Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Biol Psychiatry Cogn Neurosci Neuroimaging. Author manuscript; available in PMC 2017 September 01.

Published in final edited form as:

Biol Psychiatry Cogn Neurosci Neuroimaging. 2016 September ; 1(5): 386–392. doi:10.1016/j.bpsc.2016.05.001.

A Roadmap for the Development of Applied Computational Psychiatry

Martin P. Paulus[1,2], **Quentin J.M. Huys**[3,4], and **Tiago V. Maia**[5]

[1]Laureate Institute for Brain Research, Tulsa, OK [2]Psychiatry, University of California San Diego, La Jolla, CA [3]Translational Neuromodeling Unit, Institute for Biomedical Engineering, University of Zurich and Swiss Federal Institute of Technology (ETH) Zurich, Switzerland [4]Centre for Addictive Disorders, Department of Psychiatry, Psychotherapy and Psychosomatics, Hospital of Psychiatry, University of Zurich, Switzerland [5]Institute for Molecular Medicine, School of Medicine, University of Lisbon, Portugal

Abstract

Background—Computational psychiatry is a burgeoning field that utilizes mathematical approaches to investigate psychiatric disorders, derive quantitative predictions, and integrate data across multiple levels of description. Computational psychiatry has already led to many new insights into the neurobehavioral mechanisms that underlie several psychiatric disorders, but its usefulness from a clinical standpoint is only now starting to be considered.

Methods—Examples of computational psychiatry are highlighted, and a phase-based pipeline for the development of clinical computational-psychiatry applications is proposed, similar to the phase-based pipeline used in drug development. It is proposed that each phase has unique endpoints and deliverables, which will be important milestones to move tasks, procedures, computational models, and algorithms from the laboratory to clinical practice.

Results—Application of computational approaches should be tested on healthy volunteers in Phase I, transitioned to target populations in Phase IB and Phase IIA, and thoroughly evaluated using randomized clinical trials in Phase IIB and Phase III. Successful completion of these phases should be the basis of determining whether computational models are useful tools for prognosis, diagnosis, or treatment of psychiatric patients.

Conclusions—A new type of infrastructure will be necessary to implement the proposed pipeline. This infrastructure should consist of groups of investigators with diverse backgrounds collaborating to make computational psychiatry relevant for the clinic.

Corresponding author: Martin P. Paulus M.D., Scientific Director and President, Laureate Institute for Brain Research, 6655 S Yale Ave, Tulsa, OK 74136-3326, Phone: 918 502 5120, FAX: 918 502 5135. mpaulus@laureateinstitute.org; Web: http://www.laureateinstitute.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflicts of interest

The authors report no conflicts of interest.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Keywords

Computational psychiatry; Development pipelines; Translational psychiatry; Biomarkers; Prediction; Machine Learning

Introduction

Neuroscience has made tremendous progress in understanding the neural circuitry that underlies processes such as attention, memory, emotion, and decision-making. Yet, these advances have brought little change to the care of psychiatric patients. There are no tools for prognosis, diagnosis, or treatment monitoring based on neuroscience approaches in routine clinical use today (1, 2), and novel developments in this direction have stalled (3). Neuroscience has also had negligible impact on reshaping disorder categories in new diagnostic classifications for mental disorders (4, 5). As a consequence, it is widely recognized by many leading academic psychiatrists that clinical psychiatry has not changed fundamentally over the past 50 years (6, 7). In response to this crisis, we suggest that computational psychiatry (CP) is uniquely placed to deal with the complexities of the problem and the arising data; argue that the development of clinical tools using CP approaches will, at least initially, play a large role in the development of biomarkers.

Computational psychiatry

Computational psychiatry comprises a set of approaches aimed at arriving at a computational understanding of the neural and cognitive substrates of psychiatric disorders (8). Why should computational approaches be useful for the translation of neuroscience insights into clinical improvements for patients with psychiatric disorders? One of the most prominent reasons for the negligible effect of neuroscience on clinical psychiatry is arguably the complexity of the problem. Psychiatric disorders are intrinsically complex, multivariate phenomena that defy univariate, descriptive approaches. In combination with the ever larger and more complex datasets modern experimental techniques produce, this calls for the application of novel and powerful analytical approaches. We and others have recently argued that CP provides a broad set of tools, ranging from detailed biophysical modeling to machine learning, that are uniquely suited to address these challenges (9).

CP encompasses two broad approaches (8, 10–16): theory-driven, often mechanistic models, and data-driven approaches, often using machine-learning techniques. Theory-driven models encompass multiple levels of analysis, including (a) biophysically based models that address the cellular, synaptic, and circuit levels, (b) connectionist and neural models that address the large-scale neural systems and behavioral levels, (c) algorithmic models (e.g., from reinforcement learning) that address, at an abstract level, the algorithms that the brain uses to implement certain computations and how behavior is a result of those computations, and (d) normative models, often based on Bayesian ideas, that address the types of computations that the brain makes or should make and how behavior and neural activity does or does not conform to those normative ideals. Generative versions of all these models can also be used to simulate behavior, estimate parameters or determine the best model for individual subjects, and even to refine the experimental approach and design to obtain data in the future

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

(17). The mechanistically interpretable parameters that result from applying these models to measured behavior and brain activity can be used for both hypothesis testing and model validation (11). Moreover, CP measures may also provide estimates of hidden, disease-relevant processes that can potentially be useful as novel targets in treatment-development programs. Thus, theory-driven models in computational psychiatry can be viewed as a microscope that enables us to unveil process components of the complex dysfunctions.

