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Teaching neurophysiology, neuropharmacology, and experimental design using animal models of psychiatric and neurological disorders

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Morsink MC, Dukers DF. Teaching neurophysiology, neuropharmacology, and experimental design using animal models of psychiatric and neurological disorders. Adv Physiol Educ 33: 46–52, 2009; doi:10.1152/advan.90179.2008.—Animal models have been widely used for studying the physiology and pharmacology of psychiatric and neurological diseases. The concepts of face, construct, and predictive validity are used as indicators to estimate the extent to which the animal model mimics the disease. Currently, we used these three concepts to design a theoretical assignment to integrate the teaching of neurophysiology, neuropharmacology, and experimental design. For this purpose, seven case studies were developed in which animal models for several psychiatric and neurological diseases were described and in which neuroactive drugs used to treat or study these diseases were introduced. Groups of undergraduate students were assigned to one of these case studies and asked to give a classroom presentation in which 1) the disease and underlying pathophysiology are described, 2) face and construct validity of the animal model are discussed, and 3) a pharmacological experiment with the associated neuroactive drug to assess predictive validity is presented. After evaluation of the presentations, we found that the students had gained considerable insight into disease phenomenology, its underlying neurophysiology, and the mechanism of action of the neuroactive drug. Moreover, the assignment was very useful in the teaching of experimental design, allowing an in-depth discussion of experimental control groups and the prediction of outcomes in these groups if the animal model were to display predictive validity. Finally, the highly positive responses in the student evaluation forms indicated that the assignment was of great interest to the students. Hence, the currently developed case studies constitute a very useful tool for teaching neurophysiology, neuropharmacology, and experimental design.

face validity; construct validity; predictive validity; neurophysiology; neuropharmacology; pathophysiology; experimental pharmacology

The study of human diseases often involves performing physiological and pharmacological experiments in animal models. Generally, experimental results obtained in these models are extrapolated to the human situation, providing new insights into disease mechanisms and treatment options. To be able to reliably extrapolate results obtained in animal experiments, it is important to consider the validity of the animal model used, i.e., the extent to which the model mimics the disease (11). This validity is often characterized by 1) the resemblance in symptoms (face validity), 2) shared etiology and underlying pathophysiological mechanisms (construct validity), and 3) similarity of pharmacological responses (predictive validity) (16, 21). Hence, the analysis of face, construct, and predictive validity of animal models constitutes a very important aspect in the study of disease physiology and pharmacology.

1. the “semistarvation-induced hyperactivity model” for anorexia nervosa (17)
2. the “repeated hypoxia during the equivalent of extreme prematurity model” for attention-deficit/hyperactivity disorder (ADHD) (14)
3. the “bilateral olfactory bulbectomy model” for depression (18)
4. the “sleep deprivation model” for mania (3)
5. the “neonatal ventral hippocampal lesion model” for schizophrenia (9, 19)
6. the oxytocin knockout mouse as a model for autism (6, 13, 19)

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7. the “1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced toxicity model” for Parkinson’s disease (5, 7)

The models are described in more detail in the Supplementary Material.\(^1\)

Subsequently, the goal of the assignment was to facilitate the following learning outcomes:

1. Students have gained more insight in the phenomenology of the disease and the underlying neurophysiological changes. Typically, this means that the neurotransmitter system involved as well as its anatomy, function, and receptors are discussed during the presentation. Furthermore, aberrations that occur in the disease and the mechanism(s) of action of the neuroactive drug are explained.

2. Students have analyzed the face and construct validity of the animal model using the newly obtained insights. As a result, students can compare the symptoms, underlying neurophysiology, and etiology between the disease and animal model, thereby analyzing the level of similarity and assessing the shortcomings of the model.

3. Students have designed a pharmacological experiment in a proper fashion to assess predictive validity of the model. This means that all the necessary control groups are included and treatment schemes and administration techniques are implemented in a suitable manner. Furthermore, students can make a prediction of the experimental outcomes in each of the treatment groups if the animal model was to display predictive validity.

