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Letter to the Editor

Neuropsychology is nothing without control: A potential fallacy hidden in clinical studies

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The need of appropriate methodological approaches in cognitive neuropsychology has been repeatedly addressed for over 30 years. Most of the debate has focused on whether single-case or group studies are more appropriate for drawing inferences with respect to an unimpaired cognitive architecture (e.g., Caramazza and McCloskey, 1988; Grodinsky et al., 1999). This controversy has not been resolved in either direction and, currently, both single-cases and group studies are commonly adopted in neuropsychological research.

We will focus our attention upon the latter approach and will maintain that the presence of a control group does not *per se* guarantee an appropriate interpretation of results.

According to the group study approach, an experimental group of brain damaged patients is typically selected according to specific diagnostic tests or criteria; then an age-matched non-pathological control group is also selected on the same tests/criteria. These two groups are usually required to perform a task, which is the focus of the study. Then, in discussing the results, the immediate (and rather naïve) conclusion is to ascribe the differences between the two groups to the presence/absence of the specific pathology.

Here is where the fallacy can be incurred: the control group often differs from the experimental group, not only because of the absence of the pathology, but also because it lacks other characteristics, associated with the pathology itself. If we select a group of patients on the basis of their performance in a test for a specific neuropsychological deficit (e.g., anosognosia, apraxia, etc.) we are in fact selecting patients with that deficit and with a high probability of associated (often cognitive) impairments against patients (or healthy participants) without that deficit and with a lower probability of associated impairments. That is, collateral impairments, which are necessarily associated to the presence of a specific deficit, are often overlooked as a possible source of the differences between experimental and control groups.

This fallacy can be seen as a byproduct of a strict interpretation of the modularity approach to human cognition, according to which impairments can be confined to a single cognitive function, leaving all other functions intact.

Thus, some of the group differences described by the studies that incurred in this fallacy could potentially be the consequence of a greater difficulty to perform the experimental task (or the neuropsychological tests) simply because the experimental group is more impaired.

This criticism is not novel: in the past it was specifically leveled at the case of large group studies which compared the frequency of disorders between right versus left brain damaged patients, and where the two samples were typically heterogeneous with respect to several (uncontrolled) variables. For instance, in these studies experimenters, quite obviously, had to exclude those patients with severe comprehension deficits, because they were unable to understand task instructions and/or to perform the intelligence tests. By doing so, typically, the most severe patients were subtracted from the group of the left but not from the group of the right brain damaged patients (see De Renzi, 1982), in which comprehension deficits are much less common. Due to this bias, some researchers reported, for instance, that constructional apraxia was twice as frequent in right than in left brain damaged patients (see De Renzi, 1982 for review). After overcoming this fallacy, neuropsychologists

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reached two conclusions. The first is that constructional apraxia depends on a number of unspecific cognitive impairments. The second is that its incidence is not dissimilar following right and left hemisphere lesions, when experimental tasks with easy instructions, which can be understood by aphasic patients, were adopted (De Renzi, 1982).

The same fallacy can be observed in studies of anosognosia for motor impairments, whose incidence was thought to be higher following right than left brain lesions. Cocchini et al. (2009) recently reported that, in analogy with constructional apraxia, also anosognosia for motor impairments can be found, following left brain damage, more frequently than what was previously thought. This occurs when tests that are less dependent on language are adopted, that is when data from left brain damaged patients with aphasia are included in the study.

Despite the long history of this debate, many studies (most often in conferences but also in refereed journals) nowadays seem to ignore the fact that pathology-related selection could be very risky, when potential confounding factors are not taken into account. Perhaps, the idea is that the risk to incur in the fallacy would not be present in contemporary studies, because they are concerned with smaller groups of patients and do not aim at establishing the incidence of a given pathology.

Unfortunately, the risk of erroneously attributing the deficits shown by the experimental group to the pathology itself, rather than to the presence of uncontrolled, collateral impairments, does not decrease when sample size decreases. It does not disappear either when claims about the incidence of a specific pathology are no longer made. Even worse, the fallacy can have negative consequences also on the selection of the most appropriate rehabilitation procedure. Indeed, while it is clearly important to focus neuropsychological rehabilitation on a specific cognitive impairment, it might be equally appropriate to implement rehabilitation approaches encompassing also treatments for the associated deficits, which can have an effect by themselves or interacting with the specific pathology.

Also in clinical developmental studies, besides the distinction based on the presence/absence of a disorder, potential comorbidities, along with their atypical development trajectories, must be taken into consideration (Karmiloff-Smith, 1998). Therefore, developmental studies often adopt stringent methodological approaches (Mervis and Klein-Tasman, 2004), such as the use of performance-matched (i.e., typically younger) control participants.

Three strategies allow one to lessen the impact of the methodological fallacy we have been discussing, and, when implemented, render the results of neuropsychological group studies more solid. The first is general and consists in being very cautious in attributing the differences between the two groups to the mere presence/absence of the pathology, and especially so when the aspect under investigation is different from the known clinical manifestations of the pathology.

For instance, as authors themselves suggest (Coin et al., 2010), the finding of a positive effect of religiosity on dementia-related cognitive decline does not exclude the absence of differences between the two groups (high *vs* low religiosity) with respect to other independent variables. One could have been, for example, the quantity of social interactions and activities undertaken. Similarly, the differences in spatial remapping found by Russell et al. (2010) between right brain damaged patients, with and without constructional apraxia, could be potentially related to a higher co-occurrence of cognitive deficits, either specific (sub-clinical neglect) or unspecific (general impairment), in the group with constructional apraxia. This possibility might be more than a speculation because apraxic patients presented with much larger brain lesions with respect to non-apraxic patients. Furthermore, when excluding the presence of a deficit in a group (either the experimental or the control group) one should always make sure that the diagnostic tools (e.g., paper-and-pencil tests) are sufficiently sensitive to detect even subtle forms of it (Bonato et al., 2010, for the assessment of neglect).

Some studies provide evidence that the severity of the pathology is statistically correlated with the measure of interest. The presence of a significant covariance between the pathology and the dependent variable is suggestive of a non-incidental coupling, but it does not allow one to exclude the possibility that the observed correlation might be produced by the severity of collateral impairments (spurious correlation).

The second strategy is as simple as crucial and consists of a fine-grained matching between experimental and control groups for all those variables that may affect performance.

The third, recommended strategy consists of comparing patients' performance also in a "control" task similar to the experimental one in terms of setting (stimuli presentation, response modality) and task difficulty, but requiring cognitive processes differing from those that are the object of the study, as properly done for instance in the above mentioned study by Russell et al. (2010). If no differences between the two groups emerge in this control task, more robust conclusions about the effect under investigation being selective for the experimental group can be drawn. As an example, the interesting possibility that deficits in spatio/temporal processing of right brain damaged patients are due to neglect (Calabria et al. 2011) would have been even more convincing if such a control task was provided.

In conclusion, the risk to entrust the methodological appropriateness of a study to the mere presence of a control group cannot be overlooked. The availability of advanced methods should not push to the background a basic methodological issue that, at least for the specific case of hemispheric differences, had been very prominent in past neuropsychological research.

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