The second approach, that of machine learning, applies a wide range of techniques from statistics, computer science, and other fields, for classification, prediction, clustering, outlier detection, learning of association rules, and sequence analysis (18). Prominent examples of commonly used machine-learning tools include Random Forests (19), Support Vector Machines (20), Linear Discriminant Analysis (21), and k-Nearest Neighbor (22). These tools can not only be applied to assess a single marker, but can also be used to select among multivariable regression models and thus can be considered complex model-selection algorithms (23). Machine-learning tools have found their way into the medical field for a large number of different applications, ranging from the prediction of health-care services (24) to clinical predictions of the progression of Alzheimer's disease (25, 26). They are especially important in high-dimensional data settings, i.e., when the number of variables is much larger than the number of cases (27, 28). The combination of a mechanistically driven computational model together with a data-driven machine learning approach to optimally delineate categories and generate robust predictions may turn out to be particularly powerful to make neuroscience relevant for clinical psychiatry (12, 14, 16).

The last decade has brought several major advances that help to understand why CP is at the brink of making a major impact to integrate measurements across levels of analysis and be of practical use for the clinician. First, research in computational psychiatry has skyrocketed in the last few years; as a result, a recognizable computational psychiatry community has started to form and meet regularly in dedicated symposia, conferences, and other venues. Second, several research groups have developed toolboxes that enable researchers to apply and test different computational models on their data (29–36). Third, the use of machine-learning tools (37) applied to increasingly complex features has made it possible to classify or cluster subjects on the basis of biological and behavioral measurements (12, 38, 39). Fourth, many of the computational models require significant computational resources to disambiguate different models; the increasingly widespread availability of high computing power has made it possible to evaluate these models on a large scale.

Lessons in the development of clinical tools

For CP to bear fruits and truly accelerate the translation of neuroscience into improved patient outcomes (27, 28, 40–45), it is worthwhile considering lessons learned in three domains. The first concerns the clinical applications of biomarkers, which provide a helpful guide to potential clinical usability of neuroscience methods. The second is the distinction between significance testing and prediction. Finally, for such methods to withstand the multifaceted challenges of actual clinical practice, they have to go through a process of validation, which we suggest may take a form akin to that of the drug-development pipeline. Reference to such a pipeline may help to determine the current state of development of a

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

given tool or technique and inform decisions about further investment into neuroscience methods.

Clinical applications of biomarkers

CP techniques are likely to have a prominent translational role in the development of novel biomarkers, which have been defined as " measurable characteristics that reflect physiological, pharmacological, or disease processes" (46) or as " indicator[s] signaling an event or condition in a biological system or sample and giving a measure of exposure, effect, or susceptibility" (47). Biomarkers have had limited, if any, impact on clinical psychiatry, as exemplified in a recent review focused on schizophrenia (1). In the broader domain of medicine, however, biomarkers have been used for several well-defined clinical applications (47–49). First, biomarkers can be used in a prognostic setting to attempt to determine the likely course of the disease. A related application of prognostic biomarkers is the early detection of disease, i.e., screening. Second, biomarkers can be used to identify subgroups that respond more uniformly to certain therapeutic interventions to increase the likelihood of therapeutic success (stratification) and to select a particular drug or intervention from an available class (differentiation). Third, biomarkers can be used to replace clinical assessments to assess the progress of interventions as efficacy surrogates, allowing, for instance, early changes in treatment strategy. They can also be used to indicate risk of disease re-emergence after remission (monitoring). A fourth use is to exclude patients from certain interventions, i.e., to prevent toxicity. As a possible example within the realm of CP, it is conceivable that certain measures of learning might predict adverse effects of certain psychological interventions. In addition to requiring different data, these approaches differ in the demands they place on measures. For example, the broader the target population for a screening test, the less burdensome and costly the test can be; as another example, biomarkers to be used for monitoring or as efficacy surrogates must have particularly high test-retest reliability. Considering these issues in advance will help focus resources on the most promising CP measures early on.

Prediction versus significance

A second lesson arises in the distinction between significance testing and prediction. As in the rest of medicine, diagnosis and treatment in psychiatry initially had to be based on verbal report, observable behavior, and clinical phenomena. Clinical needs then rightly dictated the aggregation of these phenomena into nosological categories—psychiatric disorders—that achieve some reliability between clinicians (50, 51). These categories have some predictive value in that they provide rough guides to treatment, treatment monitoring, prognosis, and toxicity. However, the prevalence of trial-and-error treatment and the relatively high percentage of non-responders in psychiatry clearly attest to the insufficient predictive value of existing diagnoses.

