A prototype model for evaluating psychiatric research strategies: Diagnostic category-based approaches vs. the RDoC approach

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Abstract

In this paper, we propose a theoretical framework for evaluating psychiatric research strategies. The strategies to be evaluated include a conventional diagnostic category-based approach and dimensional approach that have been encouraged by the National Institute for Mental Health (NIMH), outlined as Research Domain Criteria (RDoC). The proposed framework is based on the statistical modeling of the processes by which pathogenetic factors are translated to behavioral measures and how the research strategies can detect potential pathogenetic factors. The framework provides the statistical power for quantifying how efficiently relevant pathogenetic factors are detected under various conditions. We present several theoretical and numerical results highlighting the merits and demerits of the strategies.

Keywords: Research Domain Criteria; Diagnostic category; DSM; ICD; statistical power
1 Introduction

Psychiatry research is experiencing two major movements: one is the introduction of computational approaches [1, 2, 3]; the other concerns research strategies in psychiatry in a more general regard, through a proposal of research strategy presented by the National Institute for Mental Health (NIMH), outlined as the Research Domain Criteria, or RDoC [4, 5, 6]. While both movements appear to be promising, whether and how these movements can improve research in psychiatry is still a matter of debate. The main focus of the present paper is related to the second movement. We propose a theoretical framework for evaluating how research strategies including those defined by RDoC are effective in psychiatric research. However, the proposed framework also provides a basis on which to evaluate the contribution of the computational approaches to psychiatry research.

1.1 Diagnostic category-based approach

Conventional psychiatric research aiming to find the pathogenetic factors of mental disorders is based on the diagnostic-category-based approach (hereafter, we simply refer to it as “category-based approach”). Researchers classify the subjects into a clinical population (patient group) and non-clinical population (control group) at first. The classification is based on the current diagnostic systems, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 2013) or the International Classification of Diseases (ICD; World Health Organization 1990). The classification is usually based on multiple criteria of symptoms or signs. Then, researchers attempt to determine the factors that significantly differ between groups. The current computational approaches to psychiatry are also mainly based on this category-based approach. For example, model parameters that are fit to the subject’s behavior or brain activities that are correlated with model latent variables are compared between the control group and patient group (e.g., [7, 8, 9, 10, 11]).

Several methodological flaws of the conventional category-based approach have been pointed out (e.g., [4, 12, 13]). One notable flaw is the heterogeneity in the population classified as the clinical population. The heterogeneity of the corresponding biological and social factors in a population precludes the researcher from detecting
Another flaw is that similar symptoms that may share similar pathogenetic factors are included in different categories of mental disorders. For example, obsessive compulsive symptoms in schizophrenia are remarkably prevalent and considered as important factors in neurobiological studies of schizophrenia [14][15]. This also can obscure determining the ultimate cause of the mental disorders. These two problems can be summarized as the lack of a strict one-to-one mapping from pathogenetic factors to the current category of the mental disorders; there appear to be many-to-one or one-to-many mappings between them.

### 1.2 Dimensional (RDoC) approach

To overcome the above mentioned problems, the NIMH proposed RDoC. We do not provide a full introduction of RDoC here (for a complete description of RDoC, see the RDoC website: [http://www.nimh.nih.gov/research-priorities/rdoc/index.shtml](http://www.nimh.nih.gov/research-priorities/rdoc/index.shtml)). The important properties that this article discusses are as follows. RDoC encourage researchers to seek the relationships among the behavioral measurements (included as “Behavior” and “Self-reports” in the unit of analysis) and biological and social factors (included as “Genes”, “Molecules”, “Cells”, “Circuits”, “Physiology” in the unit of analysis), focusing on research domains and constructs. The research domains (e.g., “positive valence systems”) contain constructs (e.g., “reward learning”). Constructs can be subcomponents of diagnostic criteria of mental disorders in DSM/ICD, but the conventional categorization of the diagnostic systems is not used. Thus, the method of the analysis would be dimensional rather than categorical. If we assume linear relationships between measures in the units of analysis, a typical statistical approach is regression or correlation analysis. The relationship, however, is not necessarily linear and can be non-linear (e.g., inverted U-shaped curve; [5]). Although we only focus on linear correlations in this article, our framework can be extended to a non-linear case.

### 1.3 Goal of this study

It seems that researchers in psychiatry largely appreciate the RDoC as promising research strategies. However, is this indeed the case? Although there are methodological flaws in the current diagnostic systems (DSM/ICD) as discussed above, the DSM/ICD
also provide advantages. One advantage is that the reliability of the diagnosis can be increased by using multiple criteria. This may lead to an increase in the likelihood that a researcher finds the pathogenetic factors of the mental disorders, compared to the RDoC approach, which decomposes the criteria used in the DSM into distinct dimensions. Therefore, it is important to clarify under what conditions the RDoC approach supersedes the conventional, category-based approaches. For this purpose, mathematical and computational models may provide a useful framework for addressing such questions quantitatively. The present study proposes a prototype for such a framework.

