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Viewpoint

Current tests and trends in single-case neuropsychology

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ABSTRACT

In this issue of Cortex, Crawford, Garthwaite and Ryan publish Bayesian statistical tests that will enable researchers to take account of covariates when comparing single patients to control samples. In this article, we provide some context for this development, from an audit of the Cortex archives. We suggest that single-case research is alive and well, and more rigorous than ever, and that current practice has been shaped considerably by Crawford and colleagues' statistical refinements over the past 12 years. However, there is scope for further tightening and standardisation of statistical methods and reporting standards. The advantages offered by the new Bayesian tests should promote the even wider use of appropriate statistical methods, with benefits for the validity of individual studies, and for cross-comparability in the single-case literature.

1. Introduction

Single-case studies are at the historical root of neuropsychology, and have remained central to the field for 150 years, not only for their power to inspire and convey ideas, but also as hard data for hypothesis testing. It has even been argued that single-cases furnish the *only* relevant facts about the functional architecture of the mind (e.g., Caramazza, 1986, 1991). Subsequent to some famous exchanges in the 1980's (e.g., Robertson et al., 1993 cf. Sokol et al., 1991), and in the face of an undimmed contribution from group-based work, this extreme view is more often rehearsed as a pedagogical exercise than as a live possibility. Nonetheless, and despite breathtaking advances in functional imaging and neurodisruption, the study of individual patients remains a crucially important investigative tool. It is a tool that has been sharpened, over the past 12 years, by the progressive refinement of statistical methods for comparing individual patients against control samples (Crawford and Garthwaite, 2002, 2005a, 2007; Crawford et al., 2003a; Crawford and Howell, 1998; Crawford et al., 1998).

In this issue, Crawford, Garthwaite and Ryan publish the latest versions of their core statistical tests, which will enable researchers to take account of covariates when comparing single cases to controls. Given the perennial difficulty of matching control samples adequately, especially where more than one patient is involved, this seems likely to be of major utility and impact in the field. In this *Viewpoint* article, we provide some context from the *Cortex* archives, considering the importance of single-cases in neuropsychology, and the extent to which current practice has been shaped by Crawford and colleagues' statistical contribution. We suggest that single-case research is alive and well, and more rigorous than ever, but that there is scope for further tightening and standardisation of statistical methods and reporting standards.

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2. Case studies in *Cortex*

Cortex is a natural home for patient-based neuropsychology. An audit of the archives gives a quick overview of patient studies in these pages across three decades. We looked at original research articles published in three 2-year periods: 1989–1990, 1999–2000 and 2009–2010. We split these articles initially into patient and non-patient studies, with 'patient' defined loosely as any person that might be compared to 'normal controls' (thus including conditions such as developmental dyslexia and synaesthesia). A first salient fact is that overall publication volume has increased dramatically in recent times, from a stable level in 1989–1990 and 1999–2000 of 104 and 99 articles respectively, to 190 articles in 2009–2010. This increased research output is accounted for largely by methodologies other than patient-based behavioural research; most notably, structural and functional brain imaging. Thus, though the number of patient-based studies was higher in 2009–2010 than in 1999–2000 or 1989–1990 (104 *vs* 75 and 79 respectively), the percentage representation was significantly lower (55% *vs* 76% and 76% respectively; Fisher's exact $p < .0005$ in both cases). Patient-based studies are more numerous than ever, but form a less exclusive core of *Cortex*'s research output.