A substantial amount of research has sought to identify variables that differ significantly across existing diagnostic categories (e.g., differences in neural processes between healthy comparison subjects and schizophrenia patients) or that are correlated with a feature of interest (e.g., the degree of depression, anxiety, or psychosis). Unfortunately, such research has done little to improve predictive value in psychiatry. For instance, no biomarkers for

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

neuropsychiatric disorders have been successfully translated to clinical practice (52). One possibility is that this approach to research has not yet progressed far enough to lead to clinical applications, and so we just need more of the same type of research. We propose a different perspective, however, arguing that this type of research may be fundamentally misaligned with the goals of prediction. We base this contention on two observations. First, these approaches generally just reify existing diagnostic categories, rather than trying to move beyond them. Second, and more fundamentally, the statistical approaches used for assessing significance are different from those required to detect useful predictors. There is no guarantee that a variable that differs significantly between two groups will be useful for prediction, nor is there any guarantee that a variable that does *not* differ significantly between groups is *not* useful for prediction (53). In fact, a variable that does not differ significantly between two groups, regardless of sample size, may be a better predictor than one that does (53). The key difference between significant and predictor variables is that significant variables are based on assumptions of the exact form of the underlying distribution.

An alternative is hence a framework in which the focus is systematically and explicitly on prediction. Such an approach has many advantages, which we suggest make it a natural focus for translational efforts. It can avoid reifying existing categories by potentially bypassing diagnostic labels entirely, instead predicting directly clinically relevant variables (e.g., treatment response) (14), but it can also easily be combined with, and naturally enhance, the current diagnostic schemes by making incremental contributions that can be made explicit (54–56). The predictive framework also brings patient-relevant outcomes into the focus of neuroscientists. CP techniques can be especially helpful for such a predictive approach. Both theory- and data-driven approaches, and indeed their combination, can be used to extract relevant predictive features from complex, high-dimensional datasets (9). Mechanistic models can achieve this by extracting meaningful, low-dimensional underlying mechanistic measures from complex, high-dimensional data (e.g., extracting a couple of parameters that characterize learning from complex learning trajectories). Machine learning (ML) techniques achieve this through general-purpose statistical data characterizations. There has been substantial recent interest in using these techniques for practical purposes such as automated classification of psychiatric disorders based on brain-imaging data (38). Integrating mechanistic and ML approaches affords an integration of predictive models with a mechanistic understanding of psychiatric disease that may actually result in improved prediction (12, 16).

Prediction, however, is not an end in itself, but merely a step on the path towards using neuroscience methods to improve therapeutic decision making and ultimately treatment outcomes and cost-effectiveness of care (56). Statistical tools can be used to estimate the size of these improvements. For instance, the statistical properties of the biomarker can be combined with information about the prevalence of the disorder and the efficacy of treatments to estimate the impact of the biomarker on patient outcomes (23, 57). However, the ultimate test of the effectiveness of a prediction tool, like any other intervention, is a Randomized Clinical Trial (RCT). In this case, the predictive test is the intervention, which is examined for its efficacy (58). Thus, a group of providers would be randomized to receive test information whereas another group of providers would be randomized to receive no

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

information. Patient outcomes are the main dependent measure, and a significantly different outcome across groups of patients treated by providers with and without test information provides support for the clinical utility of the test (58).

A development pipeline for computational psychiatry inspired by the drug-development pipeline

The development cycle of biomarkers, drugs, and medical devices involves five different types of studies including of (a) preclinical studies, (b) clinical assay development, (c) longitudinal and cross-sectional repository studies, (d) prospective studies, and (e) randomized controlled studies (47, 49, 59, 60). To accelerate the application of new knowledge in CP from discovery to implementation in clinical practice, we propose the adoption of a similar pipeline. Specifically, we propose a phased translational approach that divides the pragmatic knowledge production into phases, similar to pipelines described for the development of drugs, diagnostic markers, and other interventions.

Preclinical phase

This phase establishes a first version of the CP tool. It starts with the early stages of identifying process targets, determining what measures to employ, and developing appropriate experimental paradigms, computational models, and model-fitting routines to tap into those targets. This phase is characterized by small-scale experiments typically developed in individual laboratories by computational and theoretical neuroscientists, experimental psychologists, cognitive and behavioral neuroscientists, and other basic scientists. This phase typically uses cross-sectional studies with healthy volunteers to determine whether the empirical and computational framework appropriately probes the presumed process(es) of interest. Moreover, modeling experts may be able to use data repositories to develop computational models for a particular target population.

Phase I(a): robustness

The main aim for this phase is to assess and improve the robustness of the CP tool, i.e., to develop a complete package consisting of reliable and robust probes, measures, and analysis tools that can subsequently be used as a package in clinical studies. These studies are focused on the more “mundane” aspects of pragmatic CP, which are often underappreciated but are critical for success in the subsequent phases. Important factors include, among others, fine-tuning of the probes (e.g., recording or task lengths), test-retest reliability, external, construct and converging validity, ceiling or floor effects, training effects, sensitivity to experimental manipulation, detailed characterization and optimization of model-fitting procedures, or dependence on context and implementation. Some of these issues have been addressed in detail by the CNTRICs initiative (61), albeit not in the context of CP. These experiments will need to include a large number of healthy individuals and comprise both cross-sectional and limited longitudinal studies. As this involves a substantial research effort, it may benefit from multi-site collaborations.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Phase I(b): clinical validity

