Understanding Social Functioning Deficits in Health and First Episode Schizophrenia: A Data-driven Approach Towards Improved Identification and Treatment

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Dedication

To my parents, Kathleen and John - the force of your love made everything possible.

Abstract

Background: Schizophrenia and other psychotic disorders are characterized by severe disability in social functioning, reducing quality of life, increasing risk for poor health outcomes, and causing significant personal and societal burden. Remediating social functioning impairments is an urgent clinical need, however progress has been hindered by a poor understanding of bio-behavioral underpinnings of functional decline, and the resulting lack of both prognostic tools to identify individuals at risk for poor outcomes and robustly effective interventions to promote functional recovery. This dissertation has an overarching purpose to improve the understanding, identification, and remediation of social functioning deficits in schizophrenia spectrum disorders by leveraging data-driven approaches. Three manuscripts are presented.

Manuscript 1 critically reviews twelve studies to characterize the state of the science of individual prognostic models for functional outcomes in schizophrenia spectrum disorders. Findings indicate that development of prognostic tools is in an early stage, with a wide range of accuracies, and no clear advantage of utilizing one data modality (i.e., neurobiological data, clinical data, or functional data) over another. Results highlight a need to evaluate and directly compare predictive models which utilize different predictor modalities to understand how to optimally balance accuracy and clinical usability.

Manuscript 2 presents a study aimed to develop individual prediction models for social functioning from integrated bio-behavioral data and identify which predictors are most important for social functioning using machine learning. With data from the Human Connectome Project Healthy Young Adult sample (age 22-35, N=1,101) and machine learning methods, four prognostic models were built from variable sets of brain morphology to behavior with increasing complexity: 1) brain-only model, 2) brain-cognition model, 3) cognition-behavioral model, and 4) combined brain-cognition-behavioral model. Results show that the combined brain-cognition-behavioral and cognition-behavioral models significantly predicted social functioning with nearly identical accuracy (R^2 =0.53, 95% CI [0.38, 0.62] for each model), whereas the brain-only and brain-cognition models performed significantly worse (R^2 = 0.06, 95% CI [-

0.07, 0.16] and R^2 = 0.11 95% CI [-0.05, 0.23], respectively). Negative affect, psychological wellbeing, extraversion, withdrawal, and cortical thickness of the rostral middle-frontal and superior-temporal brain regions were the most important predictors. These results suggest that prognostic models relying on behavioral data may promote clinical usability while maintaining predictive accuracy, and identify potentially important risk markers to be explored in future research.

Manuscript 3 shifts the focus to identifying *potential causes* of functional outcomes that could be high impact treatment targets in first episode schizophrenia. We used demographic, clinical, and psychosocial measures for 276 participants from the Recovery After an Initial Schizophrenia Episode Early Treatment Program (RAISE-ETP) trial and a causal discovery algorithm, Greedy Fast Causal Inference, to model causal relationships across baseline variables and six-month social and occupational functioning. Results were validated in an independent dataset. Our primary finding was a modeled causal pathway from baseline socio-affective capacity to motivation, and from motivation to both social and occupational functioning at six months. These findings indicate that socio-affective abilities and motivation are specific high-impact treatment needs that must be addressed to promote optimal social and occupational recovery and highlight the need to integrate evidenced based treatments for these areas into gold-standard care models to promote social recovery.

Conclusions: This dissertation leverages data-driven approaches to provide foundational knowledge for developing individual prognostic models for social functioning and to guide clinical research seeking to fill critical unmet treatment needs for the remediation of functional impairments. Research and clinical agendas must continue to advance the science toward ensuring that social recovery is the expectation of mental health treatment through early identification of individuals at risk for functional decline and innovative treatments which enhance their functioning. Further synthesis and implications of this work are explored in the concluding chapter.

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Preface

The humanity we all share is more important than the mental illness we may not. What those of us who suffer with mental illness want is what everybody wants: in the words of Sigmund Freud, "to work and to love."

Elyn Saks, JD, PhD

Chapter 1: Introduction

Schizophrenia and other psychotic disorders affect approximately one percent of the global population and have a typical onset in the late adolescent and early young adult years (Moreno-Küstner, Martín, & Pastor, 2018). In the United States, 100,000 young individuals are diagnosed with a first episode of schizophrenia each year (National Institute of Mental Health, n.d.; Simon et al., 2017). Despite the relatively low prevalence, psychotic disorders are a leading cause of disability worldwide, resulting in reduced quality of life and substantial personal and societal burden (Desai, Lawson, Barner, & Rascati, 2013; GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017; Windell, Norman, Lal, & Malla, 2015). This burden is overwhelmingly due to the devastating impairments in social functioning that are characteristic of psychotic disorders, including impacts on attainment of education, employment, and the ability to sustain interpersonal relationships required for meaningful engagement in society. For example, the national cost of schizophrenia was $155 billion in 2013, and nearly 75% of this cost was due to social consequences such as unemployment and caregivers' lost productivity.

Remediating social functioning deficits is an urgent clinical need. Restoring social functioning has been identified as a primary treatment goal for individuals with psychotic disorders (Windell et al., 2015) and for the mental health field as it moves towards a recovery model of care (Frost et al., 2017; Lieberman et al., 2008). Yet, current gold standard treatments are minimally effective at improving social functioning and little progress has been made in social recovery rates in recent decades (Bertelsen et al., 2008; Jääskeläinen et al., 2013; Secher et al., 2015; Swartz et al., 2007). Progress in

remediating social functioning will rely on building a more comprehensive understanding of the bio-behavioral determinants of social functioning impairments, improved identification of individuals at risk for poor functional outcomes, and well-defined treatment targets.

Bio-behavioral Determinants of Social Functioning

Social functioning in psychotic disorders is a complex concept impacted by a range of societal, contextual, and illness related factors (Galderisi et al., 2014). As such, a range of predictors of poor social functioning in psychotic disorders have been established. These have included: sociodemographic (e.g., female sex, parental socioeconomic status, education level) (Bennett & Rosenheck, 2021; Díaz et al., 2013; Hofer et al., 2005; Santesteban-Echarri et al., 2017; Schennach-Wolff et al., 2009), clinical (e.g., positive and negative symptoms of psychosis, substance use, and duration of untreated psychosis) (Milev, Ho, Arndt, & Andreasen, 2005; Nakagami, Hoe, & Brekke, 2010; Penttilä, Jaäskeläinen, Hirvonen, Isohanni, & Miettunen, 2014), neurocognitive (e.g., deficits in attention, executive functioning, processing speed, and verbal learning and memory) (Green, Kern, Braff, & Mintz, 2000; Halverson et al., 2019), social cognitive (e.g., impaired attributional bias, emotion processing, social perception, and theory of mind) (Fett et al., 2011; Halverson et al., 2019), and neurobiological factors (e.g., changes in fronto-temporal brain regions) (Wojtalik, Smith, Keshavan, & Eack, 2018). Models of functional outcome typically rely on a small subset of these domains, potentially missing complex interactions amongst variables and leaving a large amount of variance unaccounted for in quantitative models.

Neurocognition, social cognition, and negative symptoms (e.g., expressive deficits and avolition/apathy) have been a primary focus of efforts to understand functional decline in schizophrenia due to their strong associations with functional outcome (Bhagyavathi et al., 2015; Fervaha, Foussias, Agid, & Remington, 2015; Fett et al., 2011; Green et al., 2000). When modeled together, these domains have accounted for approximately 20% of the variance in functional outcome (Gard, Fisher, Garrett, Genevsky, & Vinogradov, 2009). In one of the most comprehensive structural equation models to date, Galderisi et al. (2014) included a range of clinical symptoms, personal resources, and context-related factors (e.g., socio-demographics, social network measures, internalized stigma) – in addition to neurocognition and social cognition – and found that their model accounted for nearly 54% of the variance in functional outcomes. Research also supports a link between brain structure and function and social functioning in psychotic disorders. A recent systematic review and meta-analysis found consistent relationships between functional outcomes and fronto-temporal and limbic brain regions, including the dorsolateral prefrontal cortex, anterior and posterior cingulate, superior temporal sulcus, para-hippocampal gyrus and cerebellum (Wojtalik et al., 2018). Although many predictors of functional outcomes have been identified, a major limitation of previous research is the lack of integration of data from neurobiology to behavior in order to comprehensively understand complex relationships between predictors and the relative importance of predictors across domains.

Identification of Individuals at Risk for Poor Social Functioning

Early identification of individuals at risk for poor functional outcomes so that they may receive intensive and targeted interventions is paramount to recovery efforts. Recent

evidence suggests that the greatest prognosis for social recovery occurs if intensive treatment efforts are started in the first six months of care (Humensky, Essock, & Dixon, 2017; Phahladira et al., 2020). Substantial heterogeneity in functional outcomes is observed in psychotic disorders, with recovery rates ranging from 13 – 38% (Jääskeläinen et al., 2013; Lally et al., 2017), and impedes treatment efforts. Currently, no tools exist in standard clinical practice for identification of individuals at risk for poor functional outcomes. Development of such individual prognostic tools is in an early research stage, and it is yet unknown how predictors of functional outcomes can best be combined to optimize accuracy and clinical usefulness.

Treatment of Impaired Social Functioning

The current standard of care for schizophrenia and other psychotic disorders does not sufficiently impact functional outcomes, highlighting the need to develop more effective interventions guided by well-defined treatment targets. Coordinated Specialty Care (CSC) early intervention services are now the gold-standard treatment for individuals in the early stages of psychotic disorders. Despite promising initial evidence that CSC care improves functional outcomes in the short-term (Kane et al., 2016), such treatment models have had little impact on sustained functional recovery (Albert et al., 2017; Bertelsen et al., 2008; Norman et al., 2018; Secher et al., 2015). Similarly, antipsychotic medications, while effective for treating positive symptoms of psychosis, do not have substantial impacts on functional outcome (Swartz et al., 2007; Wunderink, Nieboer, Wiersma, Sytema, & Nienhuis, 2013).

Other interventions with evidence for improving functional outcomes – such as cognitive training and remediation, social skills training, and vocational rehabilitation –

are rarely implemented in routine clinical care and have had inconsistent and overall modest effects on functional outcomes (Miley, Hadidi, Kaas, & Yu, 2019; Modini et al., 2016; Revell, Neill, Harte, Khan, & Drake, 2015; Roberts et al., 2014; Turner et al., 2018; Vita et al., 2021; Wykes, Huddy, Cellard, McGurk, & Czobor, 2011). This suggests that interventions may be missing critical targets implicated in functional impairments, in part due to a poor understanding of the causes of impaired functioning. Identifying the treatment targets that, if modified, will result in the most robust improvements in functioning is urgently needed to foster intervention development and implementation into clinical care.

Leveraging Data-Driven Approaches

The use of data-driven approaches such as machine learning has led to advances in a number of biomedical sciences, from improved prognostication of cancer survival to development of novel treatment for neurological illnesses (Obermeyer & Emanuel, 2016). Similarly, machine learning may hold promise for achieving progress in improving social functioning outcomes in schizophrenia and other psychiatric and non-clinical populations (Dwyer, Falkai, & Koutsouleris, 2018). Such methods offer the distinct advantage of integrating large numbers of heterogeneous predictors across data modalities (e.g., clinical data, neuroimaging methods, lab measures, genetic investigations), avoiding the need to select a small number of predictors *a priori* and potentially uncovering complex and non-linear relationships among the data (Hahn, Nierenberg, & Whitfield-Gabrieli, 2016; Obermeyer & Emanuel, 2016). This can be especially beneficial for data domains that are inherently large, such as neuroimaging modalities (Hahn et al., 2016). Given the numerous predictors of social functioning

reviewed above, machine learning approaches may be uniquely situated to parse the large, multi-modal predictor space to identify a comprehensive set of predictors that could be candidate treatment targets.

Further, it remains unknown how predictors identified at the group level – which are characterized by substantial variance around the mean and only provide information about the "average" patient - translate to individual patient outcomes (Leighton et al., 2019; Obermeyer & Emanuel, 2016). Another advantage of machine learning methods is their ability to make predictions at the individual level, which is required for clinically useful prognostic models. Such models could eventually be employed in clinical practice to identify individuals with high risk for social functioning deficits and to direct treatment allocation.

Although useful for identifying candidate treatment targets and informing individual prognosis, predictive machine learning methods are nevertheless *predictive* and do not imply *causation*. Identifying the highest impact treatment targets for social functioning relies on understanding the potential causes of functional decline. Although controlled trials remain the gold standard for establishing causation (Shadish, Cook, & Campbell, 2002), they require significant time and resources. Advances in computational modeling now allow for probing causal inference from non-experimental data with novel causal discovery algorithms (Spirtes, Glymour, & Scheines, 2000). Like other machine learning methods, causal discovery algorithms have the additional advantage of modeling a large number of variables without effecting model performance (Chickering, 2002). Thus, causal discovery may be leveraged to identify the most plausible causes of

functional outcomes that can be further evaluated as treatment targets in controlled intervention studies.

