# TOWARDS A COMPUTATIONAL PSYCHIATRY OF TRANSDIAGNOSTIC DEFICITS IN COGNITIVE CONTROL

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In collaboration with:

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***Project Summary***

Current diagnosis and treatment of psychiatric disorders are not ideal: there is significant heterogeneity within disorders and co-morbidity of symptoms between disorders, neither of which is well understood. Traditional psychiatric research typically contrasts small, specific patient groups with healthy controls on process-impure behavioral tests, and has arguably failed to produce a principled understanding of mental illness. Addressing these limitations, computational psychiatry (CP) eschews diagnostic categories and disorder-specific symptom assessment in favor of probing how variability in cognitive or affective computations across individuals may characterize transdiagnostic neurocognitive endophenotypes. Here, we aim to launch a novel line of CP in the domain of cognitive control. Failures in the use of internal goals to control behavior are considered key to many psychiatric conditions, but clinical translation of cutting-edge basic research is lacking, particularly with regard to “control-learning”, the dynamic adaptation of control strategies to changing contexts. This project examines control-learning deficits as a potential transdiagnostic neurocognitive endophenotype by leveraging recent advances in modeling control-learning processes and large-scale online data collection. Specifically, using a diverse online sample, we will relate variability in control-learning model parameters to individual differences in dimensional symptom clusters derived from clinically relevant self-report measures. Significant relationships detected in a discovery data set will be validated with out-of-sample classification of data from an independent test sample. A future, federally supported phase of this project would involve validating a putative control-learning endophenotype longitudinally and pursuing clinical translation studies to ultimately produce novel diagnostic and treatment tools for mental illness.

***Relevance to DIBS Mission and Germinator Award***

This project aligns closely with DIBS' core mission to promote interdisciplinary neuroscience and translate research into health and societal solutions, advancing DIBS' strategic goals through its five core values: interdisciplinary collaboration, diversity, impact, innovation, and leadership.

Our research team builds *interdisciplinary bridges* between the fields of psychiatry, developmental psychology, machine learning, biostatistics, and cognitive psychology and neuroscience. We integrate insights across disciplines and levels of analysis into *innovative* solutions for how to diagnose and treat psychiatric disorders. By computationally specifying how deficits in learning cognitive control relate to symptoms of mental illness, we connect basic science with transdiagnostic psychiatry, thus informing our understanding of why some individuals might have a risk factor for multiple disorders, but develop a different set of symptoms, and why risk factors lead to multiple disorders. Specifically, control-learning can result in a number of deficits, such as impaired contextual adaptation with respect to attentional selectivity or to updating goals in line with changing rules. These impairments may map onto different dimensions of symptoms, with deficits in each control parameter representing its own transdiagnostic risk factor, and a combination of risk factors ultimately leading to a psychiatric diagnosis. Once we know how dynamic control is impaired across psychiatric diagnoses, we can pursue clinical translation studies that ultimately produce novel diagnostic and treatment tools for mental illness. Our interdisciplinary, computational approach ensures that DIBS remains at the forefront in methodology and analyses that are revolutionizing neuroscience.

Our team is *diverse*, comprised equally of men and women and led by an Arab-American female graduate student who would gain expertise in computational neuroscience, a field in which women are traditionally underrepresented. This Big Data project would nurture her education through interdisciplinary collaboration and training in innovative analyses, which she would then teach to other members within her lab and the community, further enhancing the student experience at Duke. It would establish her as a *leader* within her field, helping her apply for an extramural training grant, supported by pilot data obtained with Germinator funding. The Germinator funds would also put Duke, and our multi-disciplinary team, in a position to gather proof-of-principle data for securing additional external funding, as our focus on transdiagnostic neurocognitive endophenotypes perfectly matches NIMH’s Research Domain Criteria (RDoC) initiative and recent prioritization of computational psychiatry[2]. Our focus on sophisticated analysis of dynamic human behavior elevates the potential *impact* and novelty of our work and the potential for *leadership* in external funding.