During this phase, the models, paradigms, and/or techniques developed in the earlier phases are first applied to particular clinical populations. These studies focus on relatively small clinical samples and can provide the first evidence regarding whether computational modeling helps to provide a more sensitive measure or a deeper understanding of the putative process dysfunction. The experimental designs can be varied and include case-control studies, experimental designs with specific manipulations, longitudinal prospective designs, and even early interventional studies. The goal for this phase is to determine the sensitivity, specificity, validity, and explanatory value that computational approaches add to existing clinical care. In addition, similar to “dose-finding” studies, these experiments may modulate a particular parameter such as sensory processing difficulty or working memory load to optimize the estimation of a computational parameter for a particular target population. At this stage, many experiments will be conducted in individual laboratories that include a close collaboration between academic psychiatrists or psychologists and theoretical or computational neuroscientists. Phases Ia and Ib are both part of Phase I because they are interdependent. Thus, despite the seemingly linear process, it is clear that identification and development are iterative processes (62). In many cases, especially those that do not involve interventions, it may be more efficient to move to Phase Ib well before all aspects of Phase Ia are completed.

Phase II: initial proof of efficacy in a RCT

The critical step in translating neuroscience to clinical psychiatry is to clearly show the efficacy and utility of a diagnostic, prognostic, or interventional approach in a psychiatric population. Phase II randomized controlled trials (RCTs) are essential in establishing whether computational psychiatry will be relevant clinically. However, these trials need to be sufficiently powered to be confident that primary or secondary endpoints will be met. Typically, Phase II trials have to use multi-site designs and therefore require significant resources in terms of money, personnel, and infrastructure. They will therefore need to be developed as endeavors of consortia who have an interest in translating CP into the clinic. At this stage, experts in clinical trials, statisticians with clinical design expertise, and academic clinicians who can contribute expert opinions about critical measures and outcome assessments will need to integrate with the team of investigators that have conducted Phase I studies. A possible example for a Phase II CP trial could be to determine whether computational parameters extracted from behavioral or neural data can improve treatment decisions (say, deciding to stop antidepressant treatment if a patient shows a normalization of reward-related parameters). Another example could be to test if a task-derived computational parameter that indicates a greater reliance on goal-directed rather than habitual behavior (63, 64) could help to predict who would benefit from cognitive therapy.

Phase III – establish clinical effectiveness

In drug and biomarker development, Phase III studies are carried out according to strict regulations that ensure the reproducibility of the results and help to ensure transparent data acquisition and analysis. There have been no Phase III trials using computational-psychiatry approaches. Like Phase III clinical trials for novel therapeutics, these studies are going to be

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

expensive, have to be carried out at multiple sites, and will need to be based on highly robust probes, computational models, and measures. At this stage, economic analyses are essential to be able to convince organizations providing mental-health care to include novel approaches into their coverage. Interestingly, there has been relatively little discussion of what economic model would support the addition of neuroscience-based measures in general and CP approaches in particular.

Phase IV – post-marketing refinement

These studies comprise “post-marketing” surveillance of an approved procedure or biomarker aimed at detecting rare or long-term adverse effects of its use in the broader patient population. They can also be used to test for efficacy in patient populations that were not examined in Phase II or III trials (e.g., does assigning patients to cognitive therapy based on a model parameter that reflects reliance on goal-directed versus habitual responses also work for other age ranges, contexts, socioeconomic status, and so on). These studies could include CP-based patient selection or stratification of individuals with particular types of depression (e.g. post-partum, post-stroke, or trauma-related) to determine whether these individuals would be good candidates for learning-based treatment interventions.

Discussion

The goal for a pragmatic approach to research in psychiatry is to generate impactful research that makes a difference in mental health. In this article, we sought to lay out a strategy and roadmap to take computational psychiatry from the laboratory, where it still resides more comfortably, to the clinic. We called for a fundamental shift in research focus, from seeking to find statistically significant differences between groups to seeking to develop predictive models that address real clinical needs, noting that these two goals are not as well aligned as one might initially think. We also proposed a phased development pipeline, akin to that used in drug or device development, to take computational psychiatry from the initial, preclinical stages all the way to the clinic. This type of pipeline makes the key transitions explicit, which will help to clearly frame go/nogo decisions for continued development, highlight measurements that help to quantify value-added benefit, and create a timeline for the experiments and clinical studies that are necessary to move forward. The majority of CP work thus far has been at the preclinical and Phase I stages. Recent work, however, has started to show promise in the application of computational psychiatry to real clinical problems (9).

There are a number of CP tools with clinical potential. As one example, the burgeoning literature on model-free versus model-based learning (64–68) has resulted in the development of a task and a rich set of computational analyses, and it has been applied to a variety of disorders, including various substance dependences and obsessive-compulsive disorder (69, 70). As another example, neural and more abstract models of the role of dopamine in reinforcement learning have similarly led to the development of tasks and models that have been applied across a wide range of psychiatric and neurological disorders (15, 71). However, unlike standard neuropsychological (72) or cognitive approaches (73), there are no systematic initiatives that have prospectively examined the reliability and

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

clinical usefulness of computational approaches. Furthermore, there has as yet been no structured initiative within the context of computational psychiatry to bring together individuals with the various necessary skills to conduct such studies. Similar efforts in closely related fields—e.g., the cognitive neuroscience treatment to improve cognition in schizophrenia (CNTRICS) initiative (74, 75)—can provide valuable insights as to how to establish an operational environment to make these studies possible.

