



William Rivers' Croonian Lectures of 1906: an early account of blinding in medical research

(History of Neurology)

Andrew J. Larner¹, Sarah Cooper², Max Cooper³

¹ Honorary Senior Research Fellow, Department of Translational Neuroscience & Stroke, Institute of Neurology, University College London, London, United Kingdom

² Department of Neurology, Royal Sussex County Hospital, Brighton, UK

³ Department of Primary Care and Public Health, Brighton and Sussex Medical School, Brighton, UK

Corresponding Author:

Andrew J. Larner - ORCID 0000-0003-0128-8010

E-mail address: ajlarner241@aol.com

Abstract

A critical step along the path of evolution of clinical trial design, the blinding of research subjects to administered medications, was pioneered by William Rivers (1864-1922). Although best known for his work with survivors of “shell-shock” during the First World War, Rivers initially trained as a neurologist. His investigation of the effects on fatigue, both muscular and mental, of various substances, particularly caffeine and alcohol, was reported in his Croonian Lectures delivered at the Royal College of Physicians of London in 1906. Key to these controlled studies was Rivers’ method “to exclude the influence of interest, sensory stimulation, and suggestion” on the results. This article examines the setting, the study, the methodology and the aftermath of Rivers’ study. Rivers’ work is found to anticipate several key factors in controlled trial methodology, including: the need for a prolonged initial washout period; the possible confounding effect of craving; the need for placebos to be fully disguised; and the relevance and value of dramatic effects as strong evidence for an intervention.

Keywords: blinding; clinical trials; fatigue; history of neuroscience; William Rivers.

Introduction

William Halse Rivers (1864-1922) is perhaps best known to posterity for his work with soldiers suffering from “shell-shock” during the First World War, particularly the poet Siegfried Sassoon (1886-1967), even though this clinical work as a psychiatrist accounted for only a brief period of his multi-faceted career. In academic circles, Rivers is known as a founder of anthropology and ethnology, as well as experimental psychology (*Slobodin 1997*). However, initially he gained medical qualifications at St Bartholomew’s Hospital, London, in 1886 and in the early 1890s he worked as a neurologist, being taught by John Hughlings Jackson (1835-1911) at the National Hospital for the Paralysed and Epileptic, Queen Square, London (*Larner 2025a*) and contributing to the neurological literature (*Rivers 1891a*). He was elected to membership of the Neurological Society of London in 1891 and later (1897-1898) served on its Council.

Early in his career, Rivers also made presentations to the Abernethian Society, the medical and philosophical society at St Bartholomew’s Hospital, reading papers on hysteria and neurasthenia. The accounts of these meetings, as published in the *St. Bartholomew’s Hospital Reports*, are very brief (*Rivers 1891b, 1893*) but it would seem highly likely that Rivers was aware of Charcot’s work on these subjects and may have discussed them in this context. Rivers was elected to membership of the Medico-Psychological Association (the forerunner of the United Kingdom Royal College of Psychiatrists) in 1893.

In the neurological context, Rivers was later involved in a classical study of sensory nerve regeneration following the surgical section of a cutaneous nerve in the forearm of his colleague Henry Head (1861-1940) (*Head et al. 1905; Rivers and Head 1908*), work which continues to attract comment and analysis (e.g. *Watt Smith 2014, 125-163; Jacyna 2016, 125-130*). It may therefore be of some interest to historians of neurology, and indeed come as some surprise, to learn that another study by Rivers performed in the first decade of the twentieth century was “one of the first occasions, possibly the very first, on which the ‘double-blind’ procedure was used in an experiment” (*Slobodin 1997, 31*). The claim that Rivers “used double-blind placebo-controlled trials” has been repeated elsewhere (*Guest et al., 2021, p.2*).

The study in question (*Rivers 1908*) was briefly alluded to in Kaptchuk’s historical perspective of blind assessment and placebo controls in medicine (*Kaptchuk 1998, 419; 2011*) and also in a biographical article about Rivers in the Cochrane Library (*Adams 2004*) and online (<https://whrrivers.co.uk>), but none of these publications included discussion of Rivers’ methodology, nor to our knowledge has any other article specifically addressing this issue been published.

The concept of blinding, and specifically of “double-blind”, is now an integral element in clinical trial methodology with ramifications throughout clinical research and practice, including neurology. Hence the aims of the current article are to document Rivers’ rationale and methodology for blinding, and briefly to assess his contribution to clinical trial methodology.