To enhance the *impact* of this project, we will disseminate our results to *community stakeholders* with outreach events and presentations at national conferences, such as the DIBS Brain Discovery Day, Brain Awareness Week, Psychiatry Grand Rounds, and Society for Neuroscience conference. We will recruit broadly from the community and underrepresented groups for research assistants who will gain valuable laboratory experience.

In sum, our project *connects minds* through collaboration across interdisciplinary fields, *advances neuroscience* through a computational approach to transdiagnostic psychiatry, and seeks to *improve lives* through basic science that informs diagnosis and treatment of mental illness.

***Project Goals***: Every year, nearly one in five American adults suffers from an experience with mental illness[1]. Current diagnosis and treatment of psychiatric disorders are not ideal: there is significant heterogeneity within disorders and co-morbidity between symptoms of disorders, neither of which is well understood. Traditional psychiatric research contrasts small, specific patient groups with healthy controls on mechanistically impure behavioral tests and has not produced a principled understanding of mental illness. *Computational psychiatry* (CP)[2-9] addresses these limitations: this approach eschews DSM categories and disorder-specific symptom assessment in favor of computational models that specify basic mechanisms underlying multiple disorders ("transdiagnostic neurocognitive endophenotypes")[10-12]. CP thus holds the promise of identifying and treating, in a theory-driven manner, specific cognitive processing failures that are shared between different disorders. Successful CP involves three steps: (1) *basic research* – developing sophisticated tasks/models that isolate specific cognitive processes; (2) *the bridge*[13,14] – leveraging large scale data collection to assess whether those processes map onto clinically relevant individual differences (e.g., trait anxiety); and (3) *the clinical test* – testing precise model-based hypotheses derived from step 2 in (transdiagnostic) patient samples.

Here, we aim to launch a novel line of CP in the domain of cognitive control[15], which describes the strategic use of internal goals and contextual cues to guide adaptive behavior. Cognitive control is an area ripe for translation: Failures in control are considered key contributors to many psychiatric disorders[16-19]. Moreover, great progress has been made at the basic science level[20-22], with sophisticated new tasks tracing *dynamic adjustments* in control via model-based analyses. However, while CP step 1 has been accomplished, steps 2 and 3 have not: cutting-edge cognitive control research currently has little impact on the diagnosis or treatment of psychiatric disorders. The present proposal, therefore, will pursue step 2, bridging from basic research (Egner lab) to large-scale assessment of individual differences in well-defined dynamic control processes. To achieve this aim, we leverage the rich expertise of the DIBS community: The effort will be led by graduate student Bejjani (under supervision of Egner), informed by world-renowned expertise in large-sample individual difference research (Moffitt & Caspi) and powered by sophisticated machine learning techniques for identifying meaningful structure in big data (Pearson). Finally, our long-term goal is to achieve step 3, the clinical test. A clinician-researcher psychiatrist with expertise in cognitive control (Adcock) will thus advise our project.

***Background & Significance***: Recent research in psychiatry has identified symptom clusters that provide evidence for transdiagnostic vulnerability to mental illness[23-34]. This vulnerability is best captured by a model with three correlated latent factors (internalizing, externalizing, and thought disorder) and one general psychopathology (p) factor[23-25,29,31]. The internalizing factor captures fear and anxious-misery[25-28] prevalent in anxiety disorders and depression, while the externalizing factor relates to substance use and conduct disorders and the thought disorder factor relates to psychotic experiences[31] and pathological introversion[30]. Importantly, the p factor has been linked to many poor life outcomes[24,35], such as compromised early-life brain function and adult life impairment, beyond any correlation with the internalizing, externalizing, and thought disorder factors. Since poor neurocognitive outcomes relate more to the p factor than the other factors, the p factor may act as an intermediate neurocognitive endophenotype for developing transdiagnostic risk factors[16]. Transdiagnostic vulnerability to mental illness has a big impact on life outcomes, but its etiological origins are understudied.