To realize the potential of CP tools, there will need to be an effort based on a scientific community that includes researchers with a wide range of expertise. The lack of interaction between basic scientists and clinical researchers that are familiar with the intricacies of the disease is a well-know issue from other fields (49). Target populations have to be carefully selected, and important aspects beyond socio-demographics, such as substance use, physical activity, and metabolic status that can have profound influences on biological markers and may well affect cognitive processing (76) should be thoughtfully assessed. Realizing the potential of CP tools will also require an operational framework, i.e., a more systematic way of developing probes, models, and experiments, sharing insights and results, communicating findings quickly and effectively, and helping to implement models and experimental procedures across laboratories. It may also be helpful to consider Quality System (QS) regulation. This regulation requires that, before making a new test, the developers must identify relevant inputs and outputs and must establish a program for verifying and validating production processes and test performance (77). In addition to being essential for effective biomarker development and regulatory approval, guidelines on QS regulation share remarkable similarity to those recently suggested for high-impact journal publication (78), and these practices are consistent with increasingly regulated reporting of findings using publication standards such as CONSORT (79) or STARD (80).

In conclusion, we have argued that the complexity and features of the problems and data in clinical psychiatry mean that computational approaches will play a key role in making neuroscience relevant for clinical psychiatry, ultimately helping to make neuroscience relevant to day-to-day psychiatric practice. Achieving this challenging goal will require a systematic, focused approach, akin to that used in drug development; it seems quite unlikely that leaving things to chance—i.e., to disjoint, ad hoc efforts—will be able to bridge the wide gap between initial development of CP tools and their eventual use in clinical practice. We proposed a systematic pipeline to guide these efforts, and we identified limitations of current research efforts in psychiatry that may be hindering, rather than assisting, progress in the development of clinically useful tests, tools, and techniques. We hope that sophisticated computation, a systematic framework, and new organizational schemes for the operational implementation of this framework will finally translate neuroscience insights into clinical practice.

Acknowledgments

Funding

MPP is supported by a grant from the National Institute of Mental Health (R01 MH101453) and from the National Institute on Drug Abuse (U01 DA041089); QH is supported by a grant from the Swiss National Science Foundation (SNSF 320030L_153449); TVM receives funding from the Tourette Association of America and from a Breakthrough Idea Grant from Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

References

1. Prata D, Mechelli A, Kapur S. Clinically meaningful biomarkers for psychosis: A systematic and quantitative review. Neurosci Biobehav Rev. 2014
2. Fond G, d'Albis MA, Jamain S, Tamouza R, Arango C, Fleischhacker WW, et al. The promise of biological markers for treatment response in first-episode psychosis: a systematic review. Schizophrenia bulletin. 2015; 41:559–573. [PubMed: 25759473]
3. Insel TR. Next-generation treatments for mental disorders. Sci Transl Med. 2012; 4:155ps119.
4. APA APA. Diagnostic and statistical manual of mental disorders. 5th. Washington: The American Psychiatric Association; 2013.
5. Casey BJ, Craddock N, Cuthbert BN, Hyman SE, Lee FS, Ressler KJ. DSM-5 and RDoC: progress in psychiatry research? Nat Rev Neurosci. 2013; 14:810–814. [PubMed: 24135697]
6. Stephan KE, Bach DR, Fletcher PC, Flint J, Frank MJ, Friston KJ, et al. Charting the landscape of priority problems in psychiatry, part 1: classification and diagnosis. The lancet Psychiatry. 2016; 3:77–83. [PubMed: 26573970]
7. Stephan KE, Binder EB, Breakspear M, Dayan P, Johnstone EC, Meyer-Lindenberg A, et al. Charting the landscape of priority problems in psychiatry, part 2: pathogenesis and aetiology. The lancet Psychiatry. 2016; 3:84–90. [PubMed: 26573969]
8. Montague PR, Dolan RJ, Friston KJ, Dayan P. Computational psychiatry. Trends Cogn Sci. 2012; 16:72–80. [PubMed: 22177032]
9. Huys QJM, Maia TV, Frank MJ. Computational psychiatry as a bridge from neuroscience to clinical applications. Nat Neurosci. 2016 In Press.
10. Wang XJ, Krystal JH. Computational psychiatry. Neuron. 2014; 84:638–654. [PubMed: 25442941]
11. Stephan KE, Mathys C. Computational approaches to psychiatry. Curr Opin Neurobiol. 2014; 25:85–92. [PubMed: 24709605]
12. Wiecki TV, Poland J, Frank MJ. Model-based cognitive neuroscience approaches to computational psychiatry: Clustering and classification. Clinical Psychological Science. 2015; 3:378–399.
13. Huys QJ, Moutoussis M, Williams J. Are computational models of any use to psychiatry? Neural Netw. 2011; 24:544–551. [PubMed: 21459554]
14. Huys QJ, Maia TV, Frank MJ. Computational psychiatry as a bridge from neuroscience to clinical applications. Nat Neurosci. 2016; 19:404–413. [PubMed: 26906507]
15. Maia TV, Frank MJ. From reinforcement learning models to psychiatric and neurological disorders. Nat Neurosci. 2011; 14:154–162. [PubMed: 21270784]
16. Maia TV. Introduction to the series on computational psychiatry. Clinical Psychological Science. 2015; 3:374–377.
17. Daunizeau J, Adam V, Rigoux L. VBA: a probabilistic treatment of nonlinear models for neurobiological and behavioural data. PLoS Comput Biol. 2014; 10:e1003441. [PubMed: 24465198]
18. Hastie, T.; Tibshirani, R.; Friedman, JH. The Elements of Statistical Learning: Data Mining, Inference, and Prediction. New York: Springer; 2001.
19. Breiman L. Random Forests. Mach Learn. 2001; 45:5–32.
20. Cortes CRVV. Support-Vector Networks. Mach Learn. 1995; 20:273–297.
21. Misaki M, Kim Y, Bandettini PA, Kriegeskorte N. Comparison of multivariate classifiers and response normalizations for pattern-information fMRI. Neuroimage. 2010; 53:103–118. [PubMed: 20580933]
22. Zhu M, Chen W, Hirdes JP, Stolee P. The K-nearest neighbor algorithm predicted rehabilitation potential better than current Clinical Assessment Protocol. Journal of clinical epidemiology. 2007; 60:1015–1021. [PubMed: 17884595]
23. Gerds TA, Cai T, Schumacher M. The performance of risk prediction models. Biometrical journal Biometrische Zeitschrift. 2008; 50:457–479. [PubMed: 18663757]
24. Padman R, Bai X, Airoldi EM. A new machine learning classifier for high dimensional healthcare data. Studies in health technology and informatics. 2007; 129:664–668. [PubMed: 17911800]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