Statement of Purpose

With a focus on schizophrenia spectrum disorders, this dissertation has an overarching purpose to improve the understanding, identification, and remediation of social functioning deficits by leveraging data-driven approaches. Specifically, this research seeks to: build a more comprehensive understanding of the bio-behavioral underpinnings and risk-markers of social functioning deficits in schizophrenia spectrum disorders and non-clinical samples prior to the onset of overt psychopathology, improve identification of those at risk for poor functional outcomes with individual prediction models, and identify critical intervention targets for remediation of functional deficits. The purpose of this dissertation was addressed with three aims.

Dissertation Aims

Aim 1: Critically review the literature of individual prognostic models of functional outcomes in schizophrenia spectrum disorders to assess model performance and identify important predictors.

Aim 2: Evaluate models for individual prediction of social functioning outcomes using comprehensive bio-behavioral data in healthy young adults, and identify which predictors are most salient to establish a baseline for understanding further changes that may be identified in psychiatric illnesses.

Aim 3: Identify high impact treatment targets for social and occupational functioning deficits in first episode schizophrenia using causal discovery modeling.

Significance

This dissertation will expand our understanding of social functioning deficits across the spectrum of health to schizophrenia and other psychotic disorders. The manuscripts included in this dissertation represent the first known studies to 1) utilize machine learning applications for the prediction of social functioning outcomes from integrated bio-behavioral data in healthy young adults, providing important insights into the specific neurobiological, cognitive, psychological, and other behavioral underpinnings of social functioning that may be relevant in psychiatric illness; and 2) use a data-driven causal discovery analysis to model direct causal pathways between malleable treatment targets and social and occupational functioning outcomes in an early schizophrenia sample. Results from this dissertation are expected to be significant because they may inform efforts to develop clinically useful tools to identify individuals at risk for poor functional outcomes and lead to development and implementation of more targeted interventions for functional recovery.

Organization of the Dissertation

This dissertation consists of five chapters, including the present introduction (Chapter 1). Chapter 2 presents a critical review manuscript of literature detailing individual prognostic models of social and occupational functioning outcomes in schizophrenia spectrum disorders. This review is focused on the state of the science including assessment of model accuracies, important predictors in the functional outcome prognostic models, and methodological barriers for clinical translation. Chapter 3 presents a manuscript titled, “Individual prediction of social functioning outcomes in healthy young adults: a machine learning study integrating neuroanatomical, cognitive,

and behavioral data," which is currently under review. This manuscript reports results of a machine learning study of individual prediction models for social functioning outcomes using comprehensive bio-behavioral data in healthy young adults. Performance of models relying on different predictor sets are discussed and salient predictors for the models are identified. Chapter 4 is a published manuscript titled "Causal pathways to social and occupational functioning in the first episode of schizophrenia: uncovering unmet treatment needs" (Miley et. al, 2021). This manuscript details results of a study which employs causal discovery modeling to identify high impact treatment targets for social and occupational functioning in first episode schizophrenia. Finally, Chapter 5 summarizes major findings of each manuscript, discusses limitations, and highlights key implications for research and practice.

References for Chapter 1 and 5 are provided in the dissertation bibliography. References for the manuscript chapters 2, 3, and 4 are provided following each respective chapter in addition to the dissertation bibliography.

Chapter 2 (Manuscript 1)

Summary

Background: Remediating the social and occupational functioning deficits characteristic of schizophrenia spectrum disorders is an urgent clinical need. However, progress has been hindered by the significant heterogeneity in patients' functional outcomes and a poor understanding of the bio-behavioral underpinnings of functional decline. Machine learning methods for prognostication of functional outcomes may be useful to improve identification of individuals at risk for functional decline and to characterize a comprehensive set of contributors to functional impairments. *Aims:* To examine the state of the science of individual prognostic models for social and occupational functioning outcomes in schizophrenia spectrum disorders, with a focus on model accuracy, commonly identified influential predictors, and methodological barriers for clinical translation. *Methods:* A combined search of Ovid-Medline and PsychInfo was conducted to identify studies employing machine learning to predict longitudinal individual functional outcomes in clinical high risk, first episode psychosis, and chronic schizophrenia samples. *Results:* Twelve studies met inclusion criteria. Model accuracies for predicting individual functional outcomes ranged from 43-86.7%. Themes among the models' most influential predictors included structural brain measures in the fronto-temporal regions, psychosis and other psychiatric symptoms, and baseline level of functioning. Common methodological limitations included small sample sizes, choice of cross-validation methods, lack of external validation, and use of nonspecific measures of functional outcomes. *Conclusions:* Heterogeneity in methods and results characterizes the field of individual prognostic models for functional outcomes in schizophrenia spectrum disorders, limiting interpretation of findings. Further research with adherence

to methodological guidelines for machine learning prognostic studies is needed to promote clinical translation.

Prognostic Models for Social and Occupational Functioning Outcomes in Schizophrenia Spectrum Disorders: A Critical Review of Machine Learning Studies

Severe disability in social functioning is a core feature of schizophrenia spectrum disorders (SSDs) (Bromley & Brekke, 2010; Wiersma et al., 2000), which reduces individuals' quality of life (Windell, Norman, Lal, & Malla, 2015), increases risk for adverse health outcomes (Uchino, 2006), and results in significant societal burden (Cloutier et al., 2016). Functional deficits present prior to disease onset in the clinical high risk (CHR) state and persist through chronic schizophrenia (Addington, Penn, Woods, Addington, & Perkins, 2008). Thus, restoring social functioning is a critical treatment goal, yet gold-standard treatments have proved minimally effective at achieving sustained functional improvements (Bertelsen et al., 2008; Norman et al., 2018; Secher et al., 2015; Swartz et al., 2007). Alarmingly, at an epidemiological level, no major improvements in social recovery rates in SSDs have been observed since early studies published in the 1890s (Jääskeläinen et al., 2013), highlighting the urgent need for clinically translatable research in this area.

Significant heterogeneity in functional outcomes is observed at all stages of the illness, complicating treatment efforts by impeding identification of those at risk and allocation of resource limited interventions (Jääskeläinen et al., 2013; Vita & Barlati, 2018). Further, the bio-behavioral underpinnings of social functioning impairments have not been fully identified which hinders prevention and treatment efforts (Koutsouleris et al., 2016). Previous research has established a range of predictors of social functioning deficits at the group level, including socio-demographic (Hofer et al., 2005), neurobiological (Wojtalik, Smith, Keshavan, & Eack, 2018), clinical (i.e., positive and

negative symptoms of psychosis and duration of untreated psychosis) (Milev, Ho, Arndt, & Andreasen, 2005; Nakagami, Hoe, & Brekke, 2010; Penttilä, Jääskeläinen, Hirvonen, Isohanni, & Miettunen, 2014), and cognitive factors (Fett et al., 2011; Santesteban-Echarri et al., 2017). Most research has considered these predictor modalities in isolation, which risks missing complex interactions that may be important for social functioning outcomes. Further, it is unclear if *group-level* factors are useful in identifying risk for poor functional outcomes at the *individual level* (Dwyer, Falkai, & Koutsouleris, 2018). Due to the extraordinary heterogeneity observed in SSDs generally and functioning outcomes more specifically, group statistics may have substantial variation around the mean, preventing translation to individual patients (Dwyer et al., 2018; Hahn, Nierenberg, & Whitfield-Gabrieli, 2016).

Machine learning methods may hold promise for overcoming the limitations of previous research due to their unique ability to make predictions for individual patients and integrate large amounts of multidimensional data. Relevant data dimensions for psychiatric research span neuroimaging modalities, genome wide associations, lab measures, and clinical observations – among others - and associations between these variables are not always known (Orphanidou & Wong, 2017). Machine learning methods have been leveraged to identify biological disease mechanisms in SSDs due to their ability to integrate heterogenous data to uncover complex relationships, as is required for many neuroimaging and genetic investigations (Hahn et al., 2016). Machine learning has also been employed in research seeking to improve clinical diagnosis and prognosis of illness outcomes, such as symptom burden, treatment response, and more recently, functional status (Dwyer et al., 2018; Shatte, Hutchinson, & Teague, 2019). Therefore,

machine learning could be leveraged for two critical needs in the remediation of functional deficits: 1) improved identification of individuals at risk for poor outcomes so that they can receive intensive intervention, and 2) a refined understanding of the bio-behavioral underpinnings of functional deficits in order to identify risk markers and potential treatment targets.

The purpose of this critical review is to examine the state of the science of individual prognostic models for social and occupational functioning outcomes in SSD populations. A recent meta-analysis of machine learning models primarily predicting diagnostic group and full transition to psychosis in CHR samples found significant methodological heterogeneity which limited interpretation of results (Sanfelici, Dwyer, Antonucci, & Koutsouleris, 2020). Here, we use a narrative synthesis of the literature to characterize prognostic model accuracy for functional outcomes across all stages of SSDs, evaluate which predictors are commonly identified as important for functional prognosis, and identify methodological barriers for clinical translation.

Methods

Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist (Moher, Liberati, Tetzlaff, & Altman, 2009) was used as a guideline for the literature search and study selection. The search protocol included establishing eligibility criteria, database search, abstract screening, full text review, and review of reference lists. A two-stage search was conducted via the Ovid interface utilizing the Medline and PsychInfo databases. We searched for the concept of psychotic spectrum disorders with the subject headings "schizophrenia spectrum and other psychotic

disorders" OR multi-placement keywords (psychosis OR psychotic OR schizophreni*). For the concept of machine learning methods, we searched for the focused subject heading of "Artificial Intelligence" OR titles with keywords (machine learning OR support vector OR multivariate pattern* OR random forest OR deep learning OR naive bayes OR LASSO OR elastic net OR principal component* analysis). We then combined the concept searches. We limited the search to journal articles (i.e., conference abstracts were excluded) and articles written in the English language. As there are no previous reviews on this topic, no date limits were used.

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria: included a sample of patients with clinical high risk for psychosis, first episode psychosis, or chronic schizophrenia, and employed multivariate machine learning methods to predict individual longitudinal social, occupational, or global functioning outcomes. Studies were excluded if they predicted baseline outcomes only, identified predictors only (i.e., model performance results were not provided), or were conference abstracts only.

Data Extraction

A data extraction form was created to include characteristics of each study, including study identification (title, authors, publication year), sample characteristics (diagnostic group, sample size, inclusion of independent validation sample, age, ethnicity, and setting), study characteristics (statistical design/machine learning algorithm used, predictor measures, and outcome measures), and main findings.

Results

Study Selection

The initial database search returned 325 reports from Medline and 141 reports from PsychInfo. After removing duplicates, 377 studies were identified. Two additional reports were found in reference review. Initial abstract review excluded 355 reports for failing to meet inclusion and exclusion criteria. Of the remaining 25 studies, four were excluded due to not reporting results of an individual prediction model, nine were excluded based on the outcome measure used, and one was excluded due to predicting baseline outcomes only. Twelve studies met inclusion criteria and were included in this review (Figure 2.1).

