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Case Series in Cognitive Neuropsychology: Promise, Perils and Proper Perspective

Brenda Rapp

Department of Cognitive Science Johns Hopkins University

Abstract

Schwartz & Dell (2010) advocated for a major role for case series investigations in cognitive neuropsychology. They defined the key features of this approach and presented a number of arguments and examples illustrating the benefits of case series studies and their contribution to computational cognitive neuropsychology. In the Special Issue on “Case Series in Cognitive Neuropsychology” there are six commentaries on Schwartz and Dell (2010) as well as a response to the six commentaries by Dell and Schwartz. In this paper, I provide a brief summary of the key points made in Schwartz and Dell (2010) and I review the promise and perils of case series design as revealed by the six commentaries. I conclude by placing the set of papers within a broader perspective, providing some clarification of the historical record on case series and single case approaches, raising some cautionary notes for case series studies and situating both case series and single case approaches within the larger context of theory development in the cognitive sciences.

Schwartz & Dell (2010) presented a number of arguments and examples in advocating for a major role for case series investigations in cognitive neuropsychology. This Special Issue includes six commentaries on Schwartz and Dell (2010) (referred to as S&D), as well as a response to the six commentaries by Dell and Schwartz (D&S). My goal in this paper is to provide a backdrop for the complete set of papers. I will do so by first providing a brief summary of key points made in S&D, then I will discuss the promise and perils of case series design as revealed by the six commentaries; I will end by attempting to place the discussion within a broader perspective.

Schwartz & Dell (2010)

S&D begin with the premise that cognitive neuropsychology is primarily identified with the single case research approach. They argue that this is a highly limited view of the range of designs that are appropriate within cognitive neuropsychology and propose that the case series approach be promoted as a complement and alternative to the single case approach. They suggest that case series studies have already become increasingly more influential and valuable as interest in individual differences has grown and the application of statistical techniques such as correlation and regression used to exploit these differences has become more widespread.

The defining feature of case series design, as S&D describe it, is the goal of using patterns of co-variance to understand underlying cognitive mechanisms. In service of this goal, S&D describe the case series design as having the following key elements: a sample size suitable for identifying complex trends, the administration of a common set of cognitive tests that is fairly circumscribed (relative to what is common in single case studies) and generally lenient

criteria for defining a sample (e.g., broad theoretically based or even clinical and neuroanatomical criteria). The motivation underlying the leniency in selection criteria is that heterogeneity is “deemed welcome and even necessary” (pg. 479) given the centrality of correlational-type analyses. The other major component of the S&D presentation is that case series studies are typically (although presumably not necessarily) associated with the quantitative evaluation of statistical or processing models/computer simulations of the cognitive systems under investigation. That is, case series studies often include a simulation component in which the data from the case series is used to evaluate a hypothesis or set of hypotheses that have been instantiated in a simulation.

S&D emphasize a distinction between the case series approach and other approaches involving multiple brain-damaged individuals. Critically, the case series design is different from group designs that average (or otherwise agglomerate) data across participants because, in the case series approach, individual participant data are still “visible” and readily recoverable. For this reason, the various problems with averaging that have been discussed extensively in the cognitive neuropsychological literature (e.g., McCloskey & Caramazza, 1988) do not apply to case series studies. S&D also draw a distinction between case series and what they refer to as “multiple-case” designs in which there is a concatenation of two or more single case studies. For S&D, the fundamental difference between the case series and multiple-case approaches concerns whether or not there is statistical analysis of the variability between multiple factors. S&D argue vigorously for the value of variability, a position which, they claim, stands in contrast with what they refer to as the orthodox approach in cognitive neuropsychology in which variability is seen as unhelpful.