25. Maroco J, Silva D, Rodrigues A, Guerreiro M, Santana I, de Mendonca A. Data mining methods in the prediction of Dementia: A real-data comparison of the accuracy, sensitivity and specificity of linear discriminant analysis, logistic regression, neural networks, support vector machines, classification trees and random forests. BMC research notes. 2011; 4:299. [PubMed: 21849043]
26. Kohannim O, Hua X, Hibar DP, Lee S, Chou YY, Toga AW, et al. Boosting power for clinical trials using classifiers based on multiple biomarkers. Neurobiology of aging. 2010; 31:1429–1442. [PubMed: 20541286]
27. Gowin JL, Ball TM, Wittmann M, Tapert SF, Paulus MP. Individualized relapse prediction: Personality measures and striatal and insular activity during reward-processing robustly predict relapse. Drug Alcohol Depend. 2015
28. Ball TM, Stein MB, Ramsawh HJ, Campbell-Sills L, Paulus MP. Single-Subject Anxiety Treatment Outcome Prediction using Functional Neuroimaging. Neuropsychopharmacology. 2014; 39:1254–1261. [PubMed: 24270731]
29. Wiecki TV, Sofer I, Frank MJ. HDDM: Hierarchical Bayesian estimation of the Drift-Diffusion Model in Python. Frontiers in neuroinformatics. 2013; 7:14. [PubMed: 23935581]
30. Aponte EA, Raman S, Sengupta B, Penny WD, Stephan KE, Heinzle J. mpdcm: A toolbox for massively parallel dynamic causal modeling. J Neurosci Methods. 2016; 257:7–16. [PubMed: 26384541]
31. Mathys CD, Lomakina EI, Daunizeau J, Iglesias S, Brodersen KH, Friston KJ, et al. Uncertainty in perception and the Hierarchical Gaussian Filter. Front Hum Neurosci. 2014; 8:825. [PubMed: 25477800]
32. Matzke D, Love J, Wiecki TV, Brown SD, Logan GD, Wagenmakers EJ. Release the BEESTS: Bayesian Estimation of Ex-Gaussian STop-Signal reaction time distributions. Front Psychol. 2013; 4:918. [PubMed: 24339819]
33. Friston KJ, Li B, Daunizeau J, Stephan KE. Network discovery with DCM. Neuroimage. 2011; 56:1202–1221. [PubMed: 21182971]
34. Daunizeau J, den Ouden HE, Pessiglione M, Kiebel SJ, Stephan KE, Friston KJ. Observing the observer (I): meta-bayesian models of learning and decision-making. PLoS One. 2010; 5:e15554. [PubMed: 21179480]
35. Daunizeau J, Friston KJ, Kiebel SJ. Variational Bayesian identification and prediction of stochastic nonlinear dynamic causal models. Physica D Nonlinear phenomena. 2009; 238:2089–2118. [PubMed: 19862351]
36. Schrouff J, Rosa MJ, Rondina JM, Marquand AF, Chu C, Ashburner J, et al. PRoNTo: pattern recognition for neuroimaging toolbox. Neuroinformatics. 2013; 11:319–337. [PubMed: 23417655]
37. Witten, JG.; Hastie, T.; Tibshirani, R. An Introduction to Statistical Learning. New York Heidelberg Dordrecht London: Springer; 2013.
38. Wolfers T, Buitelaar JK, Beckmann CF, Franke B, Marquand AF. From estimating activation locality to predicting disorder: A review of pattern recognition for neuroimaging-based psychiatric diagnostics. Neurosci Biobehav Rev. 2015; 57:328–349. [PubMed: 26254595]
39. Brodersen KH, Deserno L, Schlagenhauf F, Lin Z, Penny WD, Buhmann JM, et al. Dissecting psychiatric spectrum disorders by generative embedding. NeuroImage Clinical. 2014; 4:98–111. [PubMed: 24363992]
40. Paulus MP, Tapert SF, Schuckit MA. Neural activation patterns of methamphetamine-dependent subjects during decision making predict relapse. ArchGenPsychiatry. 2005; 62:761–768.
41. Gowin JL, Stewart JL, May AC, Ball TM, Wittmann M, Tapert SF, et al. Altered Cingulate and Insular Cortex Activation During Risk-Taking in Methamphetamine Dependence: Losses Lose Impact. Addiction. 2013
42. Harle KM, Shenoy P, Stewart JL, Tapert SF, Yu AJ, Paulus MP. Altered neural processing of the need to stop in young adults at risk for stimulant dependence. J Neurosci. 2014; 34:4567–4580. [PubMed: 24672002]
43. Harle KM, Stewart JL, Zhang S, Tapert SF, Yu AJ, Paulus MP. Bayesian neural adjustment of inhibitory control predicts emergence of problem stimulant use. Brain : a journal of neurology. 2015

