential treatments is, however, beginning to wane as few have progressed to the stage of randomised, controlled clinical trials. In this brief commentary, we point out that the absence of trials data not only reflects the preliminary nature of new treatments, but also the practical difficulties associated with meeting the target enrolment figures of large-scale trials. These problems have likewise slowed the development of treatments for other cognitive disorders. We suggest ways in which this problem may be overcome.

Keywords: Visual attention, clinical intervention, participant recruitment

1. Introduction

Hemi-spatial neglect (or 'neglect' for short) is a debilitating, attentional disorder that most commonly arises from damage to the right-side of the brain [1]. Sufferers fail to acknowledge or respond to visual information presented on the side of space opposite their brain lesion (e.g. the left), and as such struggle with many daily routines, often bumping into obstacles, becoming lost, and failing to notice people on the affected side. Prevalence is hard to estimate because diagnostic criteria differ, but the most conservative estimate indicates that approximately 62% of those who suffer a stroke per year will show moderate and severe neglect in the acute phase, with 23% showing stable impairment beyond three months [2]. To put these numbers in context, approximately 700,000 U.S. citizens suffer a stroke each year [3].

Unfortunately, the presence of neglect is very strongly associated with poor general functional outcome. Individuals with neglect (regardless of severity) typically require additional weeks in hospital, need nearly twice as many hours of physiotherapy and occupational therapy, and are more prone to falls and persistent urinary incontinence [4]. Compared to others with the same Barthel score, patients with neglect at hospital admission score significantly lower on measures of functional independence both during hospital stay and 18 months after leaving [5]. Those who still show neglect on sim-

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ple bedside tests two months after admission have a higher risk of functional worsening at 1 year follow-up. Post-discharge, neglect patients are more likely to require ambulatory assistance and assisted living [4].

Regrettably, neglect is a refractory and difficult condition to treat. According to a recent Cochrane Review [6], "the effectiveness of rehabilitation strategies for reducing the disabling effects of neglect and increasing independence remain unproven" (p9). On a brighter note, a number of potentially more effective treatments, based mostly on sensory stimulation, are now being developed [7]. However, these have yet to be properly assessed in large-scale, randomised controlled trials [6]. Based partly on our own attempts to pilot a vestibular therapy in both the UK and US [8, 9], we wish to point out that the absence of clinical trials data not only reflects the preliminary nature of new treatment development, but also the practical difficulty of recruiting neglect patients into clinical trials. We expand on this point in the sections below, many of which speak to the failure to develop effective therapies for other cognitive disorders [10]. However, we focus on neglect given that it is the most prevalent and disabling cognitive disorder post-stoke, and also, perhaps for these reasons, because it has attracted so much research interest.

The problem of study recruitment stems from the fact that neglect patients are most commonly found on acute stroke wards. In some hospitals, staff on these wards do not routinely screen for neglect so, despite the poor prognosis of moderate and mild neglect on general functional recovery [11], only severe cases tend to prompt action. The presence of neglect can be further overlooked if either accompanied, as often the case, by more observable gross motor impairment, or the patient is subdued and non-interactive. The likelihood of study referral is further reduced by the fact that, despite their best intentions, physicians are often too busy to devote time to clinical research, and/or may be under pressure to recruit for multiple clinical trials. Also, many hospitals seek to discharge acute stroke patients within 5–6 weeks of admission, which is problematic because most neglect studies do not recruit until at least 4 weeks post-onset to allow for any spontaneous cognitive recovery to occur. This provides a brief time window in which to assess eligibility, consent, recruit and test.

Once patients leave an acute care facility, they may never set foot inside the hospital again and will most likely not see their attending doctor on follow-up. A minority of patients with neglect are moved to specialist rehabilitation units (typically to receive therapy for disorders other than neglect), though these often lack academic affiliation so lack a climate of research and do not have procedures for ethical review. The majority of patients go home or to residential care. This creates logistical difficulties that can be both costly, and time-consuming, and in instances where the patient is reluctant to travel, presents the problem of creating a controlled test environment at the individual's residence.

Once patient testing is underway, the current means of obtaining permission from the relevant institutional ethics review board to make protocol amendments can be time-consuming and bureaucratic. This hurdle is seen by some to reflect a perception within research and development officers that their role is to control researchers and protect patient well-being, as opposed to facilitate research and potentially improve well-being. Unfortunately, these attributes encourage a prescriptive form of enquiry that is especially obstructive in early-stage studies where flexibility is needed to finesse and optimise the evolving protocol.

The problems outlined above highlight a clear discrepancy between the desires of major funding agencies such as the US National Institutes for Health to translate therapies from bench to bedside, and the realities of conducting neuropsychological studies that have very specific inclusion/exclusion criteria and require participants that are geographically dispersed. The upshot is that researchers are more likely to perform underpowered trials, and worse, are discouraged from future investigation. Coupled with the intellectual challenge of finding a treatment regimen that can accommodate the heterogeneous nature of the hemi-spatial neglect, it is perhaps unsurprising that the standard, ineffective treatment of visual scanning has persisted for decades.

What can be done about these problems? We propose that greater awareness about the disabling effects of even mild and moderate neglect is needed amongst physicians and therapists of acute stroke. Second, new treatments must be cheaper and easier to implement at home to fit around the increasing pressure to reduce length of hospital stay. Third, the development of non-pharmacological interventions for cognitive disorders such as neglect requires participant numbers that cannot be delivered within most single institutions. Yet there is no established mechanism for multi-centre, city-wide or regional pooling of potential participants. We propose that research funding agencies provide infrastructure grants that would support the identification of participants with similar diagnoses who would be willing to participate in trials once they were medically stable.

The idea would be to compile a national registry of participants who had given local consent to be contacted about research participation. This anonymous database would provide basic demographic and diagnostic information, and would be publicly available. In principle, it need not be restricted to the clinical syndrome of neglect, and could carry information about other disorders. However, only those who had submitted successful grant applications would be able to apply for access to patients. Of course, such an initiative would need to meet the challenge of managing requests for the same patients from different research groups. But we consider this a small price to pay if the queue of new, promising therapies that await trials validation can be relieved.

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