In support of their position, S&D present examples of case studies research. They discuss their own work on lexical access in spoken word production (Dell et al, 1997) in which they examined the relationship between the severity of naming impairment and rates of semantic and nonwords errors. Their finding of a systematic relationship amongst these variables led them to posit that lexical access deficits can be understood by positing disruption to a single global factor within the production system, a proposal they called the “globality assumption”. Another example is based on the work of Lambon Ralph and colleagues with individuals with semantic dementia (e.g., Lambon Ralph, et al, 2007). A key observation was the strong co-variation within and across verbal and nonverbal semantic tasks; this was taken as support for the hypothesis of amodal semantic representations. A third example discussed by S&D involves the work of Patterson and colleagues (e.g., Woollams, et al., 2007) in which the relationship between semantic impairment and exception word reading (surface dyslexia) was examined (primarily in individuals with semantic dementia). The finding of a strong association between severity of semantic impairment and difficulties in exception word reading was used to support the hypothesis that semantic mediation is required for exception word reading. In turn, this provided support for the PDP triangle theory of reading that posits a division of labor between semantic and phonological pathways to reading.

Each of these lines of behavioral research reviewed by S&D was accompanied by extensive computer simulation work. S&D suggest that the association of case series studies with simulation work is productive (although presumably not required). They imply that the availability of similar behavioral measures for a set of individuals lends itself well to the testing/ fitting of computer simulations of cognitive functions of interest. In the examples that S&D develop, the simulation work was used as a form of “demonstration” of the hypotheses under investigation as well as a source of predictions regarding further data patterns that should be observed. The fit between observed and modeled data was used to argue for the validity of the hypotheses instantiated in the simulations.

S&D go on to address what they correctly perceive as a key concern for case series design: heterogeneity in the set of individuals in a case series. That is, there is concern that individuals in a case series study may differ in ways that are relevant to the conclusions that are drawn. S&D argue that risks posed by heterogeneity are very significantly reduced in case series compared to group studies because the individual patterns are recoverable and aberrant patterns can be identified as outliers (e.g., Fischer-Baum & Rapp, 2012). S&D acknowledge that the proper treatment and, in particular, the interpretation of outliers is a complex matter and they discuss various possibilities. These include removing the outliers, using regression to limit heterogeneity and, importantly, the careful examination of the outliers via single case study. The careful study of the outliers via single case study allows investigators to understand the reasons for the observed heterogeneity. One consequence of this understanding may be a reformulation of the original hypothesis.

With regard to the role of single case studies, S&D acknowledge their independent contribution to the field as well as their role as a complement/supplement to case series. They conclude that, while they support an ever more significant role for case series studies in cognitive neuropsychology, the two approaches are complementary in the contributions they make to the study of human cognition.

Promise

The authors in this Special Issue all find at least some promising aspects of the case series design. Before describing these, it is worth first noting that Nickels et al. and Olson and Romani do not agree with S&D's definition of case series itself. In particular, they reject the exclusion of the multiple case approach from the category of case series, arguing that multiple case approaches are often necessary and useful in circumstances similar to those which apply for case series (see also Shallice & Biuatti).

1-Certain types of hypothesis-testing require a case series design

Nickels, Howard & Best (this issue) argue that while certain types hypotheses can be tested with single cases, there are others that require data from multiple cases. While there is not unanimous agreement amongst the authors of this Special Issue with regard to the first claim, there is unanimous support for the second. That is, while there are different views on the role of single case studies in testing/disproving hypotheses, one thing that is clear is that the authors of the Special Issue agree that certain types of interesting hypotheses about cognitive processing do require case series data.

The most obviously relevant hypothesis type involves predictions of the following sort: as X increases (or decreases), Y should increase (or decrease). X and Y may be variables such as severity of naming impairment and rate of semantic and nonword errors (Dell et al.; 1997), severity of semantic impairment and accuracy in reading exception words (Woollams et al., 2007) or severity of sublexical damage and perseveration errors in spelling (Fischer-Baum & Rapp, 2012). Given that the evaluation of these types of predictions requires multiple individuals who show different degrees of X, a case series design involving correlation and regression approaches would seem to be necessary.

Interestingly, Nickels et al. also point out the potentially important role of case series approaches in the evaluation of treatment efficacy. They note that randomized controlled trials suffer from the weaknesses that arise from group studies that engage in data averaging. Nickels et al. discuss how case series can be used profitably in examining hypotheses related to treatment efficacy (e.g., Best, et al., 2002).