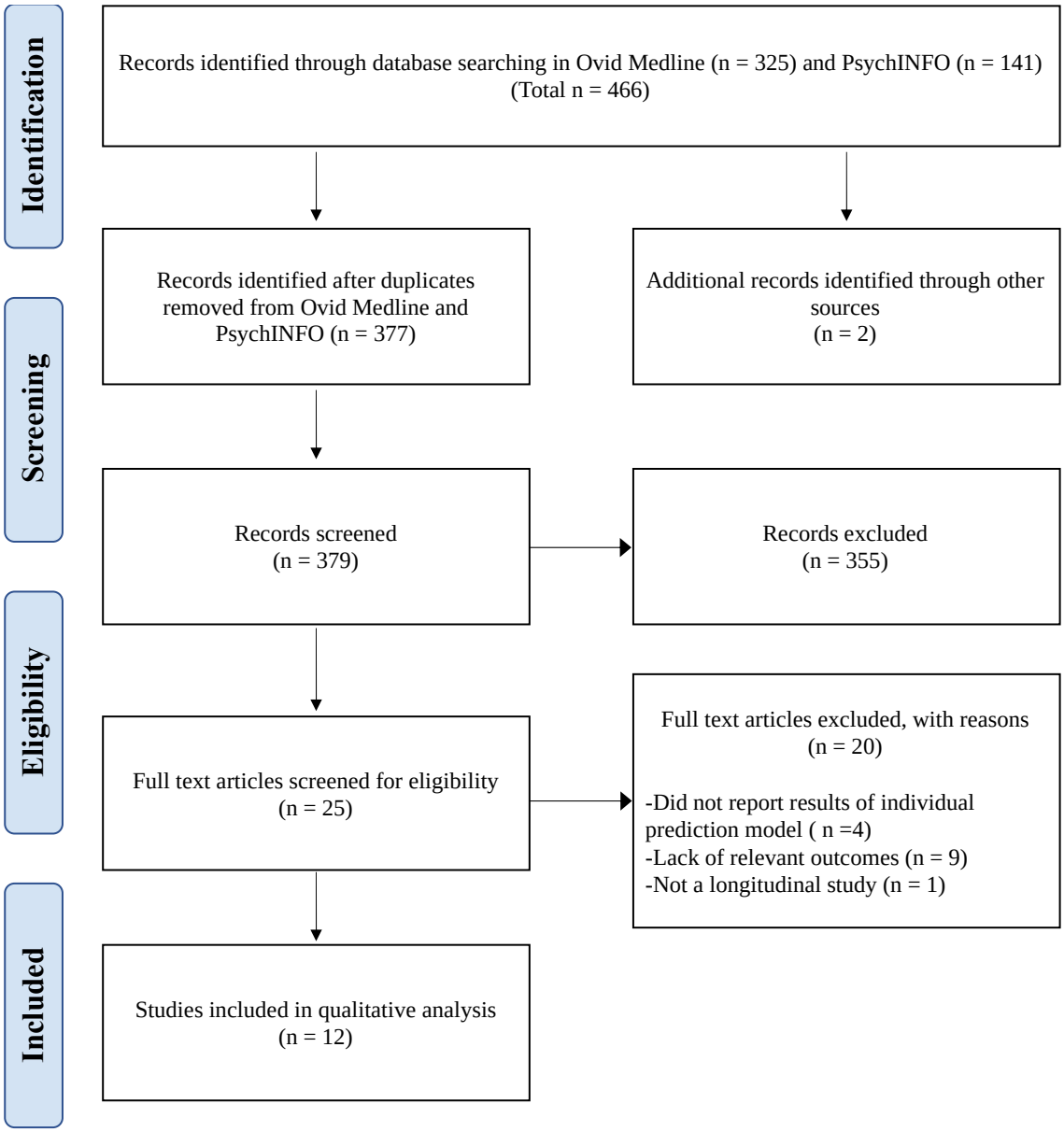

Figure 2.1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Flow Chart

Sample Characteristics

Sample characteristics for the 12 studies are summarized in Table 2.1. The diagnostic group was clinical high risk (CHR) for psychosis in six studies (Amminger et al., 2015; de Wit et al., 2017; Haining et al., 2021; Kambeitz-Ilankovic et al., 2016; Koutsouleris et al., 2018; Mechelli et al., 2017), first episode psychosis (FEP) in three studies (Koutsouleris et al., 2016; Leighton, Krishnadas, et al., 2019; Leighton, Upthegrove, et al., 2019), and chronic schizophrenia spectrum disorder (SZ) in three studies (de Nijs et al., 2021; Kambeitz-Ilankovic et al., 2021; Li et al., 2021). Sample sizes ranged from 27 to 1,767 participants. Three studies (Kambeitz-Ilankovic et al., 2021; Leighton, Krishnadas, et al., 2019; Leighton, Upthegrove, et al., 2019) included an external validation sample, defined as a sample that was collected separately from the original sample that the predictive models were developed in. A wide mean age range of 15.7 to 48.2 years was observed across studies, reflecting the different diagnostic groups across the psychosis spectrum included in this review. Across studies, males accounted for an average of 53.25% of participants. Ethnicity was reported in only three studies and ranged from 85-87% white. Nine studies included samples from multiple sites and three were single site studies. Most studies (n = 9) were conducted across the European Union and United Kingdom, with one multi-site European study also including a sample from Israel. Additionally, one study was conducted in the United States, one in China, and one in Australia. Finally, the time period for the 12 reviewed studies was more recent, ranging from 2015-2021.

Table 2.1

Sample Characteristics

Study	Diagnosis	Sample Size	Mean Age	% Male	Ethnicity[a]	Site Type	Country
Amminger et al. (2015)	CHR	80[b]	16.5	32.5	NR	Single site	Austria
de Nijs et al. (2021)	SZ	523	27.6	76.9	85.9% white	Multisite	The Netherlands & Belgium
de Wit et al. (2017)	CHR	41	15.7	65.8	NR	Single site	The Netherlands
Haining et. al (2021)	CHR	146	21.5	28.8	NR	Multisite	Glasgow and Edinburgh United Kingdom
Kambeitz-Illankovic et al. (2016)	CHR	27	23.4	70.0	NR	Single site	Germany
Kambeitz-Illankovic et al. (2021)	SZ	67[c]	47.0	78.0	NR	Multisite	United States
Koutsouleris et al. (2016)	FEP	442	26.0	59.0	NR	Multisite	14 European countries and Israel
Koutsouleris et al. (2018)	CHR	116	24.0	50.0	NR	Multisite	5 European countries
Leighton, Krishnadas et al. (2019)	FEP	162[c]	24.9	67.0	87.0% white	Multisite	United Kingdom
Leighton, Upthegrove et al. (2019)	FEP	1767[c]	23.9	65.0	85.0% white 15.0% other	Multisite	Denmark and United Kingdom
Li et al. (2021)	SZ	550	48.2	58.5	NR	Multisite	China
Mechelli et al. (2017)	CHR	96	19.7	46.0	NR	Single site	Australia

Note. CHR = clinical high risk for psychosis, FEP = first episode psychosis; NR = Not Reported; SZ = chronic schizophrenia

[a]Ethnicity data as reported, i.e., further breakdown by other ethnic groups or specification of Hispanic/Non-Hispanic not provided unless indicated

[b]Treatment groups of randomized controlled trial analyzed separately (n=40 per group)

[c]Total N including external validation sample. When external validation samples were used, sample statistics were averaged across sample

Predictor Modality

The predictor modalities used to build machine learning models varied across the 12 studies and included domains of biological (n = 6), demographics (n = 5), clinical (n = 8), cognitive (n = 2) and baseline functioning (n = 7) (Table 2.2). Three studies (Amminger et al., 2015; Kambeitz-Ilankovic et al., 2016, 2021) relied solely on biological predictors and the remaining studies used a combination of predictors across modalities. Biological predictors were most commonly from structural brain MRI (n = 4). In the remaining two studies using biological predictors, one included serum omenga-3 poly-unsaturated fatty acid levels (Amminger et al., 2015) and one included electrocardiogram results and serum prolactin levels (Li et al., 2021). Numerous clinical predictors were utilized across studies. Common clinical predictors included prodromal or acute positive and negative symptoms of psychosis, depression symptoms, substance use, and duration of untreated psychosis. Of the seven studies that included measures of baseline functioning as predictors, five of these included the same measure that was used for the longitudinal outcome measure.

Table 2.2

Study Characteristics and Prognostic Model Performance Results

Study	Predictor Data Modality	Outcome Variable	Algorithm (Validation Method)	Performance[a]	
Amminger et al. (2015)	Biological: serum Omega-3 polyunsaturated fatty acid levels	GAF (≥ 15-point increase) from baseline to 12 weeks	Gaussian process classification (LOO CV)	Treatment group: -Sens 86.7% -Spec 86.7% -BAC 86.7%; ($p < 0.001$)	Control group: -Sens 83.3% -Spec 75% -BAC 79.2% ($p < 0.001$)
de Nijs et al. (2021)	Demographics Clinical: age of onset, antipsychotic use, Community Assessment of Psychotic Experiences course of illness, depression/suicide attempts, diagnosis, DUP, PANSS, substance use, WHO QoL-short Functional: Camberwell Assessment of Need, Global Assessment of Functioning Scale	GAF (cutoff ≥ 65) at 3 and 6-year follow up	Support vector machine (k-fold nested CV and LOSO CV)	k-fold nested CV: 3-year: -Sens 66.3-74.9% -Spec 59.7-58.4% -BAC 63.5-67.6% LOSO CV: 3-year: -Sens 65.8-66.1% -Spec 60.8-63.8% -BAC 63.5-64.8%	 6-year: -Sens 81.8-84.3% -Spec 43.3-47.7% -BAC 67.3-67.6% 6-year: -Sens 65.9-71.8% -Spec 56.1-56.5% -BAC 61.2-64.0%
de Wit et al. (2017)	Biological: structural MRI including average volume, cortical thickness, gyrification, and surface area Clinical: SIPS Disorganization subscale Multiple models with separate variable combinations	Regression models: mGAF score at 6-year follow up Classification models: mGAF (cutoff ≥ 65)	Support Vector Regression, Support Vector Machine (LOO)	Regression: -r = 0.327 ($p > 0.05$) – 0.424 ($p = 0.008$)	Classification: -Sens 47-71% -Spec 42-94% -BAC 44-82% most models ($p < 0.05$)
Haining et al. (2021)	Clinical: Adverse Childhood Experiences total score, Comprehensive Assessment for the At-Risk Mental State total score and mean distress,	GAF (cutoff ≥ 65) at last follow up (6 or 12 months)	Multiple: Gaussian Naïve Bayes, Linear Discriminant Analysis, Support Vector Machine, Random	k-fold CV, averaged across models Clinical-cognitive models: -Sens 68% -Spec 56%	 Functioning only models: -Sens 84%; -Spec 74%

Study	Predictor Data Modality	Outcome Variable	Algorithm (Validation Method)	Performance[a]	
	Schizophrenia Proneness Instrument severity and mean distress Cognitive: BACS attention, executive functioning, motor speed, verbal memory, working memory, Penn Emotional Recognition accuracy Functional: GAF, Global Functioning: Social and Role, Premorbid Adjustment Scale		Forest Classification, Logistic Regression (k-fold CV and LOSO)	-BAC 63% ($p < 0.05$) LOSO CV: Clinical-cognitive models: -Sens 70% -Spec 55% -BAC 63% ($p < 0.05$)	-BAC 68% ($p < 0.05$) Functioning only models: NR
Kambeitz-Illankovic et al. (2016)	Biological: structural MRI including cortical surface area, cortical thickness, and mean curvature	GAF (cutoff ≥ 70), variable follow up time with average of 4 years	Linear L1 regularized Multivariate logistic regression (LOO)	Cortical surface area: -Sens 78.6% -Spec 84.6% -BAC 81.6% Mean curvature: -Sens 50% -Spec 69.2% -BAC 59.6%	Cortical thickness: -Sens 78.6% -Spec 7.7% -BAC 43.2%
Kambeitz-Illankovic et al. (2021)	Biological: structural MRI gray matter volumes	GAF (cutoff ≥ 45) after 40 hours of cognitive training	Support vector machine (k-fold nested CV and external)	k-fold CV -Sens 72.2% -Spec 66.7% -BAC 69.4% ($p < 0.001$)	External validation -Sens 90.9% -Spec 33.3% -BAC 62.5%
Koutsouleris et al. (2016)	Demographics Clinical: CDSS, diagnosis, extrapyramidal symptom score, medication status, MINI, PANSS Cognitive: attention, working memory, verbal learning and memory	GAF (cutoff ≥ 65) at 4 and 52 week follow up	Support vector machine (k-fold nested CV and LOSO)	k-fold CV 4-week -Sens 73.7% -Spec 76.4% -BAC 75% LOSO CV 4-week -Sens 65.6%	 52-week -Sens 88.7% -Spec 80.9% -BAC 73.8% 52-week -Sens 62.8%

Study	Predictor Data Modality	Outcome Variable	Algorithm (Validation Method)	Performance[a]	
	Functional: Camberwell Assessment of Needs items, CGI, GAF			-Spec 73.6% -BAC 69.6%	-Spec 72.7% -BAC 67.7%
Koutsouleris et al. (2018)	Biological: structural MRI gray matter volume Functional: 8 baseline Global Functioning: Social and Role scores including current, highest lifetime, and highest and lowest in past year	Global Functioning: Social and Role scale (cutoff >7) at last follow-up between 3 and 12 months	Support Vector Machine (LOSO)	Social functioning Functional model: -Sens 69.7%; -Spec 84.0% -BAC 76.9% Combined model: -Sens 83.3% -Spec 82.0% -BAC 82.7% Occupational functioning Functional model: -Sens 60.9% -Spec 74.5% -BAC 67.7% Combined model: -Sens: 59.4% -Spec 70.2% -BAC 64.8% all p-values < 0.001	MRI model: -Sens 80.3% -Spec 72.0% -BAC 76.2% MRI model: -Sens 66.7% -Spec: 46.8% -BAC 56.7%
Leighton, Krishnadas et al. (2019)	Demographics Clinical: depression history, hospital admission history, PANSS	Employment, training or education involvement at 1 year follow up	Logistic regression by elastic net regularization (k-fold-CV and external)	k-fold CV NR	External validation -Sens 81.5% -Spec 87.5% -BAC 85.1% (p < 0.001)
Leighton, Upthegrove et al. (2019)	Demographics Clinical: Age of onset, CDSS, DUP, clinical course, comorbid symptoms, family psychiatric history, insight, PANSS, Premorbid Adjustment Scale, substance use, YMRS total	Social recovery: GAF (cutoff ≥ 65) at 1 year follow-up Occupational recovery: employment or	Logistic regression by elastic net regularization, external validation models used generalized linear models (LOSO and external)	LOSO CV Social recovery: -Sens 72.2% -Spec 66.0% -BAC 68.7% (p < 0.001)	Vocational recovery: -Sens 72.2% -Spec 66.6% -BAC 69.3% (p < 0.001)