The setting

Rivers had been recruited to Cambridge University in 1893 by Michael Foster (1836-1907), founder of the Cambridge physiology school, in order to lecture on the physiology of the senses and to set up a laboratory of experimental psychology (*O’Connor 1991, 17-19*). In Cambridge, Rivers also became associated with St John’s College, eventually becoming a Fellow (1902);

his rooms in the College were also used for some of his experimental studies to ensure the necessary degree of silence. However, the demands of his teaching and research duties meant that it was “impossible, as a general rule, to carry out any experimental work during term-time” (*Rivers 1908, 16*).

Rivers spent the summer of 1893 in Heidelberg in Germany where he worked with the distinguished psychiatrist Emil Kraepelin (1856-1926), undertaking a study which attempted to measure mental fatigue, later published in Kraepelin’s house journal, *Psychologische Arbeiten* (*Kraepelin and Rivers 1896*). Rivers presented some of these experimental data to the Medico-Psychological Association at their meeting held in Cambridge in February 1896 (*Rivers 1896*). This work appears to have kindled Rivers’ interest in fatigue and was the prelude to further study of the subject undertaken several years later.

The study and its methodology

Rivers’ studies on fatigue were undertaken intermittently between August 1904 (*Rivers 1908, 42*) and, at least, September 1906 (*Rivers 1908, 38*; hence, this internal evidence contradicts the dating of “1906-7” given by *Slobodin 1997, 31*). Many of Rivers’ experiments were performed in conjunction with “Mr. H.N. Webber”, with whom some of the results were later published (*Rivers and Webber 1907, 1908*). This was Harald [*sic*] Norris Webber (1881-1954) who had taken the Natural Sciences Tripos at Cambridge in 1903 and then remained in the town until 1908 (Cambridge only gained city status in 1951) when he commenced his medical studies in London, later practising as an anaesthetist at University College Hospital (*Anon. 1955*).

Funding for “the expenses of the researches” performed by Rivers came, at least in part, from the Croonian Trust of the Royal College of Physicians of London (*Rivers 1908, Preface* [unpaginated]). The experimental findings were initially presented in Rivers’ four Croonian Lectures delivered at the Royal College of Physicians on 12th, 14th, 19th and 21st June 1906 (as announced in *BMJ* 1906;1:1311; no announcement has been found in the *Lancet* or the *Medical Press and Circular*). Hence, Rivers’ experiments continued for at least three months after the delivery of the Croonian Lectures.

The purpose of the work was to examine the time course of both mental fatigue, as per Rivers’ previous studies with Kraepelin, and muscular fatigue, and the influence upon them of certain drugs, principally caffeine and alcohol, but also cocaine, strychnine, and tobacco.

Mental fatigue was assessed by performing blocks of multiplications and typewriting, both the number of lines completed and the number of errors being quantified, with rest periods in between blocks. Mental fatigue was also assessed using a method recently devised by William McDougall (1871-1938); Rivers had been his doctoral advisor at St John’s College. McDougall’s device required the subject to hit a succession of dots printed on a Morse tape which passed before a slit, the rate of movement being just the maximal rate for the subject (*McDougall 1905; Rivers 1908, 12, 13, 125-126*).

Muscular fatigue was studied using the ergograph, a technology originally devised by Angelo Mosso (1846-1910) around 1890 and also used by Kraepelin. In this device the fingers and forearm were inserted into graduated fixtures and one finger, usually the middle, undertook repeated cycles of contraction and relaxation (in time to a metronome) to lift a weight. Movements were recorded on a kymograph. Both the number and height of the contractions could thus be recorded and hence work performed (in kilogrammetres). In Rivers’ studies, both

the weight and the evolving ergogram were hidden from the view of the test subject. This appears to be the first instance of Rivers intentionally “blinding” participants, in this case to their own performance.

The experimental subject was more frequently Webber (“Subject W”) than Rivers (“Subject R”), and in occasional studies the subject was MacDougall (*Rivers 1908, 45-46, 98-99*) using the method he had devised to assess mental fatigue.

Rivers adopted the systematic manner previously used by Kraepelin to keep all experimental conditions exactly alike on different test days, excepting the administration of the drugs being investigated on some days but not on others: “it is essential that all the conditions of life be kept as constant as possible” (*Rivers 1908, 15*), these conditions encompassing sleep, meals, exercise, and any other work performed. Accordingly, research subjects “must cut themselves off from many of the ordinary pursuits of life so long as the experiments last” (*Rivers 1908, 15-16*). In addition, exclusion of extraneous sources of test drugs was required, namely cessation of all tea, coffee, cocoa, alcohol, and tobacco, stipulations which Rivers recognised to be challenging: “So drastic a procedure is not likely to attract workers [i.e. participants] to this subject” (*Rivers 1908, 17*). Fortunately, this was no obstacle for Webber on account of his lifelong abstinence (*Rivers 1908, 84, 131*; also *Anon. 1955*: he “never drank alcohol at all”).