2 Proposed model

Here, we formally describe the proposed model. We assume that there are \( N \) potential pathogenetic factors that can be causes of mental disorders. The \( j \)-th pathogenetic factor is denoted as \( x_j \). All the pathogenetic factors are summarized as a column vector: \( X = (x_1, ..., x_N)^T \), where \( .^T \) denotes the transpose. The pathogenetic factors may include specific alleles or brain connectivity, which can be predictors of risk. They may also include the dysregulation of the neuromodulator or neurotransmitter, which can be a target of medical treatment, as well as the social environment or personal experience. One goal of basic research in psychiatry is to find pathogenetic factors that are relevant to mental disorders. In general, the measurement of the value of \( X \) is often contaminated by noise that may be caused by the estimation error or measurement error. The measured or estimated value of \( x_i \) is denoted as \( \hat{x}_i \).

Behavioral measures, including symptoms and signs that are used in DSM/ICD-based classification, are denoted as \( Y = (y_1, ..., y_M)^T \). In the RDoC framework, such behavioral measures are included in the units of analysis “Behavior”, or “Self-reports”. Here, we consider \( M \) such behavioral measures.

2.1 Mapping from pathogenetic factors to behavioral measures

The pathogenetic factors \( X \) are assumed to be translated to behavioral measures \( Y \) via some function \( f \) with some added noise \( \epsilon \). In vector form, this can be written as
\[ Y = f(X) + \epsilon, \]  

(1)

where \( \epsilon \) is an \( M \)-dimensional column vector. \( f(\cdot) \) represents a map from an \( N \)-dimensional column vector to an \( M \)-dimensional column vector. We refer to this model as a generative model. The noise may include the individual difference in resilience, any other personality trait that affects how easily the individual experiences the disorder, or the errors in the subjective report and behavioral measure.

In the following analysis and simulations, we only consider a simple, linear and Gaussian case. The noise \( \epsilon = (\epsilon_1, \ldots, \epsilon_M)^T \) is assumed to independently obey a Gaussian distribution with zero mean and common variance \( \sigma^2_\epsilon \):

\[ \epsilon_i \sim \mathcal{N}(0, \sigma^2_\epsilon) \quad \forall \, i, \]  

(2)

where \( \mathcal{N}(\mu, \sigma^2) \) indicates the Gaussian distribution with mean \( \mu \) and variance \( \sigma^2 \). We also assume that the function \( f \) is a linear transformation:

\[ f(X) = W X, \]  

(3)

where \( W \) is an \( M \times N \) matrix.

Furthermore, the pathogenetic factors are assumed to independently obey a Gaussian distribution with zero mean and unit variance:

\[ x_j \sim \mathcal{N}(0, 1) \quad \forall \, j. \]  

(4)

From the above assumptions, each behavioral measure, \( y_i \), marginally obeys the Gaussian distribution. This means that behavioral measures are continuous variables. On the other hand, many inclusion criteria in the current diagnostic systems (i.e., DSM and ICD) take on discrete values (e.g., existence or absence of a symptom), with the exception of the duration quantity that indicates how long an episode continues for. Thus, in this case, \( y_i \) may be interpreted as a behavioral phenotype, based on which a psychiatrist or a patient makes decisions regarding each symptom, rather than the criterion itself.

For simplicity of analysis, the weight parameters and noise \( \epsilon \) are re-parametrized so that the marginal distribution of each behavioral measure, \( y_j \), has unit variance (for
details, see Appendix A). By this parametrization, the same fraction of individuals are classified as patients in category-based approach, given a set of inclusion criteria. For example, if there is a single criterion and the threshold is \( h = 0.5 \) (see below for the definition of \( h \)), approximately 31% of the individuals are classified into the clinical population on average. This re-parametrization does not influence the results of the dimensional approach.

### 2.2 Category-based approach

In the proposed model, the category-based approach first classifies the subjects into the patient group or control group depending on the values of their behavioral measure, \( Y \). For example, if \( y_i \) for all \( i \) exceeds the threshold \( h_i \) (\( y_i \geq h_i \forall_i \)), the subject is classified into the patient group (in Figure 1, the subjects indicated with red dots belong to the patient group). Except for Case 1, where we examine the effect of the margin between the patient group and control group, the subjects who do not satisfy the inclusion criteria (\( y_i < h_i \exists_i \)) are classified into the control group (the subjects indicated with gray dots). In the following simulations, we set \( h_i = h = 0.5 \forall_i \).

The category-based approach seeks the component of \( X \) that significantly differs between two groups. The estimated or measured \( X \) that contains a measurement error is assumed to be generated by

\[
\hat{x}_j = x_j + \delta_j, \quad \delta_i \sim \mathcal{N}(0, \sigma_\delta^2).
\]

Note that we formally and explicitly model the measurement or estimation error by using a Gaussian variable, \( \delta_i \), rather than incorporating a specific estimation process.

In the simulation, the samples of subjects (\( n_1 \) subjects from the control group and \( n_2 \) subjects from the patient group, resulting in \( n_1 + n_2 = n \) subjects) are randomly selected from both groups, and their \( \hat{x}_j \) values are subjected to an unpaired t-test with the equal variance assumption. If the significance of the difference is detected at the significance level \( \alpha = .01 \), the factor \( x_i \) is deemed as a factor relevant to the mental disorder. When multiple candidate factors are submitted to statistical testing, a correction should be made for multiple comparisons (e.g., Bonferroni correction) to suppress family-wise error rates. However, for simplicity, we do not perform the correction in this paper. Incorporating a correction is straightforward and does not influence the qualitative results.
reported in this paper.