Study	Predictor Data Modality	Outcome Variable	Algorithm (Validation Method)	Performance[a]	
		education at 1 year follow-up		External validation	
	Functional: GAF, quality of life items from European QoL 5-dimension index			Social recovery: -Sens 78.1% -Spec 39.6% -BAC 45.6% (p = 0.04)	Vocational recovery: -Sens 58.4-89.8% -Spec 72.6-80.7% -BAC 68.0-83.8% (p < 0.001)
Li et al. (2021)	Demographics Biological: EKG, serum prolactin Clinical: antipsychotic tolerability, antipsychotic use, CDSS, CGI, comorbidities, concomitant medications, Drug Attitude Inventory, PANSS, treatment compliance, Subjective Wellbeing Under Neuroleptics scale Functional: Personal and Social Performance scale	Personal and Social Performance scale ≥ 10-point increase from baseline to 3 month follow up	Random forest (k-fold CV)	-Sens 81.8% -Spec 78.7% -BAC 79.5%	
Mechelli et al. (2017)	Clinical: Brief Psychiatric Rating Scale psychotic subscale score, Comprehensive Assessment of At- Risk Mental State subscale scores, Scale for Assessment of Negative Symptoms subscale scores Functional: GAF	Regression: Social and Occupational Functioning Assessment Scale score at average follow-up of 7.5 years Classification: (cutoff > 50)	Support vector regression, Support vector machine (k-fold CV)	Regression: -r = 0.275 (p = 0.009)	Classification: -Sens 62.5% -Spec 62.5% -BAC 62.5% (p = 0.008)

Note. BAC = Balanced Accuracy; BACS = Brief Assessment of Cognition in Schizophrenia; CDSS = Calgary Depression Scale for Schizophrenia; GGI = Clinical Global Impressions scale; CV = cross validation; DUP = duration of untreated psychosis; GAF = Global Assessment of Functioning scale; LOO = leave-out-one cross validation; LOSO = leave-one-site-out cross validation; mGAF = modified Global Assessment of Functioning scale; MINI = Mini-International Neuropsychiatric Interview; PANSS = Positive and Negative Symptom Scale; QoL = Quality of Life; Sens = Sensitivity; SIPS = Structured Interview of Psychosis-risk Syndromes; Spec = Specificity

[a]Ranges in statistics represent performance of models from different predictor sets

Outcome Variable

The most common outcome variable was the Global Assessment of Functioning (GAF) (Hall, 1995), used in eight studies (Table 2.2). Cut-off scores for good versus poor functioning varied from 45-70, and one study used a fifteen-point improvement on the GAF as the outcome. The GAF is a single item, 100-point rating scale which measures a broad range of day-to-day functioning in social and occupational domains, while also considering symptom severity. Other functional outcome measures included the Global Functioning: Role and Social scale (Cornblatt et al., 2007) (n = 1, assesses age appropriate domains of social and role functioning separately on 10-point scales), the Personal and Social Performance Scale (Morosini, Magliano, Brambilla, Ugolini, & Pioli, 2000) (n = 1, assesses socially useful activities, social relationships, self-care, and disturbing or aggressive behavior on a single item 100-point scale), the Social and Occupational Functioning Assessment Scale (Goldman, Skodol, & Lave, 1992) (n = 2, assesses global social and occupational functioning on a single item 100-point scale), and a binary assessment of current employment, training, or education involvement (n = 2). All studies operationalized the outcome as a binary variable of good or poor functioning, with two studies additionally using a continuous score for regression models (de Wit et al., 2017; Mechelli et al., 2017). Outcome assessments occurred over a wide range of timepoints, from four weeks to seven and a half years.

Analysis

The most frequently utilized machine learning algorithm was support vector machines, employed by seven studies, followed by logistic regression, employed by four studies (Table 2.2). Other machine learning algorithms included Random Forest

classification (n = 2) and Gaussian Process Classification (n = 1). Haining et al. (2021) utilized multiple algorithms and averaged results across models.

Cross-validation and external validation are important analysis steps in the development of individual prediction models (see Box 2.1 for examples of validation methods). The three studies with the smallest sample sizes (N = 27-41) used a leave-out-one cross validation scheme. Seven studies used k-fold cross validation, and five studies used a leave-one-site-out cross validation approach. Of these, three studies (de Nijs et al., 2021; Haining et al., 2021; Koutsouleris et al., 2016) used both k-fold cross validation and leave-one-site-out approaches. Three studies performed external validation of their predictive model (Kambeitz-Ilankovic et al., 2021; Leighton, Krishnadas, et al., 2019; Leighton, Upthegrove, et al., 2019).

Box 2.1

Machine Learning Validation Methods, Key Terms, and Brief Descriptions

Cross-validation (CV)	Internal validation statistical resampling method to retrain and assess a model on different iterations of the dataset with the goal of assessing and improving model accuracy and generalizability. Multiple cross-validation approaches exist including leave-one-out, k-fold, and leave-one-site-out approaches.
Training and test sets	For internal validation procedures, the full dataset is randomly split into a test and training set. The training set is used to train the model and the test set is used to assess performance of the model on previously unseen data.
K-fold CV	Cross-validation procedure in which the dataset is randomly split into k-folds. K-1 folds are then used for model training and the remaining fold is used for testing to obtain performance metrics. This procedure is repeated k times with a different fold held out for testing each time, and performance metrics are averaged across folds.
Leave-one-out CV	A subset of K-fold cross validation in which the number of folds is equal to the number of samples in the dataset. Each sample is held out once as a test set of 1, and the remaining dataset (n - 1) is used for the training set.
Leave-one-site-out CV	Cross-validation procedure used in multisite studies. The model is trained on combined data from N-1 sites and tested on the dataset from the held-out site to obtain performance metrics. Model training may include k-fold cross validation. This is repeated N times until all sites have been held out once and model performance metrics are averaged over the held-out sites.
External validation	Use of an independent dataset not used in model development for validation of a predictive model. External validation is the gold standard to assess accuracy and generalizability of a model.

Predictive Modeling Performance

Balanced accuracies of predictive models across studies ranged 43.2% to 86.7% (Table 2.2). Two studies employed regression models to predict functioning on a continuous scale, with Pearson's correlation comparing the observed versus predicted outcome score of 0.275 (Mechelli et al., 2017) and a range of 0.327 – 0.424 (de Wit et al., 2017). Trends in performance by study characteristics are detailed below.

Most studies reported model sensitivity and specificity results that were balanced (i.e., sensitivity was not drastically higher or lower than specificity). Some studies reported models with high sensitivity and low specificity (de Nijs et al., 2021; Kambeitz-Ilankovic et al., 2016, 2021; Koutsouleris et al., 2018; Leighton, Upthegrove, et al., 2019). There were no apparent characteristics across these studies that might explain this pattern. No studies reported high specificity relative to a low sensitivity.

Sample and analysis methods. Three studies reporting balanced accurizes above 80% had the smallest sample sizes (range of N's = 27 - 41) of the reviewed studies (Amminger et al., 2015; de Wit et al., 2017; Kambeitz-Ilankovic et al., 2016). Small sample sizes, especially in combination with a large number of predictor variables, can lead to overfitting (Moons et al., 2019). Additionally, small N-studies often rely on leave-one-out cross validation, as was the case in this review, which can also increase risk of overfitting (Moons et al., 2019). However, studies with larger sample sizes and more robust cross-validation methods also reported models with balanced accuracies above 80%, including Leighton, Upthegrove et al. (2019) (N = 1767) and Li et al. (2021) (N = 550). Most studies in this review used small sample sizes relative to the number of

predictor variables included in the models (Moons et al., 2019). No themes emerged in respect to the diagnostic category of the sample and predictive accuracies.

Predictor modality. Of the studies that included predictive models built using solely biological variables, one used serum levels of omega-3 polyunsaturated fatty acids (Amminger et al., 2015) and four used structural neuroimaging (de Wit et al., 2017; Kambeitz-Ilankovic et al., 2016, 2021; Koutsouleris et al., 2018). Across studies, there was a wide range of performance for neuroimaging models, ranging from balanced accuracies of 43.2 to 81.6%. Within these studies, there was also a range of performances based on the specific neuroimaging modality. For example, de Wit et. al (2017) reported accuracies of 43% and 49% of their models utilizing cortical surface area and cortical thickness measures, respectively, and 67 - 73% with models using gyrification, subcortical volume, and gray matter volume measures. Kambeitz-Illankovic et al. (2016) reported accuracies of 43.2% for cortical thickness models, 59.6% for gyrification models, and 81.6% for cortical surface area models.

Studies examining only clinical predictor modalities tended to have less variability in predictive performance, with most studies in the range of 61 - 75% accuracy. Combining clinical and functional modalities did not appear to increase model performances overall. Two studies included models using only baseline functioning variables. Haining et. al (2021) predicted global functioning with an accuracy of 68%, and Koutsouleris et. al (2018) predicted occupational and social functioning with accuracies of 68 and 77%, respectively. Two studies included multiple models with different combinations of modalities. In these studies, combining biological with clinical or functional modalities resulted in the best model performance, with accuracies of 63%

for occupational functioning, 83% for social functioning (Koutsouleris et al., 2018) and 82% for global functioning (de Wit et al., 2017).

Outcome variable. The operationalization of the functional outcome variable could impact model performance. Most studies used a measure of global functioning and reported a wide range of predictive model accuracies. Two studies predicted social and occupational functioning separately. Koutsouleris et al. (2018) reported higher accuracies across models predicting social functioning compared to occupational functioning. Leighton, Upthegrove et al. (2019) found similar predictive accuracies for models predicting social and occupational functioning during internal validation. However, they noted higher accuracies for occupational functioning models during external validation. Two studies utilized a binary outcome of current employment or education involvement and reported predictive accuracies of up to 84 - 85% in externally validated models (Leighton, Krishnadas, et al., 2019; Leighton, Upthegrove, et al., 2019). There was significant heterogeneity in the outcome timepoint, and no apparent patterns were found in results for predicting short versus long term functioning.

Top Predictors of Functional Outcome

Most of the 12 studies included in this review utilized a large set of predictors during model training and provided information on which predictors were most influential in the final models for predicting functional outcomes. Table 2.3 summarizes the top model predictors for each study. There was significant heterogeneity in included predictors and in the top predictors across models, limiting the identification of themes among these results.

Table 2.3

Summary of Top Predictors of Functional Outcomes

Study	Summary of top predictors
Amminger et al. (2015)	Biological: Specific fatty acid chains: mead acid and arachidonic acid (treatment group); nervonic acid and margaric acid (control group)
de Nijs et al. (2021)	Varied by model and outcome timepoint. Themes included: Clinical: Community Assessment of Psychotic Experience items (feeling tense, telepathy); illness variables (health related quality of life, antipsychotic use); PANSS items (hallucinations, poor judgement/insight, unusual thought content, flat affect, motor retardation, grandiosity, stereotyped thinking, difficulty with abstract thinking, emotional withdrawal, tension) Functional: Camberwell Assessment of Need items (housing and food needs); GAF disabilities and symptoms
de Wit et al. (2017)	Biological: Volumes of amygdala, basal ganglia, caudate nucleus, cerebellum, corpus callosum, fusiform gyrus, inferior frontal gyrus, lateral orbitofrontal gyrus, pallidum, precentral gyrus, thalamus, third and lateral ventricles Clinical: SIPS disorganization
Haining et al. (2021)	Not reported
Kambeitz-Illankovic et al. (2015)	Biological: Cortical surface area in cuneus, inferior frontal pars opercularis, interior parietal, lateral occipital, pericalcarine, precuneus, postcentral, rostral middle frontal, superior temporal areas
Kambeitz-Illankovic et al. (2021)	Biological: Baseline gray matter volumes in primarily cerebellum, frontal regions (anterior cingulate cortex), posterior cingulate cortex, temporal regions (superior temporal gyrus, ventral visual word form area, parahippocampal gyri), and thalamus
Koutsouleris et al. (2016)	Demographics: Low educational status of patient or mother Clinical: Haldol treatment; MINI items related to depression, schizophrenia diagnosis, and suicidality; PANSS disorganization, hyperactivity, and positive symptoms total score Functional: Camberwell Assessment of Needs in accommodation, daytime activities, information, money, psychological distress, relationship, and sexual expression domains; education difficulties; GAF
Koutsouleris et al. (2018)	Biological: Reduced baseline gray matter volumes in cingulate, insular, medial prefrontal, occipital, orbitofrontal, and temporal regions, and increased gray matter volume in cerebellar and prefrontal regions. Biological predictors relevant for social functioning models only.