However, certain environmental factors were beyond Rivers’ control. As mentioned, his teaching duties precluded experimental work during term time, so experiments were often carried out during student vacations, when the weather might influence results: the summer of 1906 was very hot, a factor which Rivers acknowledged could impact on mental vigour (*Rivers 1908, 85*) when experiments could last nine to ten hours each day over a period of nine days (*Rivers 1908, 45, 46, 47, 85, 95, 98*).

Rivers was at pains to emphasize his methodology: “in my own work I have been chiefly interested in the influence of certain psychical factors which I believe to have had a great effect on the results of previous workers” (*Rivers 1908, 4*). These factors were the “influence of interest” (presumably meaning attention or engagement), “sensory stimulation” and “suggestion”. Hence for Rivers it was “a feature of method in which lies the chief interest of the new work” which was “designed to eliminate the influence of certain psychical factors” (*Rivers 1908, 18*). He noted the “interest and excitement produced by taking a substance when the discovery of its effect is the motive of the whole experiment”, particularly so when “the subject is himself the experimenter” (*Rivers 1908, 19, 20*). Accordingly, Rivers carried out the research “with the use of control mixtures which have usually been wholly indistinguishable from those containing the active substances” such that the experimental subject was “wholly unaware whether he has taken the substance which is the motive of the experiment or some inactive imitation of it” (*Rivers 1908, 20*).

The extent to which Rivers sought to make his “control mixtures” indistinguishable is of particular note. These were prepared by Walter Ernest Dixon (1871-1931), the Cambridge pharmacologist (*Rivers 1908, 20, 66, 67, 73*; for Dixon, see *Cuthbert 2001*). Specifically, gentian and citric acid were used as a control for the active citrate of caffeine (*Rivers 1908, 21, 43*). Concealing alcohol proved more challenging. Initially Dixon prepared a control solution which contained a mixture of capsicum, cardamoms, and a small amount of chloroform (*Rivers 1908, 66*) but later a modification by means of adding some peppermint was required (*Rivers 1908, 73*).

The specific results of Rivers' drug studies comparing active versus control substances, were largely inconclusive, with different observations being sometimes made in the two principal experimental subjects.

Contemporary assessments: the immediate aftermath

One would be intrigued to know the responses of the Fellows of the Royal College of Physicians who attended Rivers' lectures in June 1906, but to our knowledge none is available.

No contemporaneous publication of the Croonian Lectures has been found in any of the weekly medical journals but two papers documenting some of Rivers' findings later appeared. The first, describing the work on caffeine, appeared in the *Journal of Physiology* (Rivers and Webber 1907; this publication was not included in the Bibliography of Rivers' works in Slobodin 1997, 275-277) and was later acknowledged in passing by Rivers (Rivers 1908, Preface [unpaginated], 29n1). The second, describing the work on alcohol, appeared in the *British Journal of Psychology* (Rivers and Webber 1908; incorrect pagination in Slobodin 1997, 277), the journal which Rivers had co-founded in 1904; again, this publication was acknowledged in passing (Rivers 1908, 69n1, 78n1).

The definitive account of the studies appeared in book form thereafter (Rivers 1908). A perfunctory, anonymous review of this book appeared in *Brain* (1908;31(1):217), the leading neurological journal. Although amounting to a meagre nine lines, the reviewer at least noted that in Rivers' experiments "every precaution was taken to avoid suggestion: control mixtures indistinguishable from those containing the drug under investigation were taken by the subject". Hence the conclusion that "In many ways this work is a considerable advance in the psychological study of the influence of drugs on man".

A longer commentary on Rivers' book appeared in the *British Medical Journal* (Anon. 1908). Again, the reviewer noted Rivers' methodology, quoting his statement to the effect that the "part played by psychical factors" had "been allowed to complicate most [other] work on this subject", and noting that:

Soon after beginning his investigation Dr. Rivers became aware of the unsatisfactory nature of previous researches on the capacity for muscular work in man, and much of his work has been occupied in perfecting exact methods and eliminating disturbing factors. The method he used was to take six series of ergographs a day, at intervals of one hour, the subject not being allowed to see either the weight lifted or the tracing produced. To eliminate physical [should this have read psychical?] factors the subject took control mixtures, so that he did not know the days when he took the drug. This last precaution is obviously most important, but does not seem to have been taken by any previous worker. (Anon. 1908, 1192).

