nature neuroscience

When once is enough

One talking pig is sufficient to prove that pigs can talk, goes a well-known argument in favor of single-case studies. We agree that papers on certain individual brain-damaged patients have a place in general-interest neuroscience journals, but they must meet high standards of scientific rigor and novelty. Which studies pass the 'talking pig test'? Here we provide some guidelines to help authors and referees answer this question.

The most obvious requirement is that the patient must have a strikingly unusual lesion or behavioral syndrome. If it is possible to find two or three more patients with a similar deficit within a reasonable length of time, then we do not see any reason to publish a paper on a single case. Of course it is not necessary that the patient be unique in history, but it should be prohibitively difficult, not merely inconvenient, to locate others. In some cases, a bilateral lesion may meet this standard even if unilateral lesions of the same type are relatively common.

The case should also have strong novelty and theoretical significance. An odd behavioral syndrome alone is not enough to justify high-profile publication. Instead the findings should shed light on the basic organization of the brain, preferably an aspect that was previously unknown or highly controversial. For example, the identification of patients who could not read but could still write gave important insight into the separation of these two aspects of language in the brain. Because it is rarely possible to draw strong anatomical conclusions from a single patient, the theoretical significance of such studies is most likely to be in determining the brain's functional organization, rather than the localization of a particular function, although anatomical information should still be provided, as discussed below.

For a single case to be interpretable, the behavioral deficit should be clear. That is, the effect should be large (non-overlapping with controls) or it should be supported by comparison to an internal control within the same patient (right versus left hemisphere in a patient with unilateral neglect, for example). The deficit should also be specific—the patient ideally should be within normal limits on a broad battery of neuropsychological tests—and stable across repeated test sessions. Along the same lines, a single case in the experimental group does not excuse authors from including an appropriate control group, which should rule out potential nonspecific effects of brain damage such as low IQ or working memory deficits, with particular attention to matching any deficits in the experimental patient that are not thought to be relevant to the interpretation. The patient should be compared to the control group by computing z-scores to show the statistical distance between his/her performance and the norm. Convergence with previous results from studies of nonhuman animals or neuroimaging further increases the credibility of a single-case study.

In addition, there is a substantial advantage in having a patient with a well-defined, small lesion. When such damage is very rare, this feature alone might justify publication of a single-case study, as such lesions can be used to demonstrate that damage to a particular brain area by itself can cause the behavioral deficit, a conclusion that cannot be drawn from a group of patients with larger lesions that include the region.

Of course, single-case studies should also meet the general requirements for neuropsychology papers in *Nature Neuroscience*. In particular, papers must include reliable anatomical information on the site and extent of the lesion, which should be illustrated for all studies, and quantified whenever possible. Magnetic resonance imaging (MRI) is usually the best approach, providing millimeter resolution. For some patients, MRI scanning is not an option, because they have metal such as a pacemaker in their bodies or because they are claustrophobic. In such cases, computerized tomography (CT) scanning may be acceptable, but only if the study's conclusions do not require distinguishing nearby areas, as CT scanning has roughly an order of magnitude less resolution than MRI. None of these technologies provides reliable results immediately after injury, so scanning should be done after the damage is stable, and preferably around the time of behavioral evaluation. Researchers should also do their best to rule out white matter involvement (which raises the possibility that disconnection of some distant region via damage to nearby axons may underlie the behavioral effects), compensatory reorganization, or temporary disruption of areas adjacent to the primary site of damage during the acute phase of injury.

Studies of multiple patients also have a few potential drawbacks that are not a problem in single-patient studies. The main risk is inappropriately averaging out anatomical differences between individuals. As brains vary, transformation onto a standard template, such as Talairach space, can blur the location of the region of interest, resulting in a loss of information. In most cases, this is compensated by the increase in statistical validity, and the ability to generalize findings outside the group studied. However, it will be an important goal for both single- and multiple-patient studies to develop MRI techniques that can resolve laminar characteristics, allowing scientists to identify a variety of cortical areas in individual scans. Along the same lines, when similar behavioral syndromes result from disruption of different anatomical elements of a network, it can be difficult to use group analysis to draw conclusions about the basis of the behavior. In such cases, combining lesion studies with functional imaging may prove beneficial.

Few, if any, papers will m*eet all* these criteria, of course. Our intention is not to define a set of absolute standards, but to indicate what factors we consider important in determining which papers to publish. From the behavioral changes of Phineas Gage to the amnesia of HM, single patients have been extremely influential in neuroscience, and we recognize, in this age of high-tech approaches to probing the brain, that such studies continue to offer considerable potential for advancing our understanding. ■