4. Students have presented their findings in a classroom presentation and critically discussed their animal model and pharmacological experiment with their fellow students and lecturers.

**METHODS**

**General outline.** In total, 38 students participated in the course and assignment. All students were third-year undergraduates who participated in the animal experimental science specialization program of the Leiden University of Applied Science. The assignment was performed by pairs of students, resulting in the formation of 19 student pairs. The pharmacology lecturer was appointed as the assignment instructor.

First, these 19 student pairs were divided into 4 groups (with 1 group containing 4 student pairs and 3 groups containing 5 student pairs). In each group, the student pairs were asked to choose one of the seven available case studies (consisting of a description of the animal model and the corresponding neuroactive drug), dividing them in such a manner that each student pair obtained a different case study. Hence, four or five different case studies were used per group.

Second, the assignment instructor gave instruction simultaneously to all the student pairs. Students were asked to look into the neurotransmitter system(s) involved and gather information about its anatomy, function, and receptors as well as aberrations that occur in the disease and the mechanism(s) of action of the neuroactive drug. Furthermore, the instruction consisted of an explanation of the concepts of face, construct, and predictive validity. Additionally, students were asked to design an experiment to assess the model’s predictive validity.

During the course, 6 h were scheduled in which each student pair was given 15–20 min to discuss the animal model and experiment with the assignment instructor. During these 15–20 min, students were able to ask questions about their animal model, the articles they had obtained, and experimental pharmacological issues. The assignment instructor provided feedback on the information gathered about the neurotransmitter system(s), the students’ ideas about the validity of their animal model, and the proposed setup of the experiment with regard to control groups, treatment schemes, means of drug administration, repetitive testing, and blinding.

Finally, a separate presentation session was held for each group. Each student pair performed a 20-min classroom presentation in the presence of their fellow group members, the assignment instructor, and the medical biology lecturer.

The exercise was scheduled in a time frame of 4 wk, starting with the first instruction given to all the students simultaneously and ending with the final presentations held by the students.

**Evaluation of student presentations.** Both the assignment instructor and medical biology lecturer evaluated the presentations using a scoring form (Table 1). In this form, the learning outcomes mentioned previously were dissected into 14 components and graded as 2 (good), 1 (intermediate), or 0 (poor). Examples of top-score answers are given for several of these components, including the analysis of neurophysiology, neuropharmacology, and face and construct validity, for each of the case studies in the Supplementary Materials. Additionally, top-score answers with regard to suitable treatment schemes, setup of control groups, and the concept of repetitive testing are provided. Using these top-score examples and the scoring form shown in Table 1, rapid and thorough evaluation of the student presentations was achieved.

For each student pair, every component of the scoring form was discussed between the assignment instructor and medical biology lecturer to obtain a consensus score. In general, the assignment instructor and medical biology lecturer rated the different components similarly. Students obtained a score for each of the 14 components with a maximum of 2 points/component, resulting in a maximum score of 28 points. The number of points was divided by 2.8 to obtain the final grade, ranging from 1 (lowest grade) to 10 (highest grade). According to the Dutch grading system, a minimal final grade of 5.5 is needed to pass.

Frequencies and averages of the final grades obtained for the different case studies are shown in Table 2.

After evaluation, student performance was assessed by calculating the percentage of students that obtained a good, intermediate, or poor score for each of the 14 components shown in Table 1. The resulting percentages are displayed in Table 3.

**Student evaluation of the assignment.** After the presentations had been given, every student (n = 38) filled in a questionnaire concerning the perceived teaching value of the assignment. This questionnaire consisted of eight statements to which the student could either fully agree, agree, partly agree and partly disagree, disagree, or completely disagree.