### 2.3 RDoC (dimensional) approach

In the proposed framework, the RDoC approach is simulated by sampling $n$ subjects irrespective of the behavioral phenotype (symptom). The statistical hypothesis test is then conducted with the null hypothesis, where the correlation coefficient between $y_i$ and $\hat{x}_j$ is zero. When the correlation is significant (the null hypothesis is rejected), the factor $x_i$ is deemed as a factor relevant to the behavioral measure, $y_i$.

### 3 Results

Below, we provide analytical and numerical results to clarify the basic properties of the proposed model. We especially focus on the statistical power, which is the probability that the pathogenetic factors are detected by the statistical hypothesis tests.

#### 3.1 Case 1: Category-based vs. Dimensional approaches

First, we compare the statistical powers of the category-based approach and the dimensional approach for the simplest case in which there is a single pathogenetic factor ($M = 1$) and single behavioral measure ($N = 1$). The transformation matrix is a scalar, identical map: $W = 1$ (with the re-parametrization given in Appendix A). The model structure is illustrated in Figure 2A. We also examine the effect of the margin (denoted by $d$) between the patient group and control group. The subjects with $y$ less than $h - d$ are classified into the control group, while the subjects with $y$ larger than $h$ are classified into the patient group (Figure 2B). The subjects with $y$ falling into the margin are not included in the study. Actual samples in psychiatry studies may include such margins either intentionally or unintentionally; the researcher may exclude the subjects who are not classified into the clinical group but present behavioral phenotypes that are close to the inclusion criteria.

Figure 2C shows the power that the pathogenetic factor $x_1$ is detected as a function of the total number of subjects. For this case, the statistical power of both methods is analytically obtained (see Appendix B, Figure 2C, lines). The symbols (squares
for the category-based approach and triangles for the dimensional approach) represent
the numerical results obtained from 10,000 runs of the Monte Carlo simulations. The
results of the analysis (lines) perfectly agree with those obtained from the simulations,
validating the analysis in Appendix B.

The results indicate that if there is no margin \( (d = 0) \), the dimensional approach
(using correlation coefficients) yields a higher power compared to the category-based
approach (using the unpaired t-test). This is because the correlation coefficients can
utilize full information on the magnitude of \( x_1 \), while the category-based approach ig-
nores the information of the distribution within the group. If there is a margin, the
category-based approach can supersede the dimensional approach. With a larger mar-
gin, the category-based approach can distinguish clusters in the distribution \( x_1 \) while
suppressing the impact of the noise added to \( x_1 \). It should be noted, however, that with
a larger margin, it becomes more difficult to find samples for the control group.

### 3.2 Case 2: The effect of the number of diagnosis criteria in the
category-based approach

As we discussed in the Introduction, the category-based approach may increase the
reliability of the diagnosis by using multiple criteria. The following results illustrate this
point. In Case 2, there are two pathogenetic factors \( (N = 2) \): \( x_1 \) is a factor relevant to
the mental disorder and is of interest. \( x_2 \) is irreverent to the mental disorder (Figure 3A).
The weight of \( x_1 \) for behavioral measure \( y_j, (j = 1, ..., M) \) is set to 1 and that of \( x_2 \) is
set to zero. When \( M = 3 \), the generative model becomes

\[
\begin{align*}
  y_1 &= x_1 + \epsilon_1, \\
  y_2 &= x_1 + \epsilon_2, \\
  y_3 &= x_1 + \epsilon_3.
\end{align*}
\]

For the vector and matrix form of the model, see Appendix C. Figure 3A illustrates the
structure of the generative model.

The standard deviation of the noise, \( \sigma_\epsilon \), and \( M \) were varied in the simulations. As
an example the histogram of \( \hat{x}_1 \) shown in Figure 3B, the larger is the number of the
criteria \( M \), the lower is \( \hat{x}_1 \) of the patient group that overlaps with that of the control
Consequently, as $M$ increases, the power increases (Figure 3C, left). The power can exceed that of the dimensional approach in which a single behavioral measure is used in each statistical test.

For the irrelevant factor $x_2$, the fraction of the factor deemed significant was kept to the preset significance level, 0.01 (Figure 3C, right).

### 3.3 Case 3: The effect of a mixture of pathogenetic factors

We now discuss the case where a single behavioral measure $y_i$ is affected by more than one pathogenetic factor, $x_j$. It is conceivable that a larger degree of mixture leads to difficulty in detecting each pathogenetic factor. For simplicity, we consider the case with two pathogenetic factors, $N = 2$, and two behavioral measures, $M = 2$.

The transformation matrix is parametrized using a parameter $c$ that represents the degree of the mixture (Figure 4A; also see Equation 32 in Appendix C). The generative model in element-wise form is

$$
\begin{align*}
y_1 &= x_1 + cx_2 + \epsilon_1, \\
y_2 &= cx_1 + x_2 + \epsilon_2,
\end{align*}
$$

with $0 \leq c \leq 1$. When $c = 1$, $x_1$ and $x_2$ equally contribute to both behavioral measures, $y_1$ and $y_2$ (complete mixture). When $c = 0$, $x_1$ and $x_2$ independently contribute to $y_1$ and $y_2$, respectively (no mixture). The effect of $c$ on the transformation is illustrated in Figure 4B.