Finally, in a position that is not shared by all of the authors (see Nickels et al.), Lambon Ralph, Patterson, & Plaut (this issue) suggest that the case series approach plays an important role in documenting associations more generally. They note that, traditionally, it has been difficult to argue for shared cognitive functions on the basis of associated deficits in single cases, due to the alternative interpretation that the association arises simply from the coincidental neuro-anatomical adjacency of two functions. They argue that the case series design provides for stronger, “more secure” demonstrations of associations than is possible in single case studies.

2-Case series are consistent with “population thinking”

According to Bub (this issue), the tension in the field does not so much concern the issue of whether case series should or should not complement single case studies, but rather it concerns a more fundamental difference regarding assumptions about the basic nature of cognitive systems. Bub suggests that, on the one hand, there is a view that assumes that humans share a common cognitive architecture while, on the other hand, there is a view that assumes diversity in underlying cognitive architectures. He associates the former position with essentialist doctrine dating back to Aristotle, while the latter view he relates to “population thinking” that is prevalent among modern evolutionary biologists. This position assumes “no idealized blueprint underlies diversity and that lawful variation itself should be the goal of theory construction” (p. XX). Bub indicates that the single case approach is commonly associated with those holding the “universality assumption” (Caramazza, 1986), while the case series approach lends itself naturally to the assumptions of population thinking. Furthermore, he seems to imply that, in this regard, case series design is on the leading edge of history.

Consistent with the “population thinking” view, Lambon Ralph et al. explicitly adopt the assumption that there is significant variability in human cognitive architectures (see also Shallice and Buiatti, this issue) and argue that, for this reason, case series should be the method of choice in cognitive neuropsychology. Specifically they claim that the case series design allows for the data reduction necessary to identify underlying central tendencies while, at the same time, providing a means for explaining variability within a population.

3-Case series design permits greater flexibility in selection criteria

Some authors, such as Olson & Romani (this issue) and Nickels, et al., quite explicitly state that selection criteria must be theoretically defined, and that, otherwise, investigators run significant risks of information distortion or loss. In contrast, S&D and Lambon Ralph et al. suggest that because analysis methods used in case series studies do not involve averaging and, therefore, do not obscure single subject results, one can be less concerned about violating assumptions of homogeneity. They propose that, for that reason, sample selection can be done in a more flexible and lenient manner, allowing broad theoretical, clinical and also neuro-anatomical criteria.

Neuro-anatomical selection criteria are of interest to a number of the authors. Interestingly, however, the various authors differ in terms of what they see as the positive outcomes of sample selection according to neuroanatomical criteria. S&D emphasize that studies based neuro-anatomical criteria provide improved understanding of the cognitive functions subserved by specific neural areas, while Lambon Ralph et al. suggest that this approach allows for a better integration of neuro-anatomical findings into cognitive theories. Shallice & Buiatti emphasize that the neuro-anatomically based inclusion approach provides various important benefits precisely because it does not involve behavioral criteria. Among these benefits, the neuro-anatomical approach limits the biasing of outcomes and interpretations that may arise when behavioral criteria used, it also provides opportunities to identify new

functional syndromes and to fractionate others and, finally, the finding that certain behavioral patterns (e.g., better performance with animate vs. inanimate objects) are found in one neuroanatomically based group and not another limits the concern that the patterns are based on premorbid abilities and experiences.

4-Uniform behavioral evaluation facilitates testing computational models

None of the authors disputes that neuropsychological data can play an important role in theory building and in testing computational models. The question, therefore, is whether the cognitive neuropsychological data collected in case series has a special role to play in this enterprise. In this regard, S&D, Lambon Ralph et al. and Olson & Romani all refer to the importance of the standardization (or greater uniformity) of the data that is provided by case series studies. Because case series typically involve the administration of a common (relatively limited) set of tasks, similar measures are available for the evaluation and testing of computational models. The availability of the same set of measurements for a group of individuals provides a classical “data set” for model testing.

Perils

All of the papers recognize that there are at least some legitimate concerns regarding variability and heterogeneity in a case series. They differ, however, in terms of how serious they think the consequences of heterogeneity are, as well as in terms of how these concerns should be dealt with. In addition, several other concerns, summarized in this section, were expressed in multiple commentaries.