First, the overall teaching value of the assignment was assessed using two separate statements (“this assignment strongly supports the theoretical lectures” and “this assignment should be included in next year’s course”). Second, three separate statements were used to evaluate whether the students had gained more insight in the concepts of face, construct, and predictive validity (“this assignment enhanced my understanding of the concept of face/construct/predictive validity”). The overall understanding of how human diseases are translated into animal models was evaluated using a separate statement. Additionally, the perceived teaching value with regard to both the understanding of the physiology and pharmacology of the central nervous system as well as the ability to design an animal experiment were assessed using two statements. Finally, students were given the opportunity to make some general remarks with regard to the assignment.

Afterward, the percentages of students that fully agreed, agreed, partly agreed and partly disagreed, disagreed, or completely disagreed were calculated for each of the eight statements (Table 4).

**RESULTS**

**Distribution of the case studies.** The 38 students who participated in the present assignment were asked to form pairs. Subsequently, the resulting 19 student pairs were divided into 4

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\(^1\) Supplemental material for this article is available online at the *Advances in Physiological Education* website.
Table 1. The presentation evaluation form

<table>
<thead>
<tr>
<th>Disease phenomenology, physiology, and animal model</th>
<th>Good</th>
<th>Intermediate</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Complete description of disease phenomenology</td>
<td>All the major symptom groups according to the Diagnostic and Statistical Manual of Mental Disorders IV are discussed</td>
<td>One symptom group is lacking</td>
<td>More than one symptom group is lacking</td>
</tr>
<tr>
<td>2. Proper discussion of the neurotransmitter system involved and the mechanisms of action of the neuroactive drug</td>
<td>The components/functions of the neurotransmitter system(s) involved are discussed and the mechanisms of action of the neuroactive drug are discussed</td>
<td>The components of the neurotransmitter system are not addressed or the function(s) of the neurotransmitter system is unclear or the mechanisms of action of the neuroactive drug are not properly described</td>
<td>Several of these aspects are not clearly discussed</td>
</tr>
<tr>
<td>3. Proper description of the animal model</td>
<td>Every aspect is clearly presented</td>
<td>One aspect is not clearly presented</td>
<td>More than one aspect is not clearly presented</td>
</tr>
<tr>
<td>4. Proper discussion of the animal model’s “face validity”</td>
<td>Overlap disease phenomenology and animal symptoms are clearly described</td>
<td>Symptoms present in the animal model and disease are described, but symptoms present in the disease but not the model are not described</td>
<td>This aspect is not clearly discussed</td>
</tr>
<tr>
<td>5. Proper discussion of the animal model’s “construct validity”</td>
<td>Overlap in underlying etiology and pathophysiology between the disease and animal model is clearly described</td>
<td>The comparison between the etiology and pathophysiology of the animal model and disease is incomplete</td>
<td>The etiology and pathophysiology of the animal model have not been compared with the etiology and pathophysiology of the disease</td>
</tr>
<tr>
<td>6. Proper discussion of the animal model’s “predictive validity” (including a prediction of the experimental outcome)</td>
<td>This concept is clearly described and a correct prediction is made with respect to the experimental outcome in the treatment groups</td>
<td>This concept is not described or a wrong prediction is made in one of the treatment groups</td>
<td>This concept is not described and a wrong prediction is made in one of the treatment groups</td>
</tr>
</tbody>
</table>

Pharmacological experiment

| 7. Suitable treatment scheme                                                                                           | Several treatment groups are made in which different treatment durations are tested throughout a realistic time frame | One treatment group is made in which one treatment duration is tested in a realistic time frame | A treatment group is designed in which no realistic time frame is applied |
| 8. Setup of control groups                                                                                             | All the necessary control groups are described                          | One control group is lacking | More than one control group is lacking |
| 9. Administration of the neuroactive drug                                                                             | Practical aspects are addressed (painful administration is minimized as much as possible, e.g., by using camnulac) | Practical aspects are addressed, although (painful) administration is not minimized | Practical aspects are not addressed |
| 10. Correct explanation of behavioral tests                                                                            | The behavioral tests used are properly explained                        | One mistake is made in the explanation of the behavior tests | More than one mistake is made in the explanation of the behavioral tests |
| 11. Implementation of behavioral tests                                                                                  | The behavioral tests are implemented correctly, preventing repetitive testing and including double-blind scoring | One mistake is made with regard to repetitive testing or double-blind scoring | More than one mistake is made with regard to repetitive testing or double-blind scoring |