Cognitive neuroscience and genetic research has provided neurobiological support for the existence of transdiagnostic risk factors. Measures of cerebral blood flow[36], functional connectivity[37-39], gray matter loss[40], and cognitive performance[41,42] have been associated with distinct dysfunction patterns across psychiatric disorders, and may arise from transdiagnostic genetic vulnerabilities[43]. In particular, mental illness profoundly impacts the anterior insula and anterior cingulate, regions in the fronto-parietal and salience networks that are crucial to cognitive control[44-46], and failures in control are indeed considered key contributors to many psychiatric disorders[16-19]. These distinct behavioral and neural patterns[47-51] suggest that deficits in control may act as transdiagnostic risk factors[16]. Therefore, we hypothesize that dysfunctions in *dynamic control-learning* are neurocognitive endophenotypes related to transdiagnostic vulnerability represented by the p factor.

To discover transdiagnostic neurocognitive endophenotypes of cognitive control, we assess and model *control-learning* – with known neural substrates, including the anterior insula and cingulate[21,66-69] – along with clinically relevant self-report measures, in a large, diverse online subject population, an approach validated in prior research[13,14,52,53]. Using Amazon Mechanical Turk (MTurk), two recent Big Data studies found that deficits in reinforcement learning and metacognition were related to symptoms on a compulsive behavior and intrusive thought dimension[13,14]. While compelling, neither study tested current models of psychiatric symptoms (e.g., internalizing, externalizing factors) or transdiagnostic risk factors. Only one other study examined behavioral biomarkers in a transdiagnostic population: anxious arousal was associated with poor inhibitory control[42], which may be a transdiagnostic risk factor[54,55]. However, this study did not use a model-based specification of the underlying transdiagnostic mechanism, and used a "stationary" inhibitory control task, where control did not

have to be *adapted* to changing contexts[56]. Indeed, conventional analyses of basic control tasks (e.g., those in the RDoC matrix) do not tap into latent control computations and fail to account for the role of learning in cognitive control. To overcome these limitations, we here combine the strengths of large-scale online data collection with performance on dynamic control-learning tasks, which we model mechanistically, as well as self-report diagnoses and symptoms that we analyze for transdiagnostic vulnerability to mental illness.

As the first study to establish links between transdiagnostic vulnerability to mental illness and deficits in dynamic cognitive control through computational modeling, we aim to inform treatment by validating models of psychiatric symptoms, generating reproducible data, and examining neurocognitive origins of transdiagnostic vulnerability[57-59]. This translational work bridges from research in the lab to improving clinical practice, so that we can ultimately understand why some individuals might have a transdiagnostic risk factor, but develop a different set of symptoms, and why transdiagnostic risk factors lead to multiple disorders[60].

***Research/Training Design & Methods***: Because cognitive control and psychiatric symptoms change as a function of age, only subjects aged 18-39 may participate. MTurk workers will first perform two tasks that allow us to track their ability to dynamically adapt cognitive control to changing contexts, in two domains: (1) Conflict-control, the ability to overcome interference from habitual stimulus-response associations, will be assessed with a variant of the Stroop task[61]; and (2) set-shifting, the ability to update and apply changing task rules, will be assessed via a cued task-switching paradigm[62]. Dynamic adjustment of control is manipulated by varying (unbeknownst to the participants) the proportion of incongruent (hard) vs. congruent (easy) Stroop and task-switch (hard) vs. task-repeat (easy) trials between task blocks. As a marker of control-learning, we examine the interaction between block type (hard/easy) and demand (incongruent/congruent or switch/repeat). We analyze block-wise Stroop congruency effects and congruency sequence effects, in which the Stroop congruency effect is reduced following incongruent trials. We also analyze standard switch costs, in which subjects are slower and more error-prone on trials that switch vs. repeat tasks, and response congruency effects, in which subjects are slower and more error-prone when response mappings clash between tasks. Neuro-typical performance involves adaptation to changes in conflict and switch-likelihood such that interference and switch effects are smaller when incongruent and switch trials are frequent. Based on our prior experience with these tasks[20-22,67,68], and the fact that they recruit the brain networks that show impairments across disorders[20,21,63-69], we expect to observe substantial variance in control-learning. Variability in specific control operations will be captured through fitting well-validated reinforcement learning models[20,21,68,69], and individual differences in model parameters will be analyzed in relation to dimensional factors identified in the questionnaires.