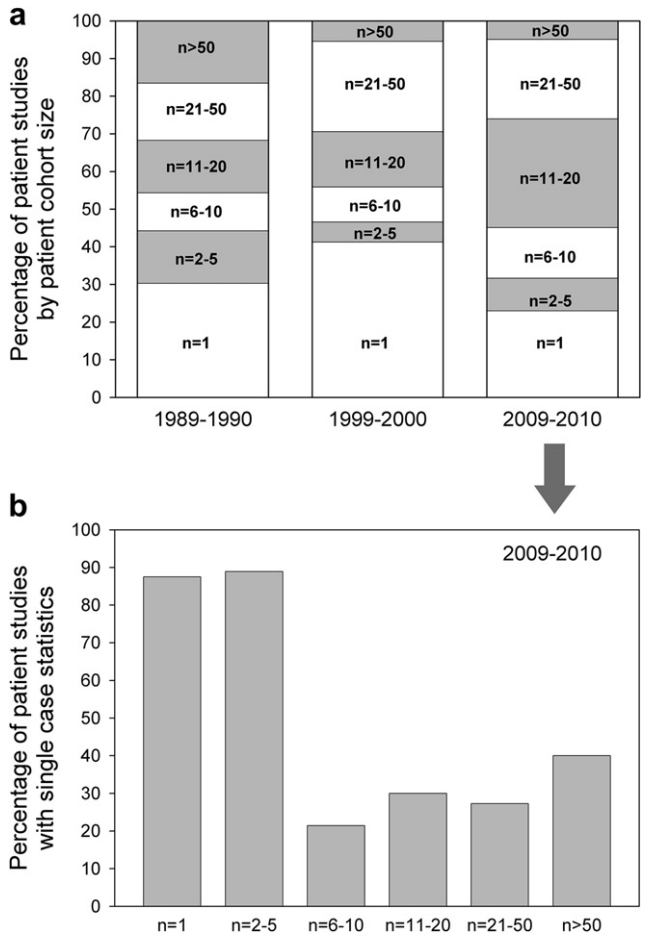

Fig. 1 – (a) Percentage of patient studies by patient cohort size for original research articles in Cortex in three 2-year periods across three decades. (b) Percentage of patient studies in which individual patients were used as a unit of inferential statistical analysis. See text for details.

For each patient study, we noted how many patients were reported, excluding those used solely as controls (Fig. 1a). Around a third (32%) of patient studies in 2009–2010 reported five patients or fewer, which is marginally lower than the 47% in 1999–2000 (Fisher's exact $p < .05$), but not significantly different to the 44% in 1989–1990. Of course, the raw *n* of a study, though readily audited, is a very blunt metric for the role of single-case statistics, since many of the larger cohort studies include single-case analyses, whilst some of the smaller scale studies are purely qualitative. A more relevant overview is obtained by unpacking the rightmost bar of Fig. 1a, according to whether or not individual patients were a unit of inferential statistical analysis (we exclude the almost ubiquitous practice of classifying patients according to cut-offs on standardised tests). Fig. 1b shows that the vast majority of reports with five or fewer patients included single-case analyses, as did a substantial percentage of the larger *n* studies. Overall, 49 (47%) of the 104 patient-based studies in *Cortex* in 2009–2010 included inferential statistics at the level of the individual patient. In 11 articles, the analyses were purely intra-individual; if the aim is to describe the modulation of a patient's symptoms under different conditions, then comparisons to controls, who lack those symptoms, may be relatively superfluous. In the vast majority, however, it was the comparison to controls that was at stake, the goal being the identification of abnormalities, usually deficits, following the traditional logic of behavioural dissociations.

3. Deficits and dissociations

Periodic reports of the death of the dissociation have so far been exaggerated. A *Cortex* Forum on this issue from 2003 had its overall mood well captured by Baddeley's title, "*Double dissociations: not magic, but still useful*" (Baddeley, 2003). In fact, at that moment, double dissociations were arguably becoming *more* useful than ever, as several key definitional and statistical issues were being addressed rigorously for the first time. In the immediately subsequent issue of *Cortex*, Crawford et al. (2003a) proposed new operational definitions for classical and strong behavioural dissociations. They pointed out that, whilst detailed consideration had been given to the inferences that can follow from such dissociations, less energy had been expended on the practical matter of how to identify them in the first place. They also suggested a similar schism in the behaviour of neuropsychological researchers, whereby painstaking attention to the design of experimental tasks could be coupled with an almost anosognosic lack of concern for the statistical tools applied to the data (see also Crawford et al., 2010; Crawford and Garthwaite, 2011). To remedy this, they proposed tighter formal requirements for establishing dissociations, at the heart of which were bespoke statistical tests for single-case neuropsychology.