We consider two cases in the category-based approach: one uses only a single behavioral measure $y_1$ as a criterion, and the other uses both behavioral measures. The resulting statistical powers are plotted in Figure 4C. As the degree of the mixture, $c$, increases, the power for the methods using a single criterion (dimensional approach and category-based approach using a single criterion) decreases. This is because the other pathogenetic factor functioned as noise in terms of detecting target $x_j$ when $c$ had a non-zero value. On the other hand, the power of the category-based approach using two criteria did not change or even increase as $c$ increased. The reason for this is as follows. This approach equally uses $y_1$ and $y_2$. $c$ does not largely change the total information extracted from $y_1$ and $y_2$. The increase in the power is due to the noise reduction effect reported in Case 2.
The additional pathogenetic factor \( x_2 \) is added to \( y_1 \) when \( c \) is non-zero; thus, \( x_2 \) is detected as a relevant pathogenetic factor even when the single criterion \( y_1 \) is used (Figure 4C, right panel).

### 3.4 Case 4: The effect of the number of pathogenetic factors

The effect of the mixture reported in Case 3 was not drastic because there were only two pathogenetic factors \( (N = 2) \). As the next simulation shows, when \( N \) is large, the effect is large: it is more difficult to detect the individual pathogenetic factor \( x_i \). We varied \( N \) and fixed the number of behavioral criteria to \( M = 1 \). The mixture parameter \( c \) was also included (Figure 5A; Equation 33 in Appendix C).

The results are shown in Figure 5B. Overall, the influence of the number of pathogenetic factors \( (N) \) and the degree of the mixture \( c \) is similar for both the category-based and dimensional approaches. When the degree of the mixture is maximum \( (c = 1) \), the statistical power drastically decreases as the number of pathogenetic factors increases. This decreases is modest when the degree of the mixture is small \( (e.g., \ c = 0.3) \). Of course, when there is no mixture \( (c = 0) \), the statistical power does not depend on the number of pathogenetic factors (data not shown).

A large-scale psychiatry study such as genome-wide analysis (GWAS) uses larger sample sizes and, accordingly, more stringent statistical criteria. For example, more than 1 million alleles from about 30,000 individuals (for both the patient group and control group) are analyzed in [16]. With such a large sample size, the factors that have very small effects on the disorder could be deemed as statistically significant. We simulated a very large sample with a stringent statistical criterion \( (p < 10^{-8}) \). The model structure is the same as that in Figure 5A. The number of behavioral measures was set to \( M = 1 \), and the degree of the mixture was set to \( c = 1 \) (i.e., all the relevant pathogenetic factors equally contributed to the disorder). Figure 6 presents the results. When the total sample size is \( n = 10,000 \), even with such a stringent criterion, the factor \( x_1 \) was detected with large statistical power close to probability 1 (Figure 6A). On the other hand, the effect of each pathogenetic factor drastically decreased as the number of relevant factors, \( N \), increased (Figure 6B). The effect size for the dimensional approach is measured by the correlation coefficient \( \rho \) given in Equation 12 in Appendix B. This \( \rho \)
is less than 0.2 if $N$ is larger than 10. The effect size for the category-based approach is the difference in the means divided by the standard deviation. This corresponds to the effect size called Cohen’s $d$ (see Appendix [B]). Cohen’s $d$ also easily fell below 0.2 as $N$ increased.

To gain more insight into the effect, we computed the fraction exceeded by computing the fraction of the patients for whom the pathogenetic factor $x_1$ exceeded the mean $x_1$ of the control group (Figure 6D). When the fraction exceeded is 0.5 and the distribution is symmetric, the pathogenetic factor is irrelevant to the disorder. Figure 6C plots the fraction exceeded as a function of $N$. When $N$ is greater than 50, the fraction exceeded is less than 60%, indicating that the fraction of patients who have a higher value for the pathogenetic factor $x_1$ than the healthy controls are only 10% above the chance level. For such situations, the treatment for the pathogenetic factor may have a limited impact.

4 Discussion

In this article, we proposed a simple model for discussing the effectiveness of research strategies in psychiatry. We intended to propose this model as a basic prototype for more realistic applications, rather than as a model for specific psychiatric disorders. Thus, there are many differences between the model assumptions and realistic situations. Before discussing the discrepancies between the assumptions and the realistic situations, we discuss the implications derived from the analysis of the model properties.

4.1 Implications

The results highlighted the effectiveness of isolating a behavioral measure directly associated with a pathogenetic factor. If a behavioral measure includes contributions from many pathogenetic factors, they may function as noise and reduce the chance of finding each relevant pathogenetic factor. Thus, the RDoC approach that decomposes the factors and measures into constructs and the unit of analysis would be promising in this regard. On the other hand, the behavioral measure can be contaminated with noise,
including errors in the subjective report, individual differences in resilience, and estimation errors in the model parameters. For example, the parameter estimates from the model fit to behavioral data can be used as behavioral measures [7, 10, 17, 11]. However, the estimator can take on an extreme (erroneous) value. Such noise also prevents the researcher from detecting the factor. The errors may be smaller for the criteria adopted in DSM or ICD compared to the model estimation. In addition, we showed that increasing the number of independent criteria can reduce the impact of such noise and make the detection of the pathogenetic factors easier (Figure 3), given that the errors are mutually independent.

Therefore, in some cases, the conventional diagnostic category-based approach could be more efficient in detecting a pathogenetic factor than the dimensional (RDoC) approach: which approach is better is decided on a case-by-case basis. Researchers should consider these issues. The proposed model provides a promising way for designing an efficient research strategy to investigate a specific target.

4.2 Limitations and possible extensions

We discuss the limitations of the results and possible extensions of the proposed framework that go beyond the limitations.