This reviewer concluded with the encomium that "Dr. Rivers is to be congratulated on the exact scientific spirit in which he has carried out these researches, and we hope to see them carried a step farther" (Anon. 1908, 1193). No review of Rivers' book has been identified in the pages of the *Lancet* or the *Medical Press and Circular*.

Kaptchuk (1998, 419-420) noted that Rivers' ideas concerning blinding were introduced to the United States by three different groups of researchers who published between 1912 and 1916 but "with only minimal effect". That little, if any, further note of Rivers' methodology was made by later investigators would be in keeping with the argument that the history of blinding was, prior to Kaptchuk's work, largely ignored.

Rivers himself never returned to the subject of blinding. His studies of fatigue (*Rivers 1908*) and of sensory nerve regeneration (*Rivers and Head 1908*) were his final forays into physiological psychology (*Slobodin 1997, 44*). Despite allusions to Webber continuing the fatigue work (*Rivers 1908, 75, 83, 107, 118*), to our knowledge he did not publish anything further. Indeed, it was later noted of Webber that he "did not make many contributions to medical literature" (*Anon. 1955*) other than co-authoring a textbook on anaesthesia (*Rood and Webber 1930*).

Discussion

The history of blinded studies dates back at least to the eighteenth century (*Kaptchuk, 1998, 2011*): the examination of animal magnetism in the late eighteenth century by Benjamin Franklin and others is often cited as the earliest example. If one includes necessarily blind assessment, i.e. by subjects who were actually blind, earlier descriptions might also be considered (*Larner 2006; 2025b, 116-118*).

In the Conclusion of his Croonian Lectures, Rivers was explicit: "The chief interest of the work which has been recorded in these lectures lies in its bearing on method. [...] One point of method has, I hope, been clearly established – viz., the absolute necessity that experiments with drugs on man should be carried out with adequate control, designed to exclude the influence of interest, sensory stimulation, and suggestion" (*Rivers 1908, 117-118*). However, nowhere did Rivers use the terminology of "blind" or "blinding", nor "concealment", "masking", or "placebo". Hence the characterisation of his work as "one of the first occasions, possibly the very first, on which the 'double-blind' procedure was used in an experiment" (*Slobodin 1997, 31*) is a retrospective judgment, likewise the argument that "Rivers needs to be given credit for blinding of subjects in a controlled study when he lectured on his research on alcohol and fatigue in 1906" (*Bader 2023, 140*). However, Rivers did speak of "disguise" as a means of eliminating the "influence of interest", a factor which he deemed to be of greater importance than either "sensory stimulation or suggestion" in affecting experimental outcomes. The word "bias" appears in his work but infrequently, specifically with respect to advocacy for either temperance or, contrariwise, the virtues of alcohol (*Rivers 1908, 52, 90*) rather than the specific notion of observer bias. Nevertheless, the latter might be implied in his recognition of accessory, psychical factors being allowed to influence previous workers and their results (*Rivers 1908, 80, 82*) which, in the case of alcohol, were "almost certainly due to defects of experimental method" (*Rivers 1908, 100*).

Exercising the benefit of hindsight (indeed, possibly the condescension of posterity), we might disparage Rivers' methods in his work on fatigue. Both mental and muscular fatigue are sensitive to contextual factors such as time of day, prior cognitive or physical activity, and environmental conditions. Rivers attempted to take these factors into consideration, although he did not document them for each individual experiment. Thus, although his studies were clearly "controlled" in the sense that the conditions of life were kept as equal as possible, nonetheless they were methodologically limited according to current standards: few

experimental subjects (two or three); no randomisation; no inferential statistics; no overt hypothesis testing. However, this is to ignore the historical context. In his studies of fatigue, Rivers seems to have inaugurated a new methodology in his work. Certainly, there is no indication of any awareness of the place of such methodology in his extensive review of previous work related to the physiology of vision (*Rivers 1900*). In the Rivers-Head experiment, which occurred contemporaneously with the fatigue studies, Rivers also made efforts to ensure that his subject, Henry Head, was blind to the nature and order of the sensory stimuli applied (*Rivers and Head 1908, 342-355*). This arrangement was commemorated in one of the classic photographs of the experiment, in which Head looks away with eyes closed as Rivers applies a stimulus (*Henson 1961, 537*). The image has often been reproduced (e.g. *Watt Smith 2014, 126; Jacyna 2016, 126*).

