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Progress in Neuro-Psychopharmacology & Biological Psychiatry 32 (2008) 1172–1178
Progress In Neuro-Psychopharmacology & Biological Psychiatry
www.elsevier.com/locate/pnpbp

Hybridizing behavioral models: A possible solution to some problems in neurophenotyping research?

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Received 22 October 2007; received in revised form 7 December 2007; accepted 7 December 2007
Available online 23 December 2007

Abstract

The use of batteries of single-domain tests for neurophenotyping research is a common strategy to achieve higher data density and explore different behavioral domains. This approach, however, is accompanied by several methodological challenges, briefly discussed here. As an alternative, this paper advocates the wider use of extensive "hybrid" protocols that assess multiple domains in parallel, or logically/logistically combine experimental paradigms, in a way that disproportionately maximizes the number of tested phenotypes per experimental manipulation. Several examples of this approach are given in this paper, demonstrating the potential to reduce time, cost and subject requirements for the experiments. Offering behavioral analyses that are lacking in the standard single-domain tests, such "hybrid" models enable innovative modeling of neuropsychiatric disorders by more thorough and broader investigation of complex phenotypical characteristics.
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Keywords: Behavioral phenotyping; Experimental models; High-throughput testing; Research strategies; Single and multiple domains

1. Introduction: current challenges

Although animal models are widely used for screening psychotropic drugs, testing neurobiological hypotheses and finding candidate genes for brain disorders (Bolivar et al., 2007; El Yacoubi and Vaugeois, 2007; Gould and Einat, 2007), neurophenotyping research is currently facing several challenges.

On one hand, mounting pressure due to increased animal/space costs (Lake et al., 1999) is leading to the extensive use of animals in intensive batteries to increase test information density (Godinho and Nolan, 2006; Sousa et al., 2006). Environment and prior test history may modify animal behavioral performance (Holmes and Rodgers, 2003; McIlwain et al., 2001), thereby influencing data validity and variability (Crabbe et al., 1999; Lathe, 2004; Wolfer et al., 2004). There are also growing concerns of neuroscientists for animal welfare (Warnick et al., 2006; Wurbel, 2007), and common problems with correct dissection of animal phenotypes in behavioral experiments (Cryan and Holmes, 2005; Kalueff et al., 2007d).

On the other hand, both academia and the industry need fast, low-cost, high-throughput behavioral screens for their expanding biomedical research (Crabbe and Morris, 2004; Godinho and Nolan, 2006; Tecott and Nestler, 2004). With the growing number of genetically modified animals (Hunter et al., 2000; MGI, 2007), including those with complex (Egashira et al., 2007; Hunter et al., 2000; Nolan, 2000) or overlapping (Clapcote et al., 2007; Szumlinski et al., 2005) phenotypes, the existing behavioral assessment techniques bolster this intensification in order to dissect multiple domains.

Moreover, it is becoming increasingly important to develop animal models for newly appreciated clinical phenomena (Kalueff et al., 2007d; Siegmund and Wotjak, 2007) and for integrative (Akiskal and Benazzi, 2005; Benazzi, 2006; Lara and Akiskal, 2006) vs. disorder-specific modeling of brain pathogenesis, see

Abbreviations: OCD, obsessive compulsive disorder; FST, forced swim test; MWM, Morris water maze; OFT, open field test; NT, neurological tests; ST, swim tests.

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0278-5846/$ - see front matter. Published by Elsevier Inc.
doi:10.1016/j.pnpbp.2007.12.010

(Einat, 2006; Einat, 2007; Gould and Einat, 2007) for discussion. Therefore, in addition to currently used experimental approaches (Tecott and Nestler, 2004) and "specific" animal models designed to mimic individual brain disorders or domains (Crawley, 2000; Sousa et al., 2006), neurophenotyping research may benefit from using alternative strategies to address the existing challenges. Here, we will argue that a wider use of "hybrid" models that comprehensively assess multiple behavioral domains may be instrumental in achieving these goals.