4.2.1 Assumptions about the model variables

The present model assumes that the variables take continuous values and obey a Gaussian distribution. While this assumption makes the theoretical analysis easier, it is an obvious over-simplification. For example, consider a genetic mutation as a pathogenetic factor. The presence or absence of an allele is represented as a categorical variable. The behavioral measure or symptom can also be categorical (e.g., the existence or absence of a specific symptom). For such cases, the translation of pathogenetic factors to behavioral measures may be better represented as a logistic function. Additionally, the distribution of scores for some symptom ratings can be best explained using an exponential distribution with a cut-off [18]. The use of the link function that maps variables onto the exponential function with a shift parameter may be suitable for such cases. Although the basic properties reported in this study may hold in various other situations,
a careful investigation would be needed depending on the situation.

Another drastic simplification in the present model is the assumption of independence among errors and also among pathogenetic factors. In realistic situations, there may be considerable correlations among them. A second-order correlation can be modeled using a multi-variate Gaussian distribution, which is a simple extension of the current model. However, there may be a higher-order interactions among pathogenetic factors. Such a correlation structure should be included in the model depending on the specific situation, especially for discussing the impact of the relationships between the pathogenetic factors.

### 4.2.2 Mapping from the pathogenetic factor to the behavioral phenotype

We only considered a linear transformation for the mapping from the pathogenetic factor $X$ to the behavioral measure $Y$. In reality, this mapping can be highly non-linear and probabilistic. We certainly desire this mapping to reflect reality. However, in many situations, it is hard to determine the exact form of the transformation. Computational modeling studies may provide an explicit form of the mapping. For example, neural network models that can generate schizophrenia-like deficits provide a map of the neural connections and resulting neural activities onto the behavioral phenotypes [19]. Additionally, a neural circuit model at the biophysical level can serve such a purpose [2].

The variables of computational models are often associated with neuromodulators [20][21][3]. If there are indeed such associations, a model parameter or a latent variable can be used as an estimate of a pathogenetic factor. Computational models, including reinforcement learning models and Bayesian models, can be used to represent the translations from such factors to behaviors. Connecting the computational models to statistical models that explicitly describe behavioral tendencies would provide an efficient way of explicitly representing the transformation (e.g., [22]). Thus, computational approaches will help connect the biological (neural) factor to the behavior, within the subconstructs of the RDoC. These approaches indicate the affinity of computational approaches for the RDoC approach.
4.2.3 Overlap of the pathogenetic factor in multiple disorders

In this article, we have considered cases with a single disorder. However, the co-occurrence of multiple disorders (i.e., comorbidity) within individuals was often observed in DSM- or ICD-based diagnoses. Additionally, the same factors (e.g., genetic mutation) may influence more than one disorder [16].

In a simple form, the proposed model may represent such situations with the following assumptions. Suppose there are three behavioral measures \( M = 3 \) and four pathogenetic factors \( N = 4 \). A subject is diagnosed to have disorder A if \( y_1 > h \) and \( y_3 > h \). Additionally, she or he is also diagnosed to have disorder B if \( y_2 > h \) and \( y_3 > h \). Behavioral measure \( y_3 \) represents the common symptom criteria between two disorders, and \( y_1 \) and \( y_2 \) are specific criteria for each disorder. The pathogenetic factor \( x_4 \) is common to both disorders, while \( x_1, x_2, x_3 \) are specific factors for each symptom. For example, this relation is represented by the following generative model,

\[
\begin{align*}
y_1 &= w_1 x_1 + w_4 x_4 + \epsilon_1, \\
y_2 &= w_2 x_2 + w_4 x_4 + \epsilon_2, \\
y_3 &= w_3 x_3 + \epsilon_3.
\end{align*}
\]

The overlap of a pathogenetic factor between diagnostic categories occurs via two routes. In one route, the factor indeed affects the distinct symptom in two disorders. In this case, \( x_4 \) corresponds to such a factor (with non-zero \( w_4 \)). In the other route, due to the common symptom, \( y_3, x_3 \) corresponds to the pathogenetic factor shared by two disorder categories. The approach solely based on a diagnostic category cannot distinguish between these cases. This fact represents an advantage of the RDoC approach.

In a more complicated form, the effectiveness of a psychiatric research strategy is more difficult to evaluate if there are multiple disorders that are shared with multiple pathogenetic factors. A systematic evaluation based on the proposed model would be useful for such situations.

4.2.4 Cluster structure in the population

We have assumed that the pathogenetic factors, the errors, are distributed continuously over the population. Several computational approaches attempt to find sub-cluster struc-
tures within the patient groups using machine learning methods [23][3][24]. The framework in the present paper can be extend to such a situation if the pathogenetic factors are assumed to be generated by a mixture of distributions. There may be subgroups in the mapping from the pathogenetic factor to a behavioral phenotype. For example, there may be subpopulations whose behavior can be easily affected by a pathogenetic factor, while the behavior of others is unaffected by the factor (e.g., resilience). Although resilience can be modeled as an error, $\epsilon_i$, there may be a case where it is better explained by a subcluster in the mapping $f$.

4.2.5 Research dynamics

The proposed model captures a single phase of a psychiatry study. The optimal research strategy may change depending on the progress in research. For example, at the beginning stage, an exploratory strategy would be suitable. As the candidates of the pathogenetic factor are narrowed down, a more detailed and careful strategy may be desirable. Including the dynamics of the research progress is a promising extension of the proposed framework.