Study	Summary of top predictors
	Functional: Highest global functioning score over the lifetime, social functioning score in the year before study inclusion for prediction of both social and role functioning models
Leighton, Krishnadas et al. (2019)	Clinical: Alcohol use, PANSS delusions, hostility, and suspiciousness items Functional: Current employment, education, or training, education level, living with spouse and children
Leighton, Upthegrove et al. (2019)	Clinical: PANSS disorganization and excitement, self-harm, substance use history (ketamine, amphetamines) Functional: Any time spent in childcare activities, employed or in educational training, education level, GAF score, Premorbid Adjustment Scale degree of interest in life and social sexual aspects items; receiving state benefits
Li et al. (2021)	Demographics: Female Clinical: Cardiovascular disease, liver-protecting drugs, mood stabilizer use, PANSS attention, excitement, preoccupation, and tension scores; PANSS general and total scale scores; Quetiapine use Functional: Employment, Personal and Social Performance scale at baseline
Mechelli et al. (2017)	Clinical: Anhedonia-asociality, attention, conceptual disorganization disorder of thought content, impaired autonomic functioning

Note: GAF = Global Assessment of Functioning scale; MINI = Mini-International Neuropsychiatric Interview; PANSS= Positive and Negative Symptom Scale; SIPS = Structured Interview of Psychosis-risk Syndromes

In the four studies that used structural brain measures as the predictor modality, a pattern of alterations in frontal and temporal regions was evident among the top predictors. Occipital, cerebellar, and thalamic gray matter volumes were also identified among the top predictors. Three of these studies were conducted in a CHR sample and one in a SZ sample. Major differences across diagnostic groups were not evident.

Clinical predictors were commonly included in the top predictive model variables. Positive symptoms of psychosis were most commonly reported (n = 7 studies), followed by general symptoms (n = 3 studies), and negative symptoms (n = 2 studies). Other

clinical themes included depression symptoms (n = 2 studies) and substance use (n = 3 studies). Themes in clinical predictors did not differ by diagnostic group.

Functional predictors were also commonly included in the top predictive variables per model. Common functional domains included global functioning, current employment, educational history, social relationships, and housing needs. When the outcome variable was included as a baseline predictor (i.e., baseline GAF predicting outcome of six-month GAF), this variable was included amongst the top predictors.

Discussion

This critical review highlights the state of the science of individual prognostic models for functional outcomes across the psychosis spectrum. As in previous reviews (Sanfelici et al., 2020), this body of literature is characterized by significant heterogeneity in methods which limits interpretation of results. Overall, we found a wide range of predictive accuracy, ranging from 43 - 86.7% across models. Models relying solely on brain MRI predictors had more heterogeneity in accuracy than models using clinical and functional predictors. Combining biological with clinical or functional modalities resulted in higher accuracies relative to models relying on only one modality. Common qualitative themes among the models' most influential predictors included structural brain measures in the fronto-temporal regions, psychosis and other psychiatric symptoms, and baseline level of functioning. These themes appeared to be independent of the diagnostic category, and thus may point to transdiagnostic signatures of functional prognosis and candidate treatment targets to be explored further in future research. Below we expand on key findings and gaps in the current literature that must be addressed for such models to be viable for clinical translation.

Model Performance

The minimum threshold of model performance in terms of accuracy, specificity, and sensitivity of any prognostic model will depend on the clinical domain and intended model use. While some studies in this review reached high levels of accuracy, overall, there was a wide range of performance and significant heterogeneity in samples and methods. Combined with methodological limitations discussed below, this suggests that individual prediction of functional outcomes in SSDs is in an early stage of development.

To be clinically useful, individual prediction models must demonstrate an advantage over clinician prognostication (Cearns, Hahn, & Baune, 2019). Koutsouleris et al. (2018) compared performance of their brain MRI, functional, and combined models to expert clinical raters. Clinical raters accurately predicted social and occupational functioning with accuracies of 71.8% (sensitivity 51.5%, specificity 92.0%) and 70.4% (sensitivity 49.3%, specificity 91.5%), respectively. In contrast, prognostic models predicted social functioning with accuracies ranging from 76.9 - 82.7% and occupational functioning with accuracies of 56.7 - 64.8%, with combined models achieving the highest accuracies. Thus, models outperformed clinicians for social but not occupational functioning outcomes. Whether the advantage of 4 - 11% in accuracy achieved by the predictive model is sufficient to justify costs of a clinical decision tool is an important question for future research. Importantly, the prognostic advantage of the combined model for predicting social functioning was highest for more ambiguous cases for whom clinician prediction would be more challenging. This may suggest a role for employing more costly and complex prognostic models in select patients when clinical

prognostication and less-resource intensive models are not sufficient (Koutsouleris et al., 2018).

Finally, most studies reported model sensitivity and specificity that were relatively balanced in performance. However, some studies found a high sensitivity and low specificity, indicating that they may be more useful in accurately identifying those at risk for poor outcomes who may need more intensive services, but may not as accurately exclude those who do not need such services. In contrast, the clinical raters in Koutsouleris et al. (2018) made predictions with low sensitivity and high specificity – a pattern of underestimating risks. Thus, there may be a potential synergistic effect between clinician and machine learning based decision aids in balancing sensitivity and specificity of predictions.

Model Predictors

Data modalities. Due to the wide range of model accuracy within each predictor modality and the lack of studies directly comparing models utilizing different modalities, results from this review do not support the superiority of one modality over another. Models with the highest accuracies (>80%) tended to be multi-modal models. SSDs are extremely heterogeneous diseases and therefore including diverse predictor types in model development may be necessary for accurate estimation of outcomes (Hahn et al., 2016; Schnack, 2019).

From a clinical implementation standpoint, results may weight towards pursuing predictive models using clinical and functional measures – which are less costly and more widely available than brain imaging or other biological measures. However, as discussed above, there may be a role for combining brain and behavioral measures to

optimize predictive accuracy when less complex models are not sufficient. de Wit et al. (2017) found that a combined model of cortical gyrification, subcortical volume, and the Structured Interview for Prodromal Symptoms disorganization subscale predicted global functioning in CHR patients at an accuracy of 82%, an improvement of 8 - 9% for models using only brain or clinical predictors. In a larger CHR sample, Koutsouleris et al. (2018) similarly found that a combined gray matter volume and baseline functioning model predicting social functioning outperformed either the brain or functional models alone by approximately 6% with a balanced accuracy of 82.7%. Further research should explore the usefulness of using combined prognostic models in select clinical cases when simpler, more cost-effective models are not sufficient. To this end, research which directly compares the relative performance of models which utilize different predictor modalities is needed to clarify which modalities result in optimal prediction of functional outcomes.

Top predictors. Comprehensive conceptual models of social and occupational functioning impairments in SSDs which consider biological, cognitive, clinical, and sociodemographic underpinnings are lacking. Refined models of social functioning which integrate these domains are needed to foster research into bio-behavioral mechanisms for novel treatment directions. Although heterogeneity in results from this review limits the conclusions that can be drawn, some apparent themes in influential model predictors may guide conceptual development.

At the biological level, frontal-temporal alterations in structural brain measures were commonly observed among top model predictors, as well as gray matter volumes of occipital, cerebellar, and thalamic structures. These results are consistent with a recent

meta-analysis which found that neural loss in prefrontal, temporal, and limbic structures have most consistently been linked to functional outcome in schizophrenia (Wojtalik et al., 2018). Alterations in some of these regions, including the middle-frontal, temporal, and occipital areas, have also demonstrated importance for the individual prediction of social functioning in bipolar disorder and recent onset depression (Koutsouleris et al., 2018; Sartori et al., 2018). Koutsouleris et al. (2018) hypothesize that due to the role of these distributed regions in salience, language, default mode, and executive functioning brain networks, cortical loss could impact social functioning through a complex interplay of social cognitive and executive functioning impairments. Kambeitz-Illankovic (2021) found that greater baseline gray matter volume reserves in the superior temporal gyrus, ventral visual form areas, thalamus, and parahippocampus predicted individual functional outcomes in response to a cognitive training intervention, suggesting a precision medicine application of prognostic models based on neurobiological characteristics. While preliminary, results from this review may point to a neurobiological signature of functional outcome, which may also serve as a marker to guide specific treatments. However, further research to confirm these findings is needed.

The most common clinical symptoms observed in the top predictor sets were positive symptoms of psychosis, followed by general and negative psychosis symptoms. Conflicting evidence has been found for positive symptoms as a predictor of functional outcomes, while negative symptoms have consistently been identified as strong predictors of functioning (Fervaha, Foussias, Agid, & Remington, 2014a; Rabinowitz et al., 2012; Santesteban-Echarri et al., 2017). Previous work has considered group level factors, and it is possible that positive symptoms are more salient for functional outcome

prediction when considered at the individual level due to the immense heterogeneity in positive symptom experiences (Hahn et al., 2016; Schnack, 2019). Findings have also been mixed regarding the role of depression and substance use disorders with functional outcome (Santesteban-Echarri et al., 2017). These domains have received less attention in the context of social functioning, and our results suggest that further research is needed to identify how these factors influence prognosis.

Current conceptual and empirical models of functional outcome in SSDs focus on the role of social cognition, neurocognition, and more recently, motivation, due to the large body of research supporting links between these domains and functional impairments (Bhagyavathi et al., 2015; Fervaha, Foussias, Agid, & Remington, 2014b; Fett et al., 2011; Fulford et al., 2017; Gard, Fisher, Garrett, Genevsky, & Vinogradov, 2009; Green, Kern, Braff, & Mintz, 2000; Halverson et al., 2019). However, these domains were largely underrepresented in individual prognostic models, with only two studies including neurocognitive predictors, one including a single measure of social cognition, and no studies including specific measures of motivation. Further research is needed to evaluate the usefulness of including these measures in model development.

Methodological Considerations

Machine learning research in psychiatry is a relatively nascent field, with very few examples of real-world clinical applications. To date, the field lacks guidelines for methodological expectations and standard procedures that will promote model evaluation, replicability, generalizability, and ultimately translation into practice (Dwyer et al., 2018; Sanfelici et al., 2020). Recently, guidelines have been developed to evaluate risk of bias in prognostic modeling, including the Prediction Model Risk of Assessment Tool

(PROBAST) (Wolff et al., 2019) and Transparent Reporting of Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) checklist (Collins, Reitsma, Altman, & Moons, 2015). These guidelines may also serve researchers in the development phase of machine learning studies to utilize methods that will reduce risk of over-optimistic results, poor generalizability, and limited applicability (Wolff et al., 2019).

More specific to the schizophrenia spectrum disorder domain, Sanfelici et al. (2020) highlight methodological pitfalls commonly seen in psychiatric machine learning studies: small sample sizes, limited use of stringent cross-validation techniques, and lack of external validation. These pitfalls were common in studies included in this review and significantly limit the conclusions that can be drawn about individual prognostication of functional outcomes from this body of research.

While specific sample size requirements have not been established, the PROBAST guidelines suggest that there should be ten to twenty cases with the outcome of interest per variable included in model development to reduce risk of overfitting (Moons et al., 2019). This threshold – the events per variable (EPV) ratio - can be difficult to reach in low prevalence diseases like schizophrenia, or when the predictor modality has an inherently large number of variables, as in the case of brain imaging. In these cases, other methods that can reduce overfitting – such as stringent cross-validation and appropriately executed feature selection within the cross-validation scheme (Moons et al., 2019) should be used. Expert-guided, theory-based feature selection can also be employed to reduce the number of predictors (Dwyer et al., 2018; Moons et al., 2019). No studies in this review meet the EPV criteria and cross-validation methods were often

difficult to evaluate due to incomplete reporting. External validation – performed by three studies in this review - can also reduce concerns related to overfitting and is an important step for model generalizability (Moons et al., 2019). The PROBAST guidelines suggest that studies without an external validation are always at high risk of bias. Achieving gold-standard methodology would be facilitated by open access datasets and multi-site collaborations to allow for adequate sample sizes and opportunities for external validation (Sanfelici et al., 2020). Team science approaches – with clinical domain and machine learning methods experts jointly guiding research efforts – could also facilitate clinical translation (Hahn et al., 2016).

Another methodological consideration is the choice of outcome measure. Most studies in this review used a measure of global functioning. There are inherent limitations to global functioning measures such as the commonly used Global Assessment of Functioning scale, which incorporate non-functioning variables like clinical symptoms into the total score (Hall, 1995) making these measures nonspecific for functional outcomes. Social and occupational functioning are distinct domains that are linked to different etiological and environmental factors and have different intervention needs. Models should thus seek to predict these outcomes separately to promote accuracy and clinical usefulness (Koutsouleris et al., 2018). Additionally, most studies created a binary outcome variable of good versus poor functioning, rather than using a continuous score. Dichotomizing variables can lead to loss of information and introduce bias into the model (Moons et al., 2019). Alternatively, methods which predict a continuous score avoid the need to set arbitrary thresholds between groups and allow for predictions to be made on a gradual scale, which can increase model accuracy. Utilizing

continuous outcomes may additionally promote usefulness for clinical decision making by allowing for more fine-tuning of treatment recommendations based an individual's predicted scores.