Whence came Rivers' epiphany as to the importance of disguise? His written text might suggest that it came from within: "In my first experiment with a drug, I soon became aware of such interest" (*Rivers 1908, 20*). Blinding may thus have emerged almost naturally within the context of research in physiological psychology as Rivers attempted to measure factors, particularly mental fatigue, which were inherently vulnerable to psychological influences such as expectation, interest, and suggestion. This could help explain why Rivers conceived of blinding in this context before it appeared in other areas of biomedical experimentation with more "hard," objectively measurable endpoints. However, contrary to this argument, Rivers' prior knowledge of the works of other investigators, whether acknowledged or not, may have contributed to this awareness, specifically the "precautions" adopted by Schumburg and by Sobierański of using "control-substances" (*Rivers 1908, 18-19*). Wacław Sobierański, working in Marburg in 1895, preceded his assessments of the effects of caffeine and cocaine on muscle strength, as measured with ergography, by saline injections and emphasized the need to control for "autosuggestion" (*Sobierański 1896; see also Kaptchuk 1998, 418*).

Whilst Webber, as "Subject W", was almost certainly blind to the drug, active or control, administered by Rivers in most cases (see below), the latter was likely aware of the sequence in which the substances were given, hence this experiment was unlikely to have been "double-blind". For "Subject R", it is difficult to conceive how Rivers could have been unaware of whether he took active or control substance: he mentions that Dixon supplied him with "two or more bottles, and it has only been at the end of the experiment that I have been made acquainted with the exact nature of their contents" (*Rivers 1908, 20*) but, nevertheless, when "the subject is himself the experimenter" (*Rivers 1908, 20*) this arrangement can only ever be "single-blind". Moreover, instances of unblinding certainly occurred: caffeine sometimes disturbed Rivers' sleep, necessitating either discontinuation of the experiment or change of protocol (*Rivers 1908, 36, 43, 127-129*), and higher doses of alcohol were recognised by Webber necessitating the modification of the control mixture (*Rivers 1908, 71, 73, 84, 131-132*). Hence, Rivers' efforts at blinding were not entirely successful. At best these studies were single- rather than double-blind; herein we disagree with previous characterizations of this work as using the double-blind methodology (*Slobodin 1997, 31; Guest et al., 2021, p.2*).

Rivers' study may be seen to incorporate several key contributions to the development of controlled trial methodology:

- The importance of a very long period of "washout" (our word) before any intervention: "For these reasons it seemed best to give up completely the use of all the stimulating articles of diet in ordinary use for several months before beginning my next research, and much of the work to be described in these lectures was done more than a year after

the use of alcohol and caffeine-containing articles of diet had been given up” (Rivers 1908, 17).

- The importance of considering the confounding effect of a “craving” (thus requiring the long washout period): “Even in those who only take such a substance [alcohol] in moderate amounts, its disuse is probably followed in some degree by the craving which is so pronounced after discontinuance of large amounts, and, slight and hardly noticeable as this craving may be, it may yet be sufficient to produce an obvious effect when the article of which the person has been deprived is administered experimentally. The effect of the substance given experimentally may be the result, not of its normal physiological action, but of the satisfaction of a craving” (Rivers 1908, 17).
- The need for placebos to be fully “disguised” and “wholly indistinguishable”, hence the need to involve a “specialist” (our word; in this case, Dr W.E. Dixon) in the process of disguising active and control substances. Shortcomings of previous attempts at disguise were evident to Rivers: “In experiments on the action of coffee, Schumberg [...] used a control coloured so as to resemble coffee, but there can have been no question here of a control wholly indistinguishable from the coffee” (Rivers and Webber 1907, 33n1).
- The recognition of the relevance and value of dramatic effects as strong evidence for an intervention. Discussing “the most satisfactory method” first adopted by Kraepelin, Rivers notes that “In many cases the drug-days will give an average which deviates from that of the normal days so greatly that there can be no question as to the action of the drug” (Rivers 1908, 15).

In addition, Rivers’ approach appears to adopt a basic cross-over method in the administration of active and control substances, a method little used hitherto (Cooper and Cooper 2026; Larner et al. 2026).

Why has this item of Rivers’ oeuvre been relatively neglected by posterity? Though of interest at the time, the inconclusive results, despite the (relative) novelty of the methodology, probably accounted for the limited uptake of Rivers’ approach. Hence the subsidiary question, what influence did Rivers’ use of blinding in his studies of fatigue have on the field of biomedical investigation, answers itself: in all likelihood, very little. Nevertheless, from our vantage point in history, this may indeed have been one of the first attempts at blinding from a neurological perspective, one episode in the gradual, cumulative development of the concept of blinding. It may be added to extraordinary breadth of Rivers’ many contributions in many disciplines, the application of this one spanning many disciplinary boundaries.

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