4.2.6 Predictive validity

The primary focus of the present study was the probability that the researcher finds a pathogenetic factor relevant to the disorders. The framework is extended to discuss the predictive validity, i.e., predictions of the disease process or outcome and response to the treatment. To discuss the predictive validity, additional assumptions are required, e.g., how the treatment affects the value of the pathogenetic factor or how the disorder progresses.

4.2.7 Designing novel diagnostic criteria

The scope of the present study is basic research strategies in psychiatry, rather than clinical use. Thus, the proposed model is not intended to provide a diagnostic criterion, as the current RDoC is not. However, based on the proposed model, one can study how to optimize the diagnostic criteria and resulting diagnostic category. The optimization may be done so that mappings from pathogenetic factors to behavioral phenotypes do
not have mixtures (i.e., so that they have a one-to-one mapping). Such an optimized
diagnosis may help provide more effective treatment. The present model (or mode
advanced models based on it) would be a useful tool for designing such new diagnostic
categories.

5 Conclusion

Psychiatry targets extremely complex processes, i.e., mental processes or mental states.
There are many factors that influence them. Accordingly, there should be various re-
search strategies in psychiatry, as well as in neuroscience and psychology. A quantita-
tive evaluation of the research strategies is required. Discussion at the verbal descrip-
tion level is limited because the target system is very complex and may not be fully
described verbally. Thus, computational and mathematical models could play impor-
tant roles. Although there is plenty of room for modification, the present study is a
first step towards such theoretical evaluations. Our study also provide an avenue via
computational approaches for contributions to psychiatric research.

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Appendix

A Standardization of the behavioral measure

Each behavioral measure $y_i$ is normalized so that the marginal distribution of the population distribution (rather than the sample distribution) has zero mean and unit variance. $y_i$ can be written as $y_i = \sum_k N w_{ik} x_k + \sigma_\epsilon z_i$, where $z_i$ is a random variable with zero mean and unit variance and $x_k$ and $z_i$ are independent. In general, the variance of the sum of independent random variables can be written as follows: for $y = ax_1 + bx_2$ where $x_1$ and $x_2$ are independent random variables, $\text{Var}(y) = a^2 \text{Var}(x_1) + b^2 \text{Var}(x_2)$. By this relation, the variance of the marginal distribution of the behavioral measure $y_i$ is $\sum_k N w_{ik}^2 + \sigma_\epsilon^2$. Thus, with reparametrization:

$$a_i = \sqrt{\sum_k N w_{ik}^2 + \sigma_\epsilon^2},$$

(5)

$$y_i \leftarrow y_i / a_i \quad \forall i,$$

(6)

the marginal distribution of $y_i$ obeys a Gaussian distribution with zero mean and unit variance. Here, the component in the $i$-th row and the $j$-th column of $W$ is denoted as $w_{ij}$. Equivalently, this normalization can be achieved with the following parameterization:

$$w_{ij} \leftarrow w_{ij} / a_i,$$

(7)

$$\epsilon_i \leftarrow \epsilon_i / a_i.$$  

(8)

In the main text and the Appendix, we used the parametrized forms of $w_{ij}$ and $\epsilon_i$.

B Power analysis

Here, we analytically derive the statistical power, the probability of the correct rejection of the null hypothesis, for the case $M = 1$ for both the category-based analysis and
correlation analysis. The formulation we consider here is summarized as

\[ y = \frac{\sum_k^N w_k x_k + \epsilon}{\sqrt{\sum_k^N w_k^2 + \sigma_\epsilon^2}}, \]

\[ \hat{x}_j = x_j + \delta, \]

with the random variables obeying Gaussian distributions:

\[ x_j \sim \mathcal{N}(0, 1) \forall j, \]

\[ \epsilon \sim \mathcal{N}(0, \sigma_\epsilon^2), \]

\[ \delta \sim \mathcal{N}(0, \sigma_\delta^2). \]

Here, we omitted the subscript for the index of \( y \). The variances of \( y, \hat{x}_j \) are respectively

\[ \text{var}(y^2) = 1, \quad \text{var}(\hat{x}_i^2) = 1 + \sigma_\delta^2. \] (9)

The covariance between \( y \) and \( \hat{x}_j \) is

\[ \text{cov}(y, \hat{x}_j) = \frac{w_i}{\sqrt{\sum_{i=1}^N w_i^2 + \sigma_\epsilon^2}}. \] (10)

The correlation coefficient between two variables \((x, y)\) is given by

\[ \rho_{x,y} = \frac{\text{cov}(x, y)}{\sqrt{\text{var}(x) \text{var}(y)}}. \] (11)

Thus, the correlation coefficients between \( x_j \) and \( y \) and between \( \hat{x}_j \) and \( y \) are given by

\[ \rho_{x_j,y} = \frac{w_j}{\sqrt{\sum_{k=1}^N w_k^2 + \sigma_\epsilon^2}}, \quad \rho_{\hat{x}_j,y} = \frac{w_j}{\sqrt{\sum_{k=1}^N w_k^2 + \sigma_\epsilon^2 \sqrt{1 + \sigma_\delta^2}}}, \] (12)

respectively.