1-Selection criteria can bias outcomes

Both Nickels et al. and Shallice & Buiatti describe the possibility that the criteria used to select participants for the case series may bias the outcomes of the study and the conclusions drawn. Both papers describe examples of this problem and draw attention to the fact that the sample must include the deficit patterns that are necessary to test the hypotheses under consideration. Overly narrow selection criteria for the evaluation of a broad hypothesis will bias the outcomes. While this general point may seem obvious, the problems can often be subtle to discern and, arguably, the case series approach with the volume of cases and data it entails, may make these problems more difficult to detect.

2-Outliers: Finding them, dealing with them, and the consequences of failing to do so

Fundamental to correlation-based analyses and, therefore, to the case series approach is the requirement for variability amongst subjects along at least one of the measurement dimensions. Relatedly, however, are two major concerns: How, amongst the appropriate variability, are outliers to be identified? Once identified what should be done with them?

While many points related to these questions were raised in the commentaries, the crux of the matter was the possibility that consideration of outliers may lead a researcher to different conclusions than would be reached if only the primary trends in the data were considered. The underlying concern is that in case series studies it may be rather easy to ignore outliers, focusing instead on the majority pattern (see below for a related discussion on “What counts as a good fit?”). This concern is illustrated with an example that S&D present from their own work. Based on consideration of outliers, Schwartz et al. (2006) fundamentally changed the conclusions they had reached previously in Dell et al. (1997) regarding the globality assumption according to which there is a common source of error for semantic, nonwords and other errors in word production deficits. Consideration of outlier cases led Schwartz et al (2006) to the conclusion that, contra the globality assumption, spoken word production deficits can arise from differential disruption to specific levels of representation and

processing within the production system. This exemplifies the important role of single case studies in “track(ing) down the deviations” (S&D, p. 489) that may be observed in a case series. Most of the other authors in this Special Issue supported this method of dealing with outliers. Essentially it allows researchers to shine a spotlight on outliers and obtain a better understanding of the reasons that differentiate them from the majority pattern. As Nickels et al. indicate, some outliers may turn out to be due merely to confounding factors, while others may represent a serious challenge that requires a different conclusion than one reached on the basis of the majority trend alone.

3-Individual differences: An easy way out?

One way to explain outliers and variability is to attribute them to pre or post-morbid individual differences. With regard to pre-morbid differences, S&D and Lambon Ralph et al. use as an example the Plaut (1997) claim that outliers that violated the majority pattern relating semantic integrity with exception word reading could be explained by positing pre-morbid differences in the reading architectures of the outlier individuals. As Goldrick (this issue) points out, and Lambon Ralph et al. concur, this type of explanation is purely speculative unless it is accompanied by independent evidence of the premorbid differences.

Goldrick also points to a more subtle problem that may arise in computational cognitive neuropsychological work, one that concerns the proper interpretation of post-morbid differences. In using a case series to test a complex hypothesis of a cognitive function, a common approach is to determine if a computational model of the cognitive function can be damaged in ways that will match the individual data points. There may be multiple ways of instantiating damage, for example, different parameters may be adjusted in different ways to generate the best fit to the data. The best-fit solution that is reached is, in essence, an account of the post-morbid differences in terms of the types or loci of disruption. In the work of Dell and colleagues, for example, the patterns of spoken production errors produced by each individual are accounted for by specific values of two parameters of the model. Goldrick points out that, the individual subject solutions that are reached in the process of model fitting do not typically have any independent behavioral motivation. In other words, a model’s attribution of performance patterns to parameters *x* and *y* is not typically supported by data (other than the data used in the model fitting) showing that the individual does, in fact, exhibit the features that would be expected from the disruptions “posited” by the simulation (see Olson & Romani for related concerns).

4-Theory testing: What counts as a good fit?