Limitations

This review relied on a narrative synthesis of the included studies, rather than a quantitative meta-analytic approach. Due to the heterogeneity in the samples, methods, and outcome measures, quantitative approaches would have limited interpretability. Although we provided a synthesis and general critique of study quality, a formal risk of bias assessment was not completed. We included three separate diagnostic groups in this review in order to provide a comprehensive assessment of functional outcome prognostic models across the schizophrenia spectrum; however, this does limit generalizability of results to specific diagnostic groups. Finally, we searched only major databases which may have prevented inclusion of negative studies published in the grey literature.

Conclusion

Individual prognostic models for functional outcomes in SSDs using machine learning hold promise for improving detection of individuals at risk for poor outcomes and informing future treatments. This review offers preliminary evidence that multi-modal models may promote accuracy of individual predictions and identification of comprehensive bio-behavioral underpinnings of functional outcome. However, our results primarily reveal that development of prognostic models for functional outcome is in an early stage, with current literature characterized by significant heterogeneity in methods and results, hindering interpretation and clinical usefulness. Clinical translation will require further research which relies on large sample sizes, adherence to state-of-the-

art methodological guidelines, and externally validated research. Due to the immense burden of functional impairment in SSDs, such research is urgently needed.

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Chapter 3 (Manuscript 2)

Summary

Poor social functioning is an emerging public health problem associated with physical and mental health consequences. However, there is limited understanding of the bio-behavioral risk factors for poor social functioning. We aimed to predict individual social functioning from bio-behavioral data and identify which predictors are most important for social functioning using machine learning. With data from the Human Connectome Project Healthy Young Adult sample (age 22-35, N=1,101), we built Support Vector Regression models to estimate social functioning from variable sets of brain morphology to behavior with increasing complexity: 1) brain-only model, 2) brain-cognition model, 3) cognition-behavioral model, and 4) combined brain-cognition-behavioral model. Predictive accuracy of each model was assessed and the importance of individual variables for model performance was determined. The combined and cognition-behavioral models significantly predicted social functioning, whereas the brain-only and brain-cognition models did not. Negative affect, psychological wellbeing, extraversion, withdrawal, and cortical thickness of the rostral middle-frontal and superior-temporal regions were the most important predictors. Results demonstrate that social functioning can be accurately predicted at the individual level from bio-behavioral data. Behavioral markers may be more significant predictors of social functioning than brain measures for healthy young adults and may represent important leverage points for preventive intervention.

Individual Prediction of Social Functioning Outcomes in Healthy Young Adults: A Machine Learning Study Integrating Neuroanatomical, Cognitive, and Behavioral Data

Poor social functioning, characterized by an individual's lack of social support and the inability to sustain the interpersonal relationships required for meaningful engagement in society, is an emerging public health problem exacerbated by the worldwide COVID-19 pandemic. It is associated with a range of negative physical and mental health consequences (Holt-Lunstad, Robles, Sbarra, & Julianne Holt-Lunstad, 2010), such as early mortality (Holt-Lunstad, Smith, Baker, Harris, & Stephenson, 2015; Pantell et al., 2013) and increased risk for cardiovascular (Valtorta, Kanaan, Gilbody, Ronzi, & Hanratty, 2016), mood (Cacioppo, Hughes, Waite, Hawkley, & Thisted, 2006; Hawkley & Capitanio, 2015; Santini et al., 2020), anxiety (Santini et al., 2016), neurocognitive (Fratiglioni, Wang, Ericsson, Maytan, & Winblad, 2000; Shankar, Hamer, McMunn, & Steptoe, 2013), and psychotic disorders (Fulford et al., 2013; Green et al., 2018). Conversely, individuals with adaptive social functioning have demonstrated better overall well-being (Chu, Saucier, & Hafner, 2010; Siedlecki, Salthouse, Oishi, & Jeswani, 2014) and improved self-management of chronic conditions (Gallant, 2003; Vassilev et al., 2011). Despite the widespread negative consequences of poor social functioning, little is known about the bio-behavioral determinants of social functioning or risk factors for social decline.

Impairments in social functioning are also a hallmark of many psychiatric illnesses and could represent a transdiagnostic risk marker for mental health disorders (Koutsouleris et al., 2018; Reniers et al., 2017). Accordingly, understanding the

neurobiological underpinnings of social functioning may inform psychiatric disease models and treatment development. Both overlapping and distinct associations between brain structure and social functioning have been observed across major psychiatric illness. For example, in individuals at high risk for psychosis, less gray matter density in frontal and limbic areas has been associated with greater functional decline regardless of transition to psychosis, supporting a transdiagnostic biomarker for social functioning deficits (Reniers et al., 2017). These trends persist in chronic schizophrenia (Wojtalik, Smith, Keshavan, & Eack, 2018) and are partially replicated in bipolar disorder with associations between gray matter volume reductions in the superior and medial prefrontal cortex and social functioning (Sartori et al., 2018). Yet, distinct neural patterns associated with social functioning impairments have been found in different patient subgroups. In patients at clinical high risk for psychosis, gray matter volume reductions in the prefrontal and temporo-parietal-occipital regions were specifically associated with poor social functioning, while in patients with recent-onset depression, gray matter volume reductions in the medio-temporal and prefrontal-perislylivan regions were instead linked to poor social functioning (Koutsouleris et al., 2018). Hence, clarifying the relationships between structural and physiological brain findings and social functioning in healthy individuals prior to disease onset could improve our understanding of brain changes associated with the onset and progression of specific diseases; however, these associations have not been adequately studied.

Models of social functioning must also consider the cognitive and psychological processes necessary for adaptive social behavior, yet no thorough investigations of these associations currently exist in healthy populations. In psychiatric diseases, a range of

cognitive and social cognitive impairments are linked to poor social functioning in schizophrenia (Fett et al., 2011; Green, Kern, Braff, & Mintz, 2000; Halverson et al., 2019), bipolar disorder (Gitlin & Miklowitz, 2017), and depression (Evans, Iverson, Yatham, & Lam, 2014). In non-clinical samples, social cognition predicts overall social functioning (Oliver et al., 2018) and supports varied social abilities such as self-regulation in conflict and empathetic engagement with others (Hooker, Gyurak, Verosky, Miyakawa, & Ayduk, 2010; Hooker, Verosky, Germine, Knight, & D'Esposito, 2010). Finally, in non-clinical samples, psychological traits such as depression, anxiety, and externalizing behaviors may lead to poor social functioning (Chou, Liang, & Sareen, 2011; Dawson, Shear, & Strakowski, 2012; Murphy, Shepard, Eisenberg, & Fabes, 2004; Santini, Koyanagi, Tyrovolas, Mason, & Haro, 2015; Teo, Lerrigo, & Rogers, 2013).

A major limitation of existing literature is the lack of models of social functioning that integrate bio-behavioral data in order to delineate the relative importance of specific biological, cognitive, psychological, and other behavioral domains to social functioning. This approach requires large datasets and analysis techniques capable of utilizing multimodal data, such as machine learning methods that do not require restricting the analysis to a small set of variables chosen *a priori*. Such data-driven methods are well suited for exploring a large breadth of data with the potential to uncover complex relationships that may be missed with hypothesis driven approaches.

In this study, we leveraged the Human Connectome Project Healthy Young Adult (HCP-YA) dataset - which includes multiple domains of cognitive, psychological, and other behavioral measures as well as high-quality neuroimaging data for a sample of over 1000 participants – and machine learning methods to investigate a comprehensive set of

possible contributors to social functioning outcomes. The two-fold purposes of this study were to 1) determine whether social functioning can be predicted from integrated brain morphology and behavioral data to identify key patterns that are present in the absence of overt psychopathology; and 2) identify which predictors are the most important for social functioning in healthy young adults in order to establish a baseline for understanding further changes that may be identified as individuals develop specific psychiatric illnesses. Additionally, we evaluated which types of data are necessary and sufficient for the prediction of social functioning by comparing models built from variable sets of increasing complexity from brain morphology to behavior.

Methods

Data Acquisition

This study utilized data from the HCP-YA sample. Access to the de-identified HCP-YA restricted access dataset was granted from the HCP consortium on June 19, 2019. The de-identified dataset was obtained from the secure HCP server. The University of Minnesota IRB deemed this research exempt and not human subjects research.

Participants

The HCP-YA study enrolled 1,206 participants aged 22-35, including twin and non-twin siblings from 2012 to 2015. Recruitment and study procedures took place at Washington University in St. Louis, Missouri and at the University of Minnesota in Minneapolis, Minnesota. A detailed report of the recruitment procedures has been documented elsewhere (Van Essen et al., 2013). Inclusion criteria for HCP participants included age 22-35 and the ability to provide valid informed consent. Exclusion criteria

included: history of psychiatric disorder, substance use disorder, neurological, endocrine or cardiovascular disease, genetic disorder, head injury, premature birth, history of chemotherapy or immunomodulatory agents, a score of $\leq$25 on the Folstein Mini-Mental State Exam (Folstein, Folstein, & Mchugh, 1975), claustrophobia, pregnancy or metal in the body. Participants were excluded from the current study if they did not have structural MRI data available or if they were missing greater than 50% of the cognitive and behavioral data.

Variables

Social functioning outcome measure. We derived the social functioning outcome variable from the Social Relationships scales included in the NIH Emotion Toolbox (NIH-ETB) (Cyranowski et al., 2013; Salsman et al., 2013). An expert panel commissioned by the NIH Neuroscience Blueprint (Insel, Landis, & Collins, 2013) led the creation of the NIH-ETB, a set of self-report measures to assess positive and negative aspects of emotional functioning. Based on item response theory, the NIH-ETB uses computer adaptive testing with extensive item banks and has undergone norming and validation. The scales representing the Social Relationships domain have demonstrated strong convergent validity with objective measures of interpersonal support, loneliness, and negative social interactions (Salsman et al., 2013). We created the Social Functioning composite measure used in this study using the formula provided by Babakhanyan et al. (Babakhanyan, McKenna, Casaletto, Nowinski, & Heaton, 2018), which includes scores for dimensions of friendship, loneliness, emotional support, instrumental support and perceived rejection. The summary score formula includes positive and negative factor loadings to reflect the positive (i.e., friendship) and negative

(i.e., loneliness) aspects of social functioning. The individual scales that comprise the composite measure in the HCP-YA dataset are provided as T-scores (mean of 50, standard deviation of 10).

Predictor variables by domain. Predictor variables are briefly described below; more detailed information for each variable collected by the HCP-YA study can be found online (Elam, 2021).

***Neurobiological predictors*.** Cortical thickness and surface area for 33 cortical and 8 subcortical regions per hemisphere were obtained from structural MRI. All participants underwent MRI on 3T Siemens scanners using 32 channel head coils. A uniform MRI protocol and processing pipeline using FreeSurfer 5.1 was implemented between sites to control for variability in scanning procedures. Scanning protocols are detailed elsewhere (Van Essen et al., 2013), and data quality has been ensured by extensive quality assurance procedures (Van Essen et al., 2013). The automated segmentation of T1 and T2 weighted brain scans, which includes the standard parcellation maps using the Conte69 brain atlas was used. Surface areas were corrected for total intracranial volume.

***Cognitive predictors*.**

Social Cognition. Our primary measure of social cognition was the Penn Emotion Recognition Task (Gur et al., 2002), a measure of emotion processing which assesses the ability to discriminate emotions on human faces. We included both the correct responses and reaction time as separate variables. In addition, we included two in-scanner tasks: the HCP Theory of Mind task and the HCP Emotion Processing task (Barch et al., 2013).

Cognition. Cognitive variables included global cognition as measured by the Mini-Mental State Exam (Folstein et al., 1975) total score and discrete cognitive domains of attention, episodic memory, working memory, language, executive function and processing speed measured by the NIH-Toolbox Cognition Battery and scored as age-adjusted T-scores.

Behavioral predictors. *Psychological variables* included the five domain scores from the Costa and McRae Neuroticism/Extroversion/Openness Five Factor Inventory (NEO-FFI) (McCrae & Costa, 2004) and the age-adjusted T scores from the Achenbach Adult Self Report (ASR) Syndrome Scales (Achenbach & Rescorla, n.d.) which includes subscales of anxious/depressed, withdrawn, somatic complaints, thought problems, attention problems, aggression, and rule breaking problems. Negative affect and psychological wellbeing were measured using the composite scores from these factors from the NIH-ETB scales (Babakhanyan et al., 2018). Reward processing and self-regulation were measured by the Delay Discounting task (Estle, Green, Myerson, & Holt, 2006).

Substance use variables included self-report measures of total number of alcoholic drinks in the last seven days, typical number of drinks per drinking day in the last 12 months, total times of use of any tobacco products in the last seven days, and total lifetime amount of cannabis use.