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

44. Whalley HC, Sussmann JE, Romaniuk L, Stewart T, Papmeyer M, Sprooten E, et al. Prediction of depression in individuals at high familial risk of mood disorders using functional magnetic resonance imaging. PLoS One. 2013; 8:e57357. [PubMed: 23483904]
45. Marhe R, van de Wetering BJ, Franken IH. Error-related brain activity predicts cocaine use after treatment at 3-month follow-up. Biol Psychiatry. 2013; 73:782–788. [PubMed: 23374638]
46. Frank R, Hargreaves R. Clinical biomarkers in drug discovery and development. NatRevDrug Discov. 2003; 2:566–580.
47. Bahn S, Noll R, Barnes A, Schwarz E, Guest PC. Challenges of introducing new biomarker products for neuropsychiatric disorders into the market. International review of neurobiology. 2011; 101:299–327. [PubMed: 22050857]
48. Trusheim MR, Berndt ER, Douglas FL. Stratified medicine: strategic and economic implications of combining drugs and clinical biomarkers. Nature reviews Drug discovery. 2007; 6:287–293. [PubMed: 17380152]
49. Drucker E, Krapfenbauer K. Pitfalls and limitations in translation from biomarker discovery to clinical utility in predictive and personalised medicine. The EPMA journal. 2013; 4:7. [PubMed: 23442211]
50. American Psychiatric A. Diagnostic and Statistical Manual of Mental Disorders (4th Edition): DSM-IV. Washington: The American Psychiatric Association; 1994.
51. Freedman R, Lewis DA, Michels R, Pine DS, Schultz SK, Tamminga CA, et al. The initial field trials of DSM-5: new blooms and old thorns. Am J Psychiatry. 2013; 170:1–5. [PubMed: 23288382]
52. Filiou MD, Turck CW. General overview: biomarkers in neuroscience research. International review of neurobiology. 2011; 101:1–17. [PubMed: 22050846]
53. Lo A, Chernoff H, Zheng T, Lo SH. Why significant variables aren't automatically good predictors. Proc Natl Acad Sci U S A. 2015; 112:13892–13897. [PubMed: 26504198]
54. Pencina MJ, D'Agostino RB Sr. Thoroughly modern risk prediction? Science translational medicine. 2012; 4:131fs110.
55. Moons KG, Kengne AP, Woodward M, Royston P, Vergouwe Y, Altman DG, et al. Risk prediction models: I. Development, internal validation, and assessing the incremental value of a new (bio)marker. Heart. 2012; 98:683–690. [PubMed: 22397945]
56. Moons KG, Kengne AP, Grobbee DE, Royston P, Vergouwe Y, Altman DG, et al. Risk prediction models: II. External validation, model updating, and impact assessment. Heart. 2012; 98:691–698. [PubMed: 22397946]
57. Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. Circulation. 2007; 115:928–935. [PubMed: 17309939]
58. Scott IA, Greenberg PB. Cautionary tales in the interpretation of studies of tools for predicting risk and prognosis. Internal medicine journal. 2010; 40:803–812. [PubMed: 20214688]
59. Goodsaid FM, Frueh FW, Mattes W. Strategic paths for biomarker qualification. Toxicology. 2008; 245:219–223. [PubMed: 18280028]
60. Czajkowski SM, Powell LH, Adler N, Naar-King S, Reynolds KD, Hunter CM, et al. From Ideas to Efficacy: The ORBIT Model for Developing Behavioral Treatments for Chronic Diseases. Health Psychol. 2015
61. Carter CS, Barch DM, Bullmore E, Breiling J, Buchanan RW, Butler P, et al. Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia II: developing imaging biomarkers to enhance treatment development for schizophrenia and related disorders. Biol Psychiatry. 2011; 70:7–12. [PubMed: 21529781]
62. Phillips KA, Van Bebber S, Issa AM. Diagnostics and biomarker development: priming the pipeline. Nature reviews Drug discovery. 2006; 5:463–469. [PubMed: 16718275]
63. Gillan CM, Otto AR, Phelps EA, Daw ND. Model-based learning protects against forming habits. Cogn Affect Behav Neurosci. 2015; 15:523–536. [PubMed: 25801925]
64. Daw ND, Gershman SJ, Seymour B, Dayan P, Dolan RJ. Model-based influences on humans' choices and striatal prediction errors. Neuron. 2011; 69:1204–1215. [PubMed: 21435563]
65. Dayan P, Daw ND. Decision theory, reinforcement learning, and the brain. Cogn Affect Behav Neurosci. 2008; 8:429–453. [PubMed: 19033240]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