Both Goldrick and Olson & Romani argue that is not enough to show that a computational theory provides a good fit to a case series data set. That is, it is not enough to know that theory can predict *X* percentage of the variance in the data. Both papers stress that, instead, theory comparison is crucial and that this requires comparing the fit of the data from the case series to alternative theories. For this to work however, it is critical that the theories actually make different predictions regarding the data set being evaluated. To illustrate the importance of this point, Goldrick presents an example based on simulation data showing that determining whether theories actually make different predictions may be a non-trivial matter. Once one has identified theories that do make different predictions, there are different approaches to comparing the fit and parsimony of the alternative theories. Olson & Romani describe a number of these approaches (e.g., minimum description length, bootstrapping and Akaike’s information Criterion).

Olson & Romani stress the importance in theory evaluation of considering the full range of a theory’s predictions. This requires determining the extent to which the full set of patterns that are predicted by the theory are, in fact, observed and whether or not patterns that are not

predicted are not observed. In other words, it is not enough to simply compare the number of cases that are fit well by a theory versus those that are fit poorly; one must ensure that most of the cases are not simply “redundant” and test only a small area of a model’s predicted space of possibilities.

Proper Perspective

1-Whoever said that the case series methods were a problem?

While it is difficult to disagree with S&D’s assertion that the cognitive psychology and neuroscience communities identify cognitive neuropsychology with single case studies, it is important to clarify the record in terms of what type of research has actually been carried out, and what has been advocated by leaders in the field.

First, as S&D themselves point out, case series studies have been carried out since quite early in the history of cognitive neuropsychology with papers such as Howard et al., (1984), Patterson and Hodges (1992), etc. These types of studies have continued to be steadily produced, although, it is quite true that they have represented a small proportion of papers in cognitive neuropsychology. There are many reasons for this but prominent among them are, most certainly, the difficulties involved in finding multiple relevant cases as well as the various interpretative and other perils that have been identified by the authors in this Special Issue.

Second, it is worthwhile to understand what has been written about single cases and group studies in the seminal papers dealing with this topic. In this regard, McCloskey and Caramazza, (1988) stated: “It is important at the outset to draw a distinction between two senses of the term group study.... Studies in which data are averaged across subjects, or otherwise aggregated in such a way that the performance patterns of individual subjects cannot be recovered from the aggregate results.... It’s this type of group study that we have argued is inappropriate in research with brain damaged patients.the term may also be used to refer to studies in which data from multiple cases, each of which maintains its individual identity, are brought to bear on the theoretical questions of interest..... addressing some sorts of theoretical questions requires the consideration of multiple cases (pg. 584).” It seems quite clear from this quote that the case series study is not the type of group study that was seen to be problematic. Furthermore, with regard to the role of single case studies in the broader enterprise of cognitive neuropsychology, in the same paper these authors wrote: “We have certainly never argued that all theoretically meaningful questions in neuropsychology can be answered by considering single-patients studies in isolation (pg. 613)”.

In sum, the promise of case series designs for cognitive neuropsychological investigation are well described in this Special Issue and the history of cognitive neuropsychology provides a record of support for this approach. Perhaps with the increasing and increasingly successful application of case series designs the perceptions of the available methods in cognitive neuropsychology will begin to change both within and outside of the field.

2-The universality assumption: Could the news of its demise be premature?

A bedrock assumption of the cognitive sciences is that humans have cognitive mechanisms that they share (at least at some level of description). This assumption is not incompatible with the existence of individual differences, something about which there is no dispute, even within the cognitive neuropsychology “orthodoxy” (e.g., see Caramazza, 1986). Thus the question is not whether or not there are individual differences, but rather whether the range of individual variation is such that it affects a researcher’s ability to test and discriminate between the hypotheses under consideration.

Clearly, an understanding of the nature and extent of individual differences in normal (premorbid) cognitive systems is important for research in cognitive neuropsychology and, for that matter, in all disciplines that deal with cognition: cognitive psychology, cognitive neuroscience, etc. In fact, this type of understanding would seem to be necessary before invoking premorbid variability as a possible explanation for heterogeneity of findings. Therefore, it is surprising that, despite the prevalence of “population thinking”, relatively little work has been done on understanding the extent and nature of individual variability with regard to the types of cognitive mechanisms commonly investigated in cognitive psychology and neuropsychology.