4. Crawford and colleagues' core tests

The traditional method of comparing a patient statistically to controls has been via the z-score [the patient's score

expressed as the number of standard deviations (SDs) it lies from the control mean], with the cut-off for significance set at a desired level (e.g., $z = 1.65$ for a one-tailed $p < .05$). In principle, provided the assumption of normality is met, the method is sound. In practice, z-scores are often not sound because, due to limited availability of matched controls, and practical constraints on time and effort, single cases usually have modest ($n \leq 20$), small ($n \leq 10$) or very small ($n \leq 5$) control samples. Scores in such samples do not follow the standard normal population distribution to which z-tables refer, but follow t-distributions. The precise shape of the t-distribution depends upon sample size, but for 50 observations or fewer, it has notably fatter tails than does the standard normal distribution, so extreme scores are more likely to be encountered by chance. Use of z-scores for small samples thus overestimates the rarity of extreme scores, making us more likely to misclassify a patient's performance as abnormal (a Type I error). The smaller the control sample, the more severe the problem. To address it, Crawford and Howell (1998) developed a modified t-test for case-control comparisons. For control samples of less than 50, their method regulates Type I errors more effectively than does the z-score method, providing a more rigorous basis for defining behavioural deficits in single patients; for samples larger than 50, the methods converge.

A behavioural deficit alone is of limited value to theory, becoming interesting only when dissociated from some other, preserved function of relevance. Classical dissociations hold the greatest inferential power, being defined as a significant deficit on one task (or group of tasks), with normal performance on a second task (or group of tasks); the next most powerful type is the strong dissociation, in which a patient is impaired for both tasks, but significantly more impaired for one than the other (Shallice, 1988). This latter definition implies that the discrepancy between a patient's scores on two tasks is abnormally large by comparison with the discrepancies amongst controls, but an agreed method to test for this was lacking prior to Crawford et al's (1998) introduction of a modified *paired*-t-test for the purpose, later refined as the *Revised Standardised Difference Test* (RSDT) (Crawford and Garthwaite, 2005a). Like Crawford and Howell's (1998) modified t-test, the RSDT constrains Type I error rate robustly even for very small control samples, and is surprisingly tolerant of non-normality, at least for modest or larger samples (Crawford and Garthwaite, 2005a; Crawford et al., 2006). Of course, the fact that these methods make it possible to use few controls does not imply that small samples are ever to be recommended. Case-control comparisons are inherently short on statistical power, and the problem is only exacerbated by small sample sizes (Crawford and Garthwaite, 2006b).

The RSDT has also assisted in tightening up the traditional definition of a classical dissociation, as a significant deficit on one task and not on another. This definition admits a substantial risk of falsely identifying a classical dissociation between two task scores that fall on opposite sides of the threshold for abnormality, yet differ little from one another. To forestall such false positives, Crawford et al. (2003a) proposed that classical dissociations should additionally require an abnormally large discrepancy between tasks to be established. A simulation study explored the effect of this additional criterion on the false identification of classical dissociations amongst simulated patients with equivalent deficits on two tasks (Crawford and Garthwaite, 2005b). Even with Crawford and colleagues' tests replacing z-score methods, the false positive rate for traditionally-defined classical dissociations was alarmingly high (up to 50% under some conditions), but the additional requirement for a significant discrepancy between tasks produced a major step reduction, driving the false positive rate below 7.5% under all conditions tested. It is now widely accepted that the minimal requirement for a behavioural dissociation should be a significant abnormality on at least one task, coupled with a significantly large discrepancy between tasks. The dissociation may be called classical where there is a deficit on one task only, and strong where there are deficits on both.[1]

5. Refinements and reporting standards

These major reforms to single-case methodology have been followed by a series of refinements and extensions. The core tests for deficits and dissociations have been adapted to take as data the slope of a regression line, correlation coefficients or other within-subject measures of association (Crawford et al., 2003b; Crawford and Garthwaite, 2004). More recently, Bayesian versions of the core tests have been developed (Crawford and Garthwaite, 2007; Crawford et al., 2010). The *Bayesian Test for a Deficit* (BTD) turns out to produce equivalent outcomes to the modified t-test under all conditions, but the *Bayesian Standardised Difference Test* (BSDT) outperforms the RSDT, as it can take account of the fact that the more extreme a patient's task scores, the more that the apparent discrepancy between them will be affected by uncertainty in estimating the SDs of control scores for the tasks (see Crawford and Garthwaite, 2007, for worked examples). In this issue of *Cortex*, Crawford, Garthwaite and Ryan extend these Bayesian methods to allow for the inclusion of covariates when testing for a deficit (BTD-cov) or a dissociation (BSDT-cov). In principle, this allows a group of controls, bracketing the patient on some task-relevant dimension (e.g., age, handedness quotient, IQ), to have their test scores adjusted statistically to those expected from an ideal control sample, all perfectly matched to the patient on that dimension. Since researchers may routinely wish to account for major demographic variables such as age, and often for other factors (e.g., IQ) that may influence task performance, it seems likely that these tests will be of major utility and impact in the field.