**B.1 Category-based approach**

To derive the statistical power of the category-based approach, we first calculate the mean and variance for each group. The mean and variance of \( x_j \) given the condition, \( y > h \), i.e., the case where the subject is classified as a patient, are (cf., [25]):
\[ E[x_j | y > h] = \rho_{x_j,y} \lambda(\alpha_1) , \]  
(13) 
\[ \text{var}[x_j | y > h] = 1 - \rho_{x_j,y}^2 \lambda(\alpha_1) [\lambda(\alpha_1) - \alpha_1] , \]  
(14) 

where 
\[ \lambda(\alpha_1) = \frac{\phi(\alpha_1)}{1 - \Phi(\alpha_1)} , \]  
(15) 
\[ \alpha_1 = \frac{h}{\text{var}(y)} = h \]  
(16) 

and 
\[ \phi(x) = \frac{1}{\sqrt{2\pi}} \exp \left( - \frac{1}{2} x^2 \right) , \]  
(17) 
\[ \Phi(x) = \int_{-\infty}^{x} \phi(u)du . \]  
(18) 

Accordingly, the mean and variance of \( \hat{x}_j \) are given by 
\[ E[\hat{x}_j | y > h] = \rho_{\hat{x}_j,y} \lambda(\alpha_1) , \]  
(19) 
\[ \text{Var}[\hat{x}_j | y > h] = 1 - \rho_{\hat{x}_j,y}^2 \lambda(\alpha_1) [\lambda(\alpha_1) - \alpha_1] + \sigma^2 , \]  
(20) 

Similarly, given \( y < h - d \) (the subject is classified into the control group), the mean and variance of \( \hat{x} \) are given by 
\[ E[\hat{x}_j | y < h - d] = -\rho_{\hat{x}_j,y} \lambda(\alpha_2) , \]  
(21) 
\[ \text{var}[\hat{x}_j | y < h - d] = 1 - \rho_{\hat{x}_j,y}^2 \lambda(\alpha_2) [\lambda(\alpha_2) - \alpha_2] + \sigma^2 , \]  
(22) 

where 
\[ \alpha_2 = -\frac{h - d}{\text{var}(y)} = d - h . \]  
(23) 

Using these expressions, the effect size of the difference between two groups can be obtained. Here, we consider the effect size defined as the difference in means \( (\mu_1 - \mu_2) \) divided by the standard deviation \( (\sigma) \) for each mean. We assume that the t-test can be performed with the assumption that the variance is common to both groups. Although this is not actually the case, when \( h \) is not so far from zero, this is good
approximation. Additionally, the t-test is known to be robust against the difference in the variance between two groups (it is known that if the ratio of the standard deviation is lower than approximately 1.5, the violation of the assumption does not influence the result).

Specifically, the effect size considered here is given by

\[ d_{\text{eff}} = \frac{\mu_1 - \mu_2}{\sigma}. \]  

(24)

This is the special case of Cohen’s \( d \) if the number of samples for both groups is the same \((n_1 = n_2 = n/2)\). The population means \((\mu_1, \mu_2)\) and the common standard deviation, \(\sigma\), are given by

\[ \mu_1 = \rho_{x,y} \lambda(\alpha_1), \]  

(25)

\[ \mu_2 = -\rho_{x,y} \lambda(\alpha_2), \]  

(26)

\[ \sigma = \sqrt{1 - \frac{\rho_{x,y}^2}{2} \left\{ \lambda(\alpha_1) \left[ \lambda(\alpha_1) - \alpha_1 \right] + \lambda(\alpha_2) \left[ \lambda(\alpha_2) - \alpha_2 \right] \right\} + \sigma_0^2}. \]  

(27)

Here, the means of the variance of both groups were used to approximate the common variance.

The test statistic used for the t-test is

\[ t = d_{\text{eff}} \times \sqrt{\frac{n_1 n_2}{n_1 + n_2}}. \]  

(28)

The test statistic \( t \) obeys the Student’s t-distribution with a degree of freedom \( n_1 + n_2 - 2 \) under the null assumption. When the alternative hypothesis \((H_1: \mu_1 \neq \mu_2)\) is correct, \( t \) obeys a noncentral t-distribution with a degree of freedom \( n_1 + n_2 - 2 \) and noncentrality parameter given by

\[ \lambda = d_{\text{eff}} \times \sqrt{\frac{n_1 n_2}{n_1 + n_2}}. \]  

(29)

Using this fact, the statistical power can be obtained by using the following R code:

```r
tcritical <- qt(1-pcritical/2, df = n1 + n2 - 2)
power <- pt(-tcritical, df = n1 + n2 - 2,
ncp = eff_size * sqrt(n1*n2/(n1+n2))) +
1 - pt(tcritical, df = n1 + n2 - 2,
ncp = eff_size * sqrt(n1*n2/(n1+n2)))
```

23
Here, the meaning of the variables is as follows; $pcritical$: significance level, $\alpha$; $eff\_size$: effect size, $d_{eff}$; $n1$: number of samples in the patient group; $n2$: number of samples in the control group.

### B.2 Dimensional approach

Next, we consider the test for correlation between $\hat{x}_j$ and $y$ where the null hypothesis is $\rho_{\hat{x}_j,y} = 0$. The test statistic is

$$t = \frac{r_{\hat{x}_j,y}}{\sqrt{1 - r^2_{\hat{x}_j,y}}} \times \sqrt{n - 2},$$

(30)

where $r_{\hat{x}_j,y}$ is the sample correlation coefficient between the $n$-samples of $\hat{x}_j$ and $y$. Under the null assumption, $t$ obeys the Student’s t-distribution with degree of freedom: $n - 2$.