Only once normal variability is understood can we develop means for dealing with pre-morbid differences in cognitive neuropsychology. Given the many the potential sources of variability--measurement error, severity differences, as well as differences in underlying cognitive architecture--a failure to distinguish amongst these on the basis of independent evidence dramatically increases the risk of vacuous speculation. In their reply to the commentaries, D&S suggest that the same parameters manipulated in the modeling of impaired performance can be used for modeling premorbid differences across individuals as well as across items. While this parsimonious approach is certainly appealing, one should be concerned that trying to simultaneously account for pre-morbid individual differences and post-morbid variability within the same parameters allows for a great many degrees of freedom. Independent constraints will be essential for this type of enterprise, and a key component must be a deeper understanding of the range and nature of individual differences in the cognitive systems under investigation. Until we have this understanding, it may well be that the news of the demise of the universality assumption is indeed premature.

3-Case series: The risk of myopia

Although not raised in the commentaries, there may well be a risk that researchers carrying out case series studies will ignore cases outside their own series. Given the elegance of studying a set of individuals who have all been administered the same or very similar tests, there may a temptation to ignore potentially relevant single case reports, or even other case series studies that use different behavioral tasks or that differ in other ways. We can see examples of this in some of the work described in the commentaries. For example, Dell et al. (1997) proposed the globality assumption despite the existence of well-documented single cases in the literature that were at odds with it and then, in revising their position vis à vis the globality assumption, Schwartz et al (2006) focused on evidence from case series studies.

Of course, as several of the papers indicate, methodological and other differences across studies may make the integration of results sometimes difficult, if not impossible, but this is certainly not always or necessarily the case. Furthermore, it is also true that it is always difficult to know how much weight should be given to discrepant findings in terms of making adjustments to a theory, and this problem is not limited to case series studies. However, researchers reporting on single case studies have strong incentives to look to other cases to provide either replication or converging evidence. In contrast, and perhaps counter-intuitively, case series may be at increased risk of developing a narrow view, focused on the methods and results that are specific to a given lab or research group.

4-Scientific progress as multiple constraint satisfaction: Single case studies are not the problem

In their paper in this Special Issue, Lambon Ralph et al. describe one of Eleanor Saffran's concerns, stating: “to make progress and have an impact, research must accumulate, and her fear was that an endless string of single case studies might be incompatible with such

accumulation. They conclude with the following: "if cognitive neuropsychology is going to make progress, we need a finite number of case series studies, not an infinite number of single cases (p. XX)". These statements suggest that single case studies, if not incompatible with accumulation of knowledge, at least represent some sort of impediment to progress in research. They further suggest that, in contrast, the case series approach will allow us to reach some endpoint of understanding in finite time. Leaving aside the question of whether there actually is an endpoint to scientific understanding, the statements reflect a surprising view of the role of single case studies within the larger enterprise. In this regard it is important to remember that it was never proposed that single case studies would be single-handedly responsible for progress, it has always been assumed that they would be one piece of a larger and broader deployment of scientific methods (see Caramazza, 1986).

It is relatively uncontroversial to assume that progress in understanding human cognition requires bringing to bear a great many (potentially indefinitely many) findings on a problem of interest. Theories are commonly seen as being developed via the pressures exerted by these multiple constraints and there are a great many sources of constraints, include evidence from psychological reaction time experiments, neuropsychological case series, fMRI studies and, also single case studies. Single case studies have long been argued to constitute experiments and, like other experiments they cannot stand alone, but rather contribute to the larger enterprise. Of course, the scientific impact of a particular experiment, set of experiments or a specific method cannot be anticipated. In this regard, however, it is clear that there have been single case studies that have had extraordinary impact. One need only consider the consequences for theories of memory of the Scoville & Milner report on HM (1957), the effect on theories of object recognition of the Goodale and Milner report on DF (1992), and many others, across a wide range of cognitive domains.

Conclusions

It is clear that all of the authors in this Special Issue think that the potential contribution of case series studies is considerable. Whether or not this potential is realized, however, will depend on the same sorts of things that the success of any approach depends on, in the end it comes down to, quite simply, whether or not findings can be used to develop strong and clear logical arguments that serve to advance our understanding of human cognition.

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