66. Dolan RJ, Dayan P. Goals and habits in the brain. Neuron. 2013; 80:312–325. [PubMed: 24139036]

67. Daw ND, Dayan P. The algorithmic anatomy of model-based evaluation. Philos Trans R Soc Lond B Biol Sci. 2014; 369

68. Huys QJM, Guitart-Masip M, Dolan RJ, Dayan P. Decision-theoretic psychiatry. Clinical Psychological Science. 2015; 3:400–421.

69. Sebold M, Deserno L, Nebe S, Schad DJ, Garbusow M, Hagele C, et al. Model-based and model-free decisions in alcohol dependence. Neuropsychobiology. 2014; 70:122–131. [PubMed: 25359492]

70. Voon V, Baek K, Enander J, Worbe Y, Morris LS, Harrison NA, et al. Motivation and value influences in the relative balance of goal-directed and habitual behaviours in obsessive-compulsive disorder. Translational psychiatry. 2015; 5:e670. [PubMed: 26529423]

71. Waltz JA, Frank MJ, Wiecki TV, Gold JM. Altered probabilistic learning and response biases in schizophrenia: behavioral evidence and neurocomputational modeling. Neuropsychology. 2011; 25:86–97. [PubMed: 21090899]

72. Delis, DC.; Kaplan, E.; Kramer, JH. Manual for the Delis-Kaplan Executive Function System (D-KEFS). San Antonio, TX: Psychological Corp.; 2001.

73. Robbins TW, James M, Owen AM, Sahakian BJ, McInnes L, Rabbitt P. Cambridge Neuropsychological Test Automated Battery (CANTAB): a factor analytic study of a large sample of normal elderly volunteers. Dementia. 1994; 5:266–281. [PubMed: 7951684]

74. Carter CS, Barch DM. Cognitive neuroscience-based approaches to measuring and improving treatment effects on cognition in schizophrenia: the CNTRICS initiative. Schizophrenia bulletin. 2007; 33:1131–1137. [PubMed: 17630405]

75. Barch DM, Braver TS, Carter CS, Poldrack RA, Robbins TW. CNTRICS final task selection: executive control. SchizophrBull. 2009; 35:115–135.

76. McEwen BS. The Brain on Stress: Toward an Integrative Approach to Brain, Body, and Behavior. Perspectives on psychological science : a journal of the Association for Psychological Science. 2013; 8:673–675. [PubMed: 25221612]

77. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=820&showFR=1

78. Nosek BA, Alter G, Banks GC, Borsboom D, Bowman SD, Breckler SJ, et al. SCIENTIFIC STANDARDS. Promoting an open research culture. Science. 2015; 348:1422–1425. [PubMed: 26113702]

79. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Annals of internal medicine. 2010; 152:726–732. [PubMed: 20335313]

80. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. Annals of internal medicine. 2003; 138:W1–W12. [PubMed: 12513067]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 1

Proposed Phase-like development pipeline for Computational Psychiatry

	Preclinical	**Phase I(a)**	**Phase I(b)**	**Phase II**	**Phase III**	**Phase IV**
Drug Development Analog	Target (a) identification, (b) optimization	Safety / Tolerability	experimental medicine / target engagment	Small Scale Efficacy	Large Scale Efficacy	Post-marketing
ORBIT(61)		Define	Refine	Proof of Concept / Pilots	Efficacy Trial	Effectiveness
Time Line	Discovery (1–6 years)		Development (6 – 12 years)			
Goals	**"to identify probe(s) / measure(s) / model(s) / intervention (s)"**	**"to establish a reliable / robust probe(s) / measure(s) / model(s) / intervention (s)"**	**"to establish target process and engagement / model application / intervention engagement"**	**"to establish clinical efficacy and validity"**	**"to confirm clinical validity and demonstrate outcome improvement"**	**"new applications"**
Stages	Identification		Validation		Launch Readiness / Release	
Population	Healthy Volunteers (HV)	HV	HV, Target Population (s) TP	TP	TP	new TP
Study Type	cross-sectional (cs)	cs, longitudinal (l)	cs, l, experimental design(s)	Randomized Controlled Trial (RCT)	RCT	cs, l, RCT
Sites	single / few sites	single - multi-site	single / few sites	single - multi-site	multi-site	single / few sites
Study Size	small n	small to large n	medium n	large n	large n	small n

Abbreviations: HV = Healthy Volunteers, cs = cross-sectional, l = longitudinal, n = number of subjects, TP = target populations, RCT = randomized controlled trial.