Presentation skills

| 12. Clear PowerPoint slides                                                                                             | A short text and clear figures are used                                | The text is too long or figures are not clear  | The text is too long and figures are not clear |
| 13. Clear storyline                                                                                                      | No questions are needed throughout the presentation                     | One question is needed throughout the presentation | More than one question is needed throughout the presentation |
| 14. Answering questions and discussion with the audience                                                                | The majority of the questions are answered correctly                   | Half of the questions are answered correctly | A minority of the questions is answered correctly |

*For the model of Parkinson’s disease, the symptoms described in Ref. 5 should be discussed.

groups, and, in each group, these pairs were asked to choose one of the seven available case studies. The frequency in which the different case studies were chosen is shown in Table 2.

Evaluation of student presentations. The presentations of the students were evaluated by the lecturers according to the scoring form shown in Table 1. Top-score answers are provided in the Supplementary Materials. Grading was performed over the following three broad categories: 1) disease phenomenology, physiology, and animal model; 2) pharmacological experiment; and 3) presentation skills. Table 3 shows the assessment of the student presentations.
Table 2. Frequencies and averages of the final grades obtained for the different case studies

<table>
<thead>
<tr>
<th>Case Study</th>
<th>Frequency</th>
<th>Average of Final Grades</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>2</td>
<td>9.3</td>
</tr>
<tr>
<td>Attention-deficit hyperactivity disorder</td>
<td>3</td>
<td>8.9</td>
</tr>
<tr>
<td>Depression</td>
<td>3</td>
<td>8.2</td>
</tr>
<tr>
<td>Mania</td>
<td>2</td>
<td>7.5</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>3</td>
<td>7.8</td>
</tr>
<tr>
<td>Autism</td>
<td>4</td>
<td>8.4</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>2</td>
<td>9.3</td>
</tr>
</tbody>
</table>

Strikingly, students performed exceptionally well in describing disease phenomenology, extensively explaining the anatomy and functions of the neurotransmitter system involved and presenting the mechanism(s) of action of the neuroactive drug. None of the students scored poorly in these subcategories, and the percentage of students that obtained an intermediate score was also very low.

With regard to the subcategories of describing and discussing the animal model, the majority of the students scored well again, although the percentage of students with an intermediate score for the “description of the animal model” component was somewhat high (44%). Here, in a number of cases, the animal model was not presented clearly, and the lecturers needed to ask some questions about the setup of the animal model. On the other hand, face validity of the animal models was critically discussed, and, in several cases, the students presented alternative behavioral tests that they thought should be performed with the model to see whether face validity could be improved. An illustrative example was the testing of negative symptoms in the animal model for schizophrenia.

With respect to construct validity, 44% of the students did not give a complete overview of the similarities between the disease and animal model etiology and pathophysiology. In this case, students failed to recognize that additional etiological and pathophysiological processes may be involved other than described in the case studies. For example, the animal model for ADHD is solely based on hypoxia during early life and may therefore only “cover” a subgroup of patients who suffer from this disease. Furthermore, during the discussion of the construct validity of the olfactory bulbectomy model for depression, there seemed to be some ambiguity as to whether construct validity was high (similar underlying physiological changes in brain serotonin content) or low (removal of the olfactory bulb cannot be directly linked to the etiology of depression in humans).

Currently, 11% of the students performed poorly on the discussion of the animal model’s predictive validity, thereby failing to include a description of the concept itself and making a wrong prediction of the experimental outcome in one of the treatment groups. Interestingly, the majority of false predictions was made in the experimental group in which control animals received the neuroactive drug. Students wrongly predicted that in this group, a change in behavior would be observed compared with untreated controls.