Next, MTurk workers will complete the International Cognitive Ability Resource[70] as an indirect measure of IQ, and demographic questions assessing their socioeconomic status and family history of psychopathology. To capture the internalizing and externalizing factors, subjects will fill out the normed 126-item ASEBA[71] Adult Self-Report form, which covers syndromal (anxious/depressed, withdrawn, somatic complaints, thought problems, attention problems, aggressive behavior, rule-breaking behavior, and intrusive thought) and DSM-oriented scales for comparison in our analysis. We will supplement the thought disorder factor by also having subjects fill out the 43-item Short Scales for Measuring Schizotypy[72]. Because sleep disturbance has been proposed as a transdiagnostic risk factor[73], we include the 22-item Pittsburgh Sleep Quality Index[74]. Likewise, since stress and emotion regulation are potential transdiagnostic risk factors[75], we further include the 10-item Perceived Stress scale[76] and 10-item Emotion Regulation scale[77]. Finally, because cognitive control is impaired in ADHD and ASD[19,78], which are considered opposite ends of a *cognitive flexibility/stability* spectrum and may further correspond to externalizing and internalizing factors, we include the 18-item adult self-report ADHD scale[79] and the 28-item reduced Autism Spectrum Quotient[80]. All symptoms will be reported as a function of the past year to ensure accurate reporting of symptoms and maintain longitudinal consistency if we were to obtain federal funding to re-contact our subjects. We will use confirmatory factor analysis to extract individual-specific scores on the latent variable factors, and input self-report diagnoses and symptoms into an agglomerative hierarchical clustering with Ward error sum of squares algorithm to identify putative subtypes.

For optimal power and inference, we will collect a “discovery” (E1) and “test” (E2) sample data set of 1,000 subjects each; we expect to exclude ~20% of data for quality issues[13,14,53]. Relationships identified in E1 data will be validated with out-of-sample classification of E2 data. The experiment will take ~1 hour.

***Training/Milestones***: In Fall 2018, the team will preregister this project on the OSF framework, and Bejjani and Egner will apply for external funding (pre-doctoral NRSA, NIH R01), supported by E1 pilot data. In Spring 2019, Bejjani will submit to Society for Neuroscience, finalize E1 analyses and results, continue computational training, and collect and analyze E2 data. By summer 2019, the team will prepare the manuscript for submission to a high-impact journal, post the preprint to bioRxiv to increase the project’s visibility, and if federally funded, validate the endophenotypes longitudinally. Bejjani will promote the work at SfN 2019.

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***Budget***

We will use Amazon Mechanical Turk (MTurk) to run these experiments. MTurk charges 20% on any fee transacted through their site, whether that means the flat fee for a batch of Human Intelligence Tasks (HITs) or an individual-specific bonus for performance on certain tasks. MTurk also charges 20% extra for batches that have greater than 9 HITs (1 HIT = 1 participant).

Per participant:

- $6 flat fee for participating + 20% MTurk general fee ($1.20) + 20% MTurk large batch fee ($1.20) + $3 bonus for good performance and following instructions + 20% MTurk general fee on that $3 ($0.60) = $12 *per participant.*
    - $3-10 is the standard range of payment for a HIT duration of an hour.
    - A bonus is also a standard method of motivating subjects to perform well on the task and complete the HIT to the best of their ability.

We are aiming to run 1,000 participants per experiment. This suggests a cost of $12,000 per experiment, and a total budget of $24,000 for our two proposed experiments.