Physical functioning variables included the NIH Toolbox endurance, gait speed, dexterity and strength assessments (Reuben et al., 2013), the Pittsburg Sleep Quality Questionnaire (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) total score and Body Mass Index (BMI).

Sensory functioning was operationalized by four measures from the NIH Toolbox that assess sensory and neurological functioning: Words-in-Noise test (measure of audition), Odor Identification test, Regional Taste Intensity test, and the Pain Interference Survey. Vision measures included the Mars Contrast Sensitivity test (Arditi, 2004).

Statistical Analysis

Missing data. Individual participants were excluded if they had incomplete neuroimaging data or were missing 50% or greater of the cognitive or behavioral data. The remaining missing values were imputed using K-Nearest Neighbors (k = 5). As an inclusion criterion for this study was complete structural MRI data, imputation only applied to cognitive and behavioral variables. For the training dataset, imputation was performed separately in each cross-validation fold to prevent information leakage that could lead to overfitting.

Multicollinearity evaluation. We evaluated multicollinearity (Pearson's r > 0.70) by examining a correlation matrix of all variables. Two variables were highly correlated with NEO-FFI neuroticism: Negative affect (r = 0.72) and the ASR anxiety/depression scale (r = 0.71). Multicollinearity was primarily addressed by using the Recursive Feature Elimination step during model training. Secondarily, multicollinearity was addressed by estimating models with and without NEO-FFI neuroticism. No significant differences in model performance were found, and thus this variable was included in the final model.

Descriptive statistics. Descriptive statistics were calculated for social functioning, cognition, behavioral variables, and demographics, with means (SD) for

continuous variables and percentages for categorical variables. All descriptive analyses were calculated in SPSS version 26 (IBM Corp., 2019).

Machine Learning Analysis

Model training and cross validation. We used a linear support vector regression (SVR) (Fan, Chang, Hsieh, Wang, & Lin, 2008) to estimate individual participants' social functioning score from brain morphological, cognitive, and/or behavioral data. We chose a regression, rather than a classification, approach because regression algorithms avoid the need to set arbitrary thresholds between groups (i.e., creating a social functioning cut-off score for good vs poor functioning) and allow for increased prediction accuracy due to their ability to make predictions based on a gradual scale (James, Witten, Hastie, & Tibshirani, 2013; Moradi, Khundrakpam, Lewis, Evans, & Tohka, 2017; Sarica, Cerasa, & Quattrone, 2017). The SVR is an established approach for uncovering non-linearities in the dataset that would not be uncovered by general linear models and is a robust approach for multi-modal data and large feature sets.

We trained four separate linear SVR models predicting social functioning composite scores: 1) a brain-only model, trained on structural MRI measures only; 2) a brain-cognition model, trained on brain and cognition measures only; 3) a cognition-behavioral model, trained on the cognition and behavioral measures only; and 4) a combined model, trained on the brain, cognition, and behavioral measures. The subsets of variables chosen for our models build in levels of biological to behavioral complexity, allowing for examination of which domains are necessary or sufficient for the prediction of social functioning. Additionally, as cognitive and behavioral measures are less invasive and expensive to obtain relative to brain measures, we tested these models

separately because they are more practical for use in most clinical contexts. The machine learning analysis was implemented using the Scikit-learn Python toolbox (Pedregosa et al., 2011) which uses the LIBLINEAR library of functions (Fan et al., 2008).

The full dataset was randomly split into a training and testing dataset, with 10% of participants assigned to the testing dataset (N = 111). In the model training set, a nested five-fold cross validation (CV) procedure was used. To address potential bias due to heritability, samples were split into CV folds such that all related individuals are in the same fold, preventing leakage of information across folds. Prior to training, the data were standardized to have a mean of zero and standard deviation of one. We used Recursive Feature Elimination with the ridge regression estimator as a feature selection step to reduce the feature space. This step was embedded within the CV to determine the optimal number of variables to select for each model. The frequency that a specific variable was selected in the five CV folds was calculated.

The optimal values for the hyperparameters for the linear SVR, including the C-value and epsilon, were determined during the CV procedure using grid search. The epsilon insensitive, or L1, loss function was used. The parameter "dual" was set to false, which is the default when the number of samples is greater than the number of features.

Model testing and evaluation. Using the hyperparameters learned during the testing and cross validation phase for each model, the learned SVR algorithm was applied to the held-out test dataset to evaluate model performance on unseen data. Model performance was measured based on the coefficient of determination, R^2, and the mean squared error (MSE) of the learned model. The R^2 value represents the proportion of variance of the outcome variable that can be explained by the independent variables in

the model and is a measure of goodness of fit for the model. A model which always predicts the correct score would have an R^2 score of 1, and a constant model which always predicts the mean value of the outcome variable would have an R^2 score of zero. Thus, the R^2 score can be negative if it performs worse than a constant prediction of the mean. The MSE represents the mean of the squared differences between the actual outcome value and the model-predicted value (lower scores indicate better model performance).

We calculated 95% confidence intervals for the R^2 and MSE metrics using a bootstrapping procedure with 1000 resamples. Significance was evaluated using the 95% confidence interval of each model's R^2 value. Performances of the four models were compared by calculating the 95% confidence interval for the differences in the bootstrapped R^2 results of two models at a time. P-values (two tailed, alpha = 0.05) were calculated by inverting the confidence interval.

Exploratory Analysis of Mis-predicted Cases

To identify demographic groups or individual profiles for whom the model may not generalize well, we examined trends in the performance of the combined model by examining individual cases in the test dataset. The methods and results of this analysis are detailed in the Supplementary Methods and Results (Appendix B).

Results

Sample

One hundred and five participants were excluded for missing MRI data or having greater than 50% missing behavioral data. The remaining 1,101 participants met eligibility criteria and were included in the analysis and split into the training (N = 990)

and testing (N = 111) datasets. Demographics and social functioning score descriptive statistics for the full analysis sample are provided in Table 3.1. The social functioning composite score ranged from -13.0 to 15.2 with a mean of 5.6 and standard deviation of 5.0. Descriptive statistics for the individual scales that comprise the social functioning composite score are provided in Supplementary Table 3.1 (Appendix B). Descriptive statistics for all cognitive and behavioral variables are provided in Supplementary Table 3.2 (Appendix B).

Table 3.1

Demographics and Outcome Measure Descriptive Statistics (N = 1,101)

	Mean (SD) or %
Demographics	
Age (years)	28.8 (3.7)
Gender: female	54.4
Education (years)	14.9 (1.8)
Race	
American Indian or Alaskan Native	0.2
Asian, Native Hawaiian or Other Pacific Islander	5.7
Black or African American	14.9
White	74.9
More than one	2.5
Unknown or not reported	1.7
Ethnicity: Hispanic or Latino	8.6
Outcome Measure	
NIH Emotion Toolbox Social Functioning Composite Score	5.6 (5.0)

Note: SD = standard deviation

Machine Learning Analyses

Model performance. Model performance statistics, including R^2 and MSE, for all models are provided in Table 3.2. The combined model and the cognition-behavioral model significantly predicted individual social functioning scores (R^2 =0.53, 95% CI [0.38, 0.62] for each model). The brain-only model and the brain-cognition model

performances were not significant in predicting social functioning scores (R^2 = 0.06, 95% CI [-0.07, 0.16] and R^2 = 0.11 95% CI [-0.05, 0.23], respectively). These models performed significantly worse than the combined and cognition-behavioral models. No significant differences in model performance were noted between the brain-only and brain-cognition models or between the combined and cognition-behavioral models.

Table 3.2

Model Performance Summary Statistics and Model Comparison

Model	**R^2 (95% CI)**	**Mean Square Error (95% CI)**
Brain	0.06 (-0.07, 0.16)	21.36 (16.85, 26.2)
Brain-cognition	0.11 (-0.05, 0.23)	20.16 (15.64, 24.65)
Cognition-behavioral*	0.53 (0.38, 0.62)	10.73 (8.86, 12.73)
Combined brain-cognition-behavioral*	0.53 (0.38, 0.62)	10.68 (8.60, 12.88)
Model Comparison		
Model	**Point Estimate (95% CI)[a]**	**p-value**
Brain vs. Brain-cognition	0.05 (-0.06, 0.16)	0.35
Brain vs. Cognition-behavioral	0.47 (0.32, 0.60)	<0.0001
Brain vs. Combined	0.47 (0.33, 0.60)	<0.0001
Brain-Cognition vs. Cognition-behavioral	0.41 (0.27, 0.56)	<0.0001
Brain-Cognition vs. Combined	0.42 (-0.26, 0.57)	<0.0001
Cognition-behavioral vs. Combined	-0.05 (-1.30, 1.20)	0.90

Note: CI = confidence interval; *Statistically significant model based on 95% confidence interval; [a]Point estimate and 95% confidence interval represents differences in the bootstrapped R^2 values of the two models compared

Feature selection and importance. The selected features, or predictor variables, from the best performing models (combined and cognition-behavioral) are provided in Table 3.3, along with their feature coefficient and the frequency with which they were selected by the SVR algorithm during five-fold cross validation to be included in the model. The weight of the feature coefficient (absolute value) indicates the relative importance of the specific variable to the model. Features selected for the model at high

frequencies during cross validation can be interpreted as being more reliable predictors relative to those selected infrequently. The highest weighted and most consistent features in the combined model included negative affect, psychological wellbeing, withdrawn symptoms, extraversion, and the cortical thickness in right and left rostral middle frontal gyri and the left superior temporal gyrus. The highest weighted and most consistent features in the cognition-behavioral model included negative affect, psychological wellbeing, withdrawn symptoms, extraversion, agreeableness, and aggression symptoms.

Table 3.3

Feature Importance for Combined and Behavioral-only Models

Combined brain-cognition-behavioral model		
Feature	**Feature Coefficient**	**CV Frequency (maximum = 5)**
Negative affect	-1.53	5
Psychological well-being	1.37	5
ASR withdrawn symptoms	-0.82	5
NEO-FFI extraversion	0.76	5
R rostral middle frontal thickness	-0.56	4
L superior temporal thickness	0.49	5
L supramarginal thickness	-0.45	1
L rostral middle frontal thickness	0.42	3
L temporal pole area	-0.37	1
NEO-FFI agreeableness	0.32	1
R superior parietal area	0.31	1
R inferior parietal thickness	0.25	1
Cognition-behavioral model		
Feature	**Feature Coefficient**	**CV Frequency (maximum = 5)**
Negative affect	-1.71	5
Psychological well-being	1.33	5
ASR withdrawn symptoms	-0.85	5
NEO-FFI extraversion	0.76	5
NEO-FFI agreeableness	0.37	4
ASR aggression symptoms	0.35	4
Education level	0.19	1

Note: ASR = Achenbach Adult Self Report scale; L = left; NEO-FFI = Neuroticism, Extraversion, Openness Five Factor Inventory; R = right

Discussion

In this study, we leveraged a large dataset of integrated biological, cognitive, and behavioral data and machine learning to predict social functioning at the individual level in a large sample of healthy young adults. We found that social functioning can be reliably predicted to identify individuals at risk for poor functional outcomes and possible future psychopathology. Our findings suggest that behavioral variables in the psychological domain that capture aspects of negative affect, psychological well-being, and personality traits, may be more robust predictors of social functioning than cognitive or neuroanatomical measures. Further, combining neuroanatomical measures with cognitive and behavioral measures did not improve model accuracy but highlighted potential neuroanatomical regions that may be important to the prediction of social functioning when considered along with behavioral variables. Below we highlight key findings in relation to existing literature.

Individual Prediction of Social Functioning from Integrated Bio-behavioral Data

The combined brain-cognition-behavioral model significantly predicted social functioning, however it performed at an equal accuracy as the cognition-behavioral model, suggesting no additional benefit of including neuroanatomical measures. These models performed at similar accuracies when compared to existing machine learning research seeking to predict mental health outcomes (Cearns, Hahn, & Baune, 2019; Schnack, 2019; Vieira et al., 2020), and thus the more cost-effective cognition-behavioral model may be a useful tool in identifying those at risk of social functioning deficits if applied to longitudinal data. Interestingly, the brain-only and brain-cognition models failed to significantly predict social functioning, but neuroanatomical measures were

included amongst the top predictors in the combined model. Thus, while neuroanatomical measures may not be necessary or sufficient in the prediction of social functioning in a healthy adult sample, integrating the neuroanatomical measures with other behavioral data may point to potential critical brain regions that play a role in social functioning.

We found that the brain-only and brain-cognition models performed very poorly in the prediction of social functioning. This was unexpected given 1) previous studies in psychiatric populations that have successfully used support vector machines to predict functional outcomes from neuroanatomical data in first episode psychosis (Koutsouleris et al., 2018), early depression (Koutsouleris et al., 2018), and bipolar disorder (Sartori et al., 2018) and 2) research consistently linking cognitive and social cognitive impairments to social functioning in psychiatric disorders (Berk & Berk, 2017; Fett et al., 2011; Iosifescu, 2012; Millan et al., 2012). That successful prediction models for social functioning can be built from neuroanatomical data in psychiatric disorders – especially in the early years of illness – suggests that the changes in brain structure that occur in these disorders, especially in fronto-temporal regions, are significant enough to meaningfully contribute to social functioning deficits. Thus, the mechanisms by which this neuropathology contributes to social functioning deficits in the context of disease expression should be further investigated.