The pharmacological experiments designed by the students were evaluated using criteria such as using a suitable treatment scheme, setup of control groups, means of administration, and description and implementation of the behavioral tests. In general, students designed multiple treatment groups in which the administration of the neuroactive drug was tested over multiple time intervals. The means of administration and behavioral test description and implementation were discussed very well. Strikingly, student performance was lowest with respect to the setup of all the necessary control groups. In half of the designed experiments, one control group was lacking, generally the group containing control animals treated with the neuroactive drug.

Finally, students’ presentation skills were evaluated in terms of clear PowerPoint slides, a clear storyline, and the ability to answer questions from the audience and to critically discuss the animal model and pharmacological experiment. In several cases, the lecturers had to ask questions to clarify certain aspects of the presentation. However, the majority (83%) of the students obtained a “good” score for discussing their animal models and pharmacological experiments with the lecturers and audience.

We observed no large differences between the different case studies with regard to final grades. The averages of the final grades are shown in Table 2 and ranged from 9.3 for Parkinson’s disease and anorexia nervosa (highest) to 7.5 for mania (lowest).

Student evaluation of the assignment. To assess the students’ opinion about the assignment, a survey with eight questions in the form of statements was distributed among the students.
The assignment was very well received by the students, since a large majority of the students either agreed or fully agreed with the statements that the assignment strongly supplements the theoretical lectures (98%) and that the assignment should be included in next year’s course (92%). A large majority agreed to the statements that the assignment enhanced the understanding of the concepts of construct, face, and predictive validity, showing almost equal responses between fully agree and agree. Moreover, when asked whether the students gained more insight into how human diseases can be translated into animal models, again the majority of the students either fully agreed (21%) or agreed (63%).

Finally, the students clearly appreciated the assignment in terms of learning about the physiology and pharmacology of the central nervous system and designing an animal experiment since (1) 79% of the students (fully) agreed with the statement that the assignment increased the understanding of the physiology and pharmacology of the central nervous system and (2) 87% of the students (fully) agreed with the statement that the assignment enhanced the ability to design an animal experiment.

In addition to the eight statements to which the students could either agree or disagree, the survey also included the possibility for the students to make general remarks about the assignment. Several students stated that although the assignment took quite some effort, it was very interesting and provided them with more insight into neurophysiology and designing animal experiments. Interestingly, one student made the remark that less information should be made available in the description of the animal model itself and that the students should perform independent searches of scientific literature.

**DISCUSSION**

Presently, we have developed a theoretical assignment in which students are working on the analysis of several animal models of psychiatric and neurological diseases. The assessment of face, construct, and predictive validity of these animal models typically involves the analysis of disease physiology, pharmacology, and experimental design, thus constituting a multidisciplinary learning activity.

One of the expected learning outcomes of our assignment was for the students to obtain more insight into the phenomenology of the disease, the underlying neurophysiological system, and the mechanism(s) of action of the neuroactive drug. This learning outcome was clearly facilitated by the assignment since (1) students scored very well in these categories and (2) a large majority of the students stated in the evaluation forms that they had gained more insight into the physiology and pharmacology of the central nervous system after performing the assignment. We suggest that the combination of psychiatric/neurological disease, neurotransmitter systems, and neuroactive drugs is a topic of great interest to the students and motivates them to work on the assignment. This is in line with a previous report from Near and Martin (12), in which a physiology course was centered around psychoactive drugs and which was very well received by undergraduate students. Therefore, we believe that the currently developed assignment constitutes a valuable asset in the teaching and learning of neurophysiology and neuropharmacology at the undergraduate level, which can easily be implemented into a theoretical course covering these topics.

In addition to being a useful tool in teaching neurophysiology, neuropharmacology, and experimental design, the present assignment is also valuable in teaching face, construct, and predictive validity. In this respect, an interesting observation was that the students were very capable of dealing with the concept of face validity and, in some cases, even came up with alternative behavioral tests to further investigate the animal model. This indicates that the students obtained a thorough insight in the phenomenology of the disease that was appointed to them. Furthermore, for future use of the assignment, the current presentation evaluation form can be expanded by including an application of alternative behavioral tests as an additional evaluation point.