Like many new technologies, these tests also create new pitfalls and opportunities for abuse. Crawford et al. (this issue) warn explicitly against 'fishing expeditions' in which multiple combinations of covariates are explored in order to finesse a desired result. Ideally, candidate covariates should be defined in advance, with transparent criteria for inclusion in the analysis, such as a correlation of at least .3 with at least one of the dependent measures. Moreover, the *interpretation* of the

[1] However, simulations suggest that, even if the false positive rate for dissociations *per se* is controlled adequately, there remains a high likelihood of misclassification of dissociation *type*, especially misclassification of a strong dissociation as classical (Crawford and Garthwaite, 2006a).

Table 1 – Types of analysis in patient-based original research articles in *Cortex* 2009–2010. The lower right section focuses on 38 articles in which individual patients were compared to a control sample, with crosses indicating statistical. * Indicates that Bayesian version of test was used.

Group-based analysis only

Angwin et al. (2009)
Bava et al. (2010)
Bosch et al. (2010)
Cavézian et al. (2010)
Ciaramelli et al. (2009)
Clément et al. (2010)
Colman et al. (2009)
Copland et al. (2009)
Corriveau and Goswami (2009)
De Luca et al. (2010)
Dhar et al. (2010)
Fahim et al. (2010)
Fielding et al. (2009)
Frassinetti et al. (2010)
Gainotti et al. (2009)
Grahn and Brett (2009)
Hanley and Nickels (2009)
Hochstadt (2009)
Jacobs et al. (2009)
Leppänen et al. (2010)
Lu et al. (2010)
Majerus et al. (2009)
Marinus and de Jong (2010)
Marsh et al. (2009)
Matuszewski et al. (2009)
McLean et al. (2010)
Monetta et al. (2009)
Muller et al. (2010)
Olk et al. (2010)
Péran et al. (2009)
Pia et al. (2009)
Ptak et al. (2009)
Rimrodt et al. (2010)
Salillas et al. (2009)
Serra et al. (2010)
Shamay-Tsoory et al. (2010)
Simner et al. (2009)
Skelton et al. (2009)
Smith et al. (2010)
Teichmann et al. (2009)
Tracy et al. (2009)
Wagner et al. (2010)
Willcutt et al. (2010)
Wimmer et al. (2010)

Single-case analysis: qualitative only

Picard (2010)
Suarez et al. (2010)

Single-case analysis: standardised tests only

Angelelli et al. (2010)
Antoniello et al. (2010)
Baillieux et al. (2010)
Caine et al. (2009)
Catsman-Berrevoets and Aarsen (2010)
Funnell and Pitchford (2010)
Mariën et al. (2009a)
Mariën et al. (2009b)
Tavano and Borgatti (2010)

Single-case statistical analysis: within-subject only

Blangero et al. (2010a)
Conson et al. (2009)
Cristinzio et al. (2009)
Davis et al. (2010)
Dipietro et al. (2009)
Gvion and Friedmann (2010)
Hamilton et al. (2010)
Mätzig et al. (2009)
Riddoch et al. (2010)
Savazzi et al. (2009)
Thimm et al. (2009)