In healthy controls who are expected to have less variance in brain structure, however, these relationships may not be evident without much larger sample sizes to detect differences (Masouleh, Eickhoff, Hoffstaedter, Genon, & Alzheimer's Disease Neuroimaging Initiative, 2019). The limited variance in cortical thickness and gray

matter volumes in a healthy population likely contributed to the inability of the machine learning algorithm to discriminately use brain features in prediction. This is supported by Sartori et al. (2018) who found that neuroanatomical data led to successful prediction of social functioning in bipolar disorder, but not in the healthy control sample. Likewise, recent large scale replicability studies linking personality features and other psychological variables to brain morphometry in healthy adults have failed to detect associations, which has been attributed to limited variance and small effect sizes even in samples greater than 1000 participants (Avinun, Israel, Knodt, & Hariri, 2020; Baranger et al., 2020; Masouleh et al., 2019). Limited variance and overall higher performance in cognitive functioning (i.e., ceiling effects) in our healthy population likely also contributed to the poor performance of the brain-cognition model.

Salient Variables and Data Modalities for the Individual Prediction of Social Functioning

A primary aim of this study was to identify which variables were the most important to the prediction of social functioning. In the combined and cognition-behavioral models, the most predictive variables included negative affect, psychological well-being, withdrawn symptoms, and the extraversion personality trait. This is not surprising, as these measures – especially withdrawn symptoms and extraversion - have some conceptual overlap with social functioning. Nonetheless, these results indicate that monitoring these domains is useful for identifying individuals at risk for poor social functioning outcomes. Preliminary research has linked negative affect and psychological well-being to social functioning outcomes across healthy and psychiatric populations (Dawson et al., 2012; Grove et al., 2016; Huppert, 2009). Thus, these domains may serve

as potential intervention targets, which are amenable to psychological therapies (Dunn et al., 2020; Fava & Ruini, 2003; Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012; Weiss, Westerhof, & Bohlmeijer, 2016), to improve social outcomes and thus longer-term well-being.

Due to the large body of evidence linking cognitive and social cognitive impairments to social functioning in psychiatric disorders (Berk & Berk, 2017; Fett et al., 2011; Iosifescu, 2012; Millan et al., 2012), it was an unexpected finding that no cognitive variables were selected in our best performing models. While the importance of cognition could have been masked by the more heavily weighted variables in our combined and cognition-behavioral models, the brain-cognition model failed to significantly predict social functioning, which suggests that cognition was not highly predictive of social functioning in this healthy sample of young adults. As discussed above, this may be attributed to limited variance in cognitive functioning in a healthy young adult sample. Additionally, the construct of social functioning used in this study was very broad; the primary social cognition measure of emotion recognition may instead be a better predictor of specific aspects of social functioning (Fett et al., 2011; Janssens et al., 2012).

Despite the poor performance of the brain-only model, cortical thickness of the middle frontal and superior temporal regions were consistently selected as important variables in predicting social functioning in the combined brain-cognition-behavioral model. These represent important hubs of the social brain, and their structure and function has been linked to higher order social cognitive processes such as theory of mind and emotion recognition (Adolphs, 2009; Blakemore, 2008; Pinkham, 2014; Van

Overwalle, 2009). The structure and function of these brain regions have been consistently linked to social functioning deficits in schizophrenia (Wojtalik et al., 2018). Additionally, machine learning studies predicting functional outcomes from neuroanatomical data in psychiatric samples have also found these regions to be important for their prediction models. Sartori et al. (2018) found that gray matter volume of the superior and rostral middle frontal cortex were the most relevant features for functional outcome prediction in patients with bipolar disorder. While Koutsouleris et al. (2018) found divergent neuroanatomical patterns predicting social functioning in patients at clinical high risk for psychosis versus those with first episode depression, medial prefrontal and temporal regions were important for their predictive models in both populations. Thus, it is possible that structural measures of the middle frontal and temporal regions may serve as a transdiagnostic risk marker for social functioning across the spectrum of health to psychiatric illness.

Limitations and Future Research

The results of this study must be interpreted in the context of several limitations. Although efforts were made by the HCP research consortium to build a representative sample of participants based on U.S. Census data (Van Essen et al., 2013), the majority of young adult participants were non-Hispanic whites, and their average education attainment was relatively high. Therefore, the generalizability of results to diverse racial, cultural, and socioeconomic groups may be limited. Many measures used in this study – including the social functioning outcome score - were self-reports, which may be less reliable than objective measures. However, use of high quality and psychometrically sound self-report measures is becoming increasingly important in health research seeking

to promote patient centered outcomes that reflect perceived quality of life (Hahn et al., 2007; Riley, Pilkonis, & Cella, 2011; Smith et al., 2016). Nonetheless, it is possible that the prediction accuracy of machine learning models may improve with more objective measures. Although the top performing models had statistically significant performance, social functioning scores were mis-predicted in nearly 20% of the test sample. Finally, this study analyzed cross sectional data. Clinically useful models must predict longitudinal outcomes and future research should extend our models to the prediction of social functioning at later timepoints using baseline data.

Given the enormous burden of social functioning deficits on mental and physical health and the lack of treatment options for persistent social functioning deficits across psychiatric disorders, identifying individuals who are at risk in early adulthood – if not earlier -- and addressing potential treatment targets is a critical research need. Models predicting longitudinal outcomes that demonstrate superiority over clinician prediction (Koutsouleris et al., 2018) are needed to promote clinical utility.

Conclusions

To our knowledge, this is the first machine learning study to predict social functioning outcomes from integrated bio-behavioral data in a large sample of healthy young adults. Our findings indicate that machine learning methods can be used to identify individuals at risk for poor long-term outcomes due to impaired social functioning. While a renewed focus on understanding biological underpinnings of complex behaviors such as social functioning characterizes the state of the science, our results suggest that the study of psychological constructs may be more impactful in

understanding the potential intervention points for poor social functioning that can be leveraged to improve an individual's long-term well-being.

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Chapter 4 (Manuscript 3)

Citation

Miley, K., Meyer-Kalos, P., Ma, S., Bond, D. J., Kummerfeld, E., & Vinogradov, S. (2021). Causal pathways to social and occupational functioning in the first episode of schizophrenia: uncovering unmet treatment needs. *Psychological Medicine*, 1-9. https://doi.org/10.1017/S0033291721003780.

Summary

Background. We aimed to identify unmet treatment needs for improving social and occupational functioning in early schizophrenia using a data-driven causal discovery analysis. *Methods.* Demographic, clinical, and psychosocial measures were obtained for 276 participants from the Recovery After an Initial Schizophrenia Episode Early Treatment Program (RAISE-ETP) trial at baseline and six-months, along with measures of social and occupational functioning from the Quality of Life Scale. The Greedy Fast Causal Inference algorithm was used to learn a partial ancestral graph modeling causal relationships across baseline variables and six-month functioning. Effect sizes were estimated using a structural equation model. Results were validated in an independent dataset (N=187). *Results.* In the data-generated model, greater baseline socio-affective capacity was a cause of greater baseline motivation (ES = 0.77), and motivation was a cause of greater baseline social and occupational functioning (ES = 1.5 and 0.96, respectively), which in turn were causes of their own six-month outcomes. Six-month motivation was also identified as a cause of occupational functioning (ES = 0.92). Cognitive impairment and duration of untreated psychosis were not direct causes of functioning at either timepoint. The graph for the validation dataset was less determinate, but otherwise supported the findings. *Conclusions.* In our data-generated model, baseline socio-affective capacity and motivation are the most direct causes of occupational and social functioning six months after entering treatment in early schizophrenia. These findings indicate that socio-affective abilities and motivation are specific high-impact treatment needs that must be addressed in order to promote optimal social and occupational recovery.

Causal Pathways to Social and Occupational Functioning in the First Episode of Schizophrenia: Uncovering Unmet Treatment Needs

Schizophrenia and other psychotic disorders are characterized by severe disability in social and occupational functioning (Wiersma et al., 2000), reducing quality of life and causing significant societal burden (Cloutier et al., 2016). Though these impairments are evident early, specialized early intervention services have failed to drastically alter long term functional outcomes (Norman et al., 2018; Secher et al., 2015). Indeed, the greatest improvements in social and occupational functioning (when present) are observed during the first six months of treatment, with little significant gain thereafter (Humensky, Essock, & Dixon, 2017; Phahladira et al., 2020). While numerous predictors of functional outcome have been identified (including positive and negative symptoms, cognitive impairment, and duration of untreated psychosis, to name a few) (Fett et al., 2011; Milev, Ho, Arndt, & Andreasen, 2005; Nakagami, Hoe, & Brekke, 2010; Penttilä, Jaäskeläinen, Hirvonen, Isohanni, & Miettunen, 2014; Santesteban-Echarri et al., 2017), some of them, such as positive symptoms, do not robustly affect functional outcomes even when they are altered by treatment (Swartz et al., 2007; Wunderink, Nieboer, Wiersma, Sytema, & Nienhuis, 2013). This suggests that many clinical predictors of functional outcomes *may not necessarily cause* functional outcomes.

Previous research identifying predictors of functional outcomes has been limited by statistical methods that are not informed by causal theory. Identifying treatment needs with the greatest potential impact requires identifying which predictors are *most plausibly causes* of functional outcomes. Causal modeling algorithms are novel methods which combine graph theory, statistics, and machine learning to produce hypothetical causal

models (Spirtes, Glymour, & Scheines, 2000). Such models have been demonstrated to outperform predictive statistical approaches, such as structural equation models (SEMs) and other regression-based methods in the identification of treatment targets (Maathuis, Kalisch, & Bühlmann, 2009; Shen, Ma, Vemuri, & Simon, 2020; Stekhoven et al., 2012; Taruttis, Spang, & Engelmann, 2015). SEM analysis, for example, relies on *a priori* model selection to test a specific causal structure, and the effect estimate resulting from SEM is accurate only when the hypothesized causal structure is accurate, a condition hard to guarantee. SEM also requires specifying the causal structure of all included variables, which is rarely known in a complex causal system containing many variables. In contrast, the causal discovery analysis employed here uses a data-driven approach to search the space of possible SEMs to identify the causal network structure that best fits the data, including identification of causal effects of latent (unmeasured) variables (Ogarrio, Spirtes, & Ramsey, 2016). Thus, in addition to generating statistically defensible models of underlying causal structures (Shen et al., 2020), causal discovery offers the advantage of modeling a more comprehensive set of treatment target candidates.

In order to identify plausible causes of functional outcomes during the six-month critical window for early intervention, we applied a novel data-driven causal modeling method to data from the Recovery After an Initial Schizophrenia Episode Early Treatment Program (RAISE-ETP) trial. Our aim was to identify variables that are modeled *to cause, rather than only predict or associate with*, social and occupational functioning, and thus represent high impact unmet treatment needs for promoting functional recovery in early schizophrenia. We validated our results in an independent

dataset drawn from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study.

Methods

Data Acquisition

De-identified data were obtained from the National Institute of Mental Health National Database for Clinical Trials (https://data-archive.nimh.nih.gov/). The University of Minnesota Institutional Review Board approved this research as exempt from human subjects research.

Participants

Participants for Study 1 were drawn from the RAISE-ETP randomized controlled trial (Kane et al., 2016). RAISE-ETP enrolled 404 participants across 21 states. Inclusion criteria were: ages 15-40; diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, or psychosis not otherwise specified; only one lifetime episode of psychosis; and duration of antipsychotic use less than six months. RAISE-ETP participants who completed baseline and six-month follow up assessments were included in this analysis (N = 276). Participants from both arms of the RAISE-ETP trial were included because we sought to identify variables that causally impact functional outcome regardless of treatment program; the treatment arm was included in the model to assess any effect on the estimated causal network structure.

Participants for Study 2 were drawn from the CATIE trial (Stroup et al., 2003). CATIE enrolled 1600 participants across 50 sites; inclusion criteria were: ages 18-65 years and a schizophrenia diagnosis. Exclusion criteria were psychotic symptoms for less than three years and antipsychotic use less than one year. We studied CATIE participants

who were 40 years of age and younger, had antipsychotic duration of less than five years, and who completed baseline and six-month assessments of our primary outcome measures; our goal was to attain similarity with the RAISE-ETP participants while maximizing the sample size (N = 187).

Study 1 Variables and Measures

The outcome variables for our analysis included social and occupational functioning derived from the interviewer-rated Heinrichs-Carpenter Quality of Life Scale (QLS) (Heinrichs, Hanlon, & Carpenter, 1984), which was the primary outcome measure in the RAISE-ETP trial. Consistent with RAISE-