However, more difficulties were encountered with the concept of construct validity. A group of students was unable to obtain a broader overview of disease etiology and pathophysiology apart from what was provided in the animal model case reports. Hence, these students should be further directed toward searching the scientific literature to assess which other neurophysiological systems are also involved in the disease. Additionally, the discussion of the olfactory bulbectomy model for depression clearly demonstrated the fact that the analysis of construct validity does not necessarily provide a straightforward answer. Construct validity in this model can be regarded as low since removal of the olfactory bulb cannot be directly linked to the etiology of depression in humans. On the other hand, the reduced brain serotonin content and change in the function of the amygdala in the animal model are thought to be very similar to the pathophysiology of the disease in humans (18), indicating high construct validity. Therefore, the two
components that make up the concept, i.e., similarity in etiology and underlying pathophysiology (19), can each be appreciated in a different manner, resulting in a different estimation of construct validity. Our assignment facilitated a thorough dissection of this concept by having the students analyze their animal model for construct validity and discuss the results during the classroom presentations.

With respect to predictive validity, it was observed that some of the students had difficulties with the group containing control animals treated with the neuroactive drug. This was reflected by the fact that 1) this group was absent in several of the experimental designs and 2) a number of students made wrong predictions of the experimental outcome of this group if the animal model were to display predictive validity. It must be noted that if this group was absent in the experimental design, students could still receive a full score on the prediction of the experimental outcome since (in our opinion) one mistake should not affect the final grade twice. From an experimental point of view, this control group is equally important as the other control groups since it allows the discrimination between a general action of the neuroactive drug and a more specific interaction of the drug with the disease state. Thus, by discussing all the control groups and predicted experimental outcomes during the student presentations, the current assignment was very successful in revealing the misconceptions of the students regarding experimental design.

During the presentations, students were also evaluated with regard to their presentation skills and their ability to conduct a proper discussion. Since no major problems were encountered, we believe that the assignment in its present form perfectly suits the presentation capabilities of our undergraduate students. In this respect, it is interesting to note that having students present and discuss learning content is believed to augment the learning process (2, 22). This may possibly have had a positive effect on the current performance of our students.

Interestingly, one of the students stated that less information should be made available to the students in the case studies. This, to a certain extend, contrasted with the remarks made by several other students, who stated that the assignment took considerable effort. Therefore, one of our future goals is to systematically assess whether less information should be made available to the students in the case studies. In this respect, the case studies can easily be adjusted to different levels of difficulty, shifting toward case reports or problem-based learning cases (1, 4, 10), simply by altering the amount of information given in the case reports and adjusting the corresponding lectures.

Determining whether there were any differences in student performance, depending on the different case studies, is currently impossible due to the small number of participants. However, this may become possible in the future when more students have participated in the assignment.

Our present assignment can be regarded as a “whole task approach” in which students are working on authentic tasks (20). These are real-life tasks that can be encountered in the future careers of the students. In our assignment, students are asked to analyze the disease, assess the applicability of the animal model, and design an experiment with the model, taking into account all the practical aspects as well. Thus, the assignment constitutes a whole task that, to a large extend, mimics a realistic professional situation. The whole task approach enhances the learning of students since it maximizes the transfer of knowledge to new and different situations (20). In this respect, it is interesting to note that students agreed on the facts that 1) the assignment enhanced their understanding on how human diseases can be translated into animal models and 2) the assignment enhanced their ability to design an animal experiment.

Overall, the students’ responses to the assignment were extremely positive. How this response is affected by the small numbers of students enrolling in the animal experimental specialization program or biased by the fact that these students may constitute a very specific population is unknown. Nevertheless, the use of animal models for psychiatric and neurological diseases can be of great interest to a broad category of undergraduate medical and biology students.

In conclusion, the present assignment is very useful in teaching neurophysiology, neuropharmacology, experimental design, and the validity of animal models for human diseases. Moreover, we believe that the use of animal models, as presented here, will constitute a successful approach in teaching other areas of physiology as well.

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