2. Methodological considerations

Although it is crucial that researchers avoid basing their interpretations of behavioral data on individual tests or domains (Crawley, 1999; Crawley, 2000), investigators interested in a particular trait sometimes perform a very restricted behavioral analysis, limited to the domain of interest (Tecott, 2003). The importance of an in-depth assessment of multiple domains for correct interpretation of neurobehavioral data has been recognized in the literature; see Tecott (2003) for review. One solution to optimize the throughputfulness of the experiments is to use behavioral models that allow the researchers to register as many parameters as possible. For example, the elevated plus maze test of anxiety targets several different domains (exploration, activity, risk assessment) and can be used for their simultaneous assessment in animals (Doremus et al., 2006; Walf and Frye, 2007).

Another solution, as already mentioned, is the use of batteries of specialized tests (Fig. 1A) that focus on different domains. At this stage, however, it is crucial to consider how behaviors can be affected by the previous testing experience of the animal, and what measures should be taken to ensure that the data are not compromised as a result. For example, timing is an important issue. Some studies indicate that mice respond differently when tested in a battery rather than in individual tests alone (McIlwain et al., 2001), showing that some behavioral tests are more susceptible to previous experience of the animal, while others are not. Other studies suggest that the inter-test time interval has little effect on overall performance (Paylor et al., 2006), which opens the opportunity for accelerated research techniques. Moreover, if one test does alter behavior in another, that fact does not disqualify the test from further use. In fact, the combination of the tests may provide opportunities for eliciting clinically relevant behaviors that could not be achieved with either test alone.

In addition to the test batteries' effect on animal behaviors, the nature of behavioral tests *per se* may sometimes preclude them from being able to form a battery. For example, the

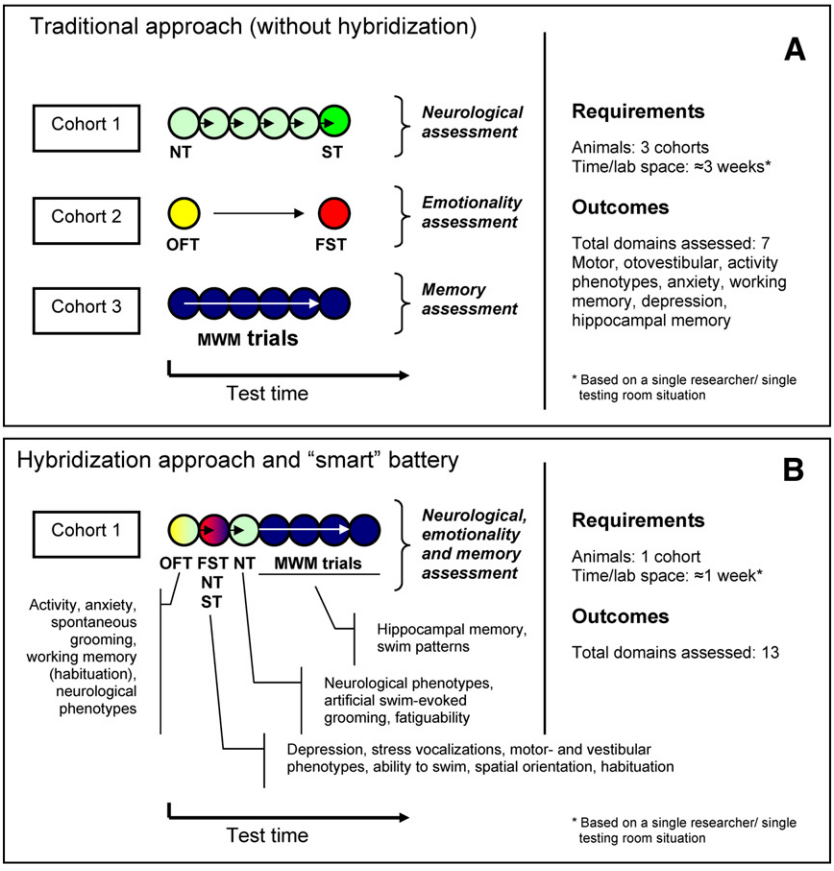

Fig. 1. Traditional neurophenotyping approaches (A) and the use of a combination of novelty-, activity- and swim-based tests to create a "smart" battery of "hybrid" tests (B) that helps maximize animal behavioral information. NT—different neurological tests; ST—swim test (ability to swim); OFT—open field test; FST—Porsolt's forced swim test, MWM—Morris water maze (see text for details).