Single-case statistical analysis: case-control design

			Crawford and colleagues' test		
		Control n	*For deficit*	*For discrepancy*	*Other*
Berteletti et al. (2010)		5	X		
Blangero et al. (2010b)		7			X
Bultitude and Rafal (2010)		8			X
Busigny and Rossion (2010)		10.75	X		
Castles et al. (2010)		13.5	X		
Cloutman et al. (2009)		50			X
Dalla Barba and Decaix (2009)		10	X		
Daprati et al. (2010)		12	X		
De Smedt et al. (2009)		25			X
Drane et al. (2009)		n/a			X
Dubois et al. (2010)		9	X	X*	
Friedmann et al. (2010a)		11	X		
Friedmann et al. (2010b)		10	X		
Georgiou et al. (2010)		233			X
Herbert and Best (2010)		8	X	X	
Hubbard et al. (2009)		8	X	X	
Jarick et al. (2009a)		14		X	
Jarick et al. (2009b)		10		X	
Laganaro et al. (2009)		15			X
Laiacona et al. (2009)		22			X
Lallier et al. (2010)		30	X		
Lee et al. (2010)		18.5	X		
Loetscher et al. (2010)		17	X*		
Nijboer et al. (2009)		6	X		
Osiurak et al. (2009)		41		X	
Overney et al. (2009)		5			X
Peters et al. (2009)		27	X		
Piwnica-Worms et al. (2010)		6			X
Ramon and Rossion (2010)		12			X
Rapcsak et al. (2009)		31			X
Ronchi et al. (2009)		21	X		
Sprengelmeyer et al. (2010)		30			X
Starrfelt et al. (2010)		5	X		
Stieglitz Ham et al. (2010)		23	X	X	
Tree and Wilkie (2010)		20			X
Tsapkini and Rapp (2010)		11	X	X	
Uno et al. (2009)		240			X
van Kessel et al. (2010)		20			X

relationship between a covariate and a dependent variable is, as ever, the responsibility of the researchers. It would obviously be unwise to enter as a covariate anything that might itself be influenced by the key behaviours at stake (in evaluating a patient on a test of neglect, we should not wish to control for spatial IQ). Nonetheless, with proper application, the ability to statistically match a control sample to one or more patients on one or more covariates will enhance power to distinguish true deficits and dissociations. It should also allow greater tolerance in the pre-matching of controls, making it easier to collect larger control samples, thereby facilitating further increases in power.

In refining their tests for deficits and dissociations, a parallel aim of Crawford and colleagues' has been to extend the range of useful parameters reported. First, the exact *p*-value provides a point estimate of the abnormality of the patient's performance (*p* is the proportion of the control population expected to obtain a more extreme score), and the associated effect size is given directly by the traditional z-score (how many SDs the patient lies from the control mean). An initial extension of the modified *t*-test provided confidence intervals on the point estimate of abnormality (Crawford and Garthwaite, 2002), and the latest versions of the Bayesian tests now provide 95% credible intervals (the Bayesian analogue of 95% confidence intervals) on both the estimated abnormality and effect size. Recently, Crawford et al. (2010) have proposed new reporting standards for single-case studies, recommending that, for each test of deficit or dissociation, authors should tabulate the control sample size, the control mean and SD, the patient's score, the *t*-value and exact *p* for the comparison, and point estimates of abnormality and effect size with 95% credible or confidence intervals on both. Fortunately, the onus is light and clerical, as the relevant values are computed readily using free software from John Crawford's web-pages at the University of Aberdeen.[2]

6. Current trends in single-case research

As noted earlier, we audited 104 patient-based studies in *Cortex* in 2009–2010. The right side of Table 1 lists the 49 studies that included inferential statistics at the level of the individual patient, and the lower right section focuses on those 38 studies in which individual patients were compared to a control sample. Twenty-two (58%) of these used at least one of Crawford and colleagues' tests for a deficit and/or a dissociation. Of the remaining 16, three made non-parametric comparisons only (setting a cut-off at the lowest control score), and 13 made parametric comparisons to the control distribution. Of these, one used the *t*-distribution, and 12 others used (explicitly or implicitly) the standard normal distribution (i.e., z-scores). These 12 studies tended to have larger control samples (median $n = 23.5$, range: 6–240) than the 22 that used Crawford and colleagues' tests (median $n = 11$, range: 5–41) (Mann–Whitney $U = 195.5$, $z = 2.29$, $p = .02$). The broad patterns suggest that Crawford and colleagues' tests are now the tests of choice for single-case comparisons, especially where control numbers are low. Statistical practice in neuropsychology has thus been reshaped considerably by these methods, though a subset of studies are still using z-scores even for small control samples.

Of the 22 studies using Crawford and colleagues' tests in *Cortex* in 2009–2010, only two explicitly reported the estimated abnormality of the patient's test score, and only one put a confidence interval on this estimate. Seven studies reported an exact *p* value (from which a point estimate of abnormality can be inferred), but the remaining 13 reported *p* value ranges only (e.g., $p < .05$). No studies included an explicit estimate of effect size, and only 14 gave sufficient information for the calculation of one (patient score, control mean and SD). So, whilst Crawford and colleagues' tests have been adopted enthusiastically by the neuropsychological community, traditional reporting of statistical parameters has barely changed. Notably, the reporting of effect-sizes has been largely absent, even though this standardised measure may be particularly useful for a literature in which we often wish to compare a patient's performance across tasks that use very different scales, or to compare patients across studies. It will be interesting to see whether such parameters are more commonly reported in future, given Crawford et al.'s (2010) recent call for updated reporting standards, and a growing appreciation of effect-size measures in science more generally.

A further feature of current practice suggested by Table 1, is worth noting. Where Crawford and colleagues' tests were used, tests on the abnormality of a task score (tests for deficit) were much more common than tests on the abnormality of a discrepancy between tasks (19 *vs* 8 instances). A focus on deficits, rather than dissociations is perhaps unsurprising in clinical descriptions, but even in theoretically-motivated experimental studies, formal tests of dissociation in single patients were rare (exceptions were: Dubois et al., 2010; Herbert and Best, 2010; Stieglitz Ham et al., 2010; Tsapkini and Rapp, 2010). A more detailed audit than ours would be required to assess whether the apparently low number of demonstrated dissociations is due to under-adoption of available tools, or any shift in emphasis away from dissociation logic itself. If such a shift in emphasis were real, it would further be interesting to know whether it reflects a change in scientific preference, or simply that the lowest-hanging fruit of neuropsychological dissociations have mostly been had.

Finally, despite the traditional status of double dissociations as the holy grail of neuropsychology, we found no studies in *Cortex* in 2009–2010 that tested for a double-dissociation between two patients. At least part of the explanation must lie in the practicalities of patient work, which is always a collaboration with chance. We may be lucky enough to find one-patient with a clear behavioural dissociation, but our chances of finding a second patient with a complementary pattern, in the same time-window, are vanishingly slim. Double dissociations are more usually inferred across studies, so the patients may have been studied by different research groups, tested on different tasks, and compared to different control samples, often by different statistical means. An

[2] The free software is for Windows, but we have found it to run perfectly in a Windows emulator (e.g., WINE) on Macintosh or Linux operating systems. Some of the tests have also been implemented in a free *singlecase* package for the R statistical programming environment, by Matthieu Dubois at the Université Catholique de Louvain. The *singlecase* package is available on CRAN, the R Archive Network.

apparent double-dissociation may thus have its substantive basis in a qualitative contrast of patterns, rather than any direct quantitative comparison between patients. Crawford and colleagues' methods cannot address the vagaries of patient availability, but they do suggest appropriate standards to help maximise the scope for cross-study quantitative comparisons and meta-analyses.

7. Conclusions

Our audit of the *Cortex* archives suggests that single-case research is alive and well. The recent work of Crawford and colleagues means that it may also be more rigorous than ever, due to the widespread adoption of improved quantitative methods for case-control designs. However, there is still scope for tightening and standardisation of statistical practices. This includes the active testing for dissociations, over and above deficits, and the reporting of adequate summary statistics and scale-independent effect-sizes (Crawford et al., 2010). In the interests of comparability, single-case researchers should strive to use comparable or identical behavioural tasks to those used for similar patients, and the larger the control sample the better. The use of *identical* tasks would make possible the re-use of control data across studies, facilitated by the fact that Crawford and colleagues' statistical tests accept summary control data as inputs. In this issue of *Cortex*, Crawford, Garthwaite and Ryan publish Bayesian tests that allow for the inclusion of covariates when testing for single-case deficits and dissociations. The advantages offered by these new tests should promote the even wider use of appropriate statistical methods, with benefits for the validity of individual studies, and for cross-comparability in the single-case literature.

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