The statistical power for this case can be obtained by using the “pwr” package in R that uses the approximation proposed in [26]. Specifically, the following R code is used:

```r
pwr.r.test(n = n, r = rho, sig.level = 0.01)
```

Here, the meaning of the variables is as follows; $n$: number of total samples; $\rho$: (true) correlation coefficient, $\rho_{\hat{x}_j,y}$, given in Equation [12].

### C Simulation procedure

All the simulations and numerical calculations presented in this paper were performed in R version 3.2.0 [27]. The details of the simulation settings for each case are described below. Common settings for the model parameters are $\sigma_\delta = 1$, $\sigma_\epsilon = 1$, unless otherwise specified.

The Gaussian random variables in the models are sampled from the “rnorm” function in R. We sampled the data for 10,000 individuals for each run. To obtain the statistical power numerically, the simulation was run 100,000 times for each condition, and we count the fraction where a factor was deemed as significant.
The data generation was performed based on matrix multiplication. Examples of the matrix and vector forms are provided below. For Case 2, where \( M = 3 \), the vectors and matrix become

\[
Y = \begin{pmatrix} y_1 \\ y_2 \\ y_3 \end{pmatrix}, \quad W = \begin{pmatrix} 1 & 0 \\ 1 & 0 \\ 1 & 0 \end{pmatrix}, \quad X = \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}.
\] (31)

For Case 3, the transformation matrix \( W \) becomes

\[
W = \begin{pmatrix} 1 & c \\ c & 1 \end{pmatrix},
\] (32)

with \( 0 \leq c \leq 1 \). For Case 4, when \( N = 4 \), the transformation matrix \( W \) becomes a row vector:

\[
W = \begin{pmatrix} 1 & c & c & c \end{pmatrix},
\] (33)

with \( 0 \leq c \leq 1 \).
Figures

Figure 1: Illustration of the proposed model. Each dot represents an individual subject. The samples were generated by the model under a linear, Gaussian case with $N = 2$, $M = 2$, and $c = 0.4$ (in Equation 32). The individuals are classified as patients (clinical) if both behavioral measures $y_1$ and $y_2$ have larger values than $h_1$ and $h_2$, respectively (here, we used the common criterion: $h_1 = h_2 = 0.5$). The red dots represent the patient group, and the gray dots represent the control group.
Figure 2: Comparison of the statistical power of the category-based approach and dimensional approaches in Case 1. (A) The schematic of the generative model in Case 1. This case includes a single pathogenetic factor ($N = 1$) and single behavioral measure ($M = 1$). (B) Illustration of the category-based approach with a margin. See the main text for details. (C) The statistical power (with the significance level $\alpha = .01$) of both methods as a function of the total number of subjects, with variable margin $d$ for the category-based approach. The solid lines represent the analytical results (see Appendix [B]). Symbols represent the results of the Monte Carlo simulations (see Appendix [C]).
Figure 3: The effect of the number of diagnosis criteria, $M$, in the category-based approach (Case 2). (A) The schematic of the generative model in Case 2. Here, the model includes two pathogenetic factors ($N = 2$; $x_2$ is irrelevant) and $M$ behavioral measures. (B) The distribution of the estimated pathogenetic factor $\hat{x}_1$ for three $M$ cases. (C) The statistical power (with significance level $\alpha = .01$) of both methods as a function of $M$, with varying standard deviation of the noise, $\sigma_\epsilon$. The horizontal lines at $M = 1$ represent the analytical results (see Appendix B). The symbols and the lines connecting the symbols for $M$ for the category-based approach represent the results of Monte Carlo simulations.
Figure 4: The effect of a mixture of pathogenetic factors (Case 3). (A) The schematic of the generative model in Case 3. Here, the model includes two pathogenetic factors ($N = 2$) and two behavioral measures ($M = 2$). The parameter $c$ indicates the degree of the mixture. (B) The scatter plot of $Y$ for two $c$ cases. (C) The statistical power (with critical value $\alpha = .01$) of both methods as a function of $c$, with varying standard deviation of the noise, $\sigma_\epsilon$. The dash-dot lines for the dimensional approach and the dashed lines for the category-based approach with a single criterion denote the analytical results (see Appendix B). Symbols and solid lines for the category-based approach using two criteria represent the results of the Monte Carlo simulations.
Figure 5: The effect of the number of pathogenetic factors, \( N \). (A) The schematic of the generative model in Case 4. The model includes \( N \) pathogenetic factors and one behavioral measure \( (M = 1) \). (B) The statistical power (with critical value \( \alpha = .01 \)) of both methods as a function of \( N \). The dash-dot lines and solid lines denote the analytical results. Symbols represent the results of the Monte Carlo simulations.
Figure 6: The effect of the number of pathogenetic factors, $N$, in the large sample case. (A) The statistical power (with the critical value $\alpha = 10^{-8}$) as a function of $N$. (B) The effect size as a function of $N$. The effect size for the dimensional approach is the correlation coefficient. The effect size for the category-based approach is Cohen’s $d$. (C) The fraction exceeded as a function of $N$. The fraction exceeded is defined as the fraction of the patients whose pathogenetic factor $x_1$ exceeds the mean $x_1$ of the control group, as illustrated in (D). The lines are obtained from the analytical results. The squares denote the numerically obtained fraction with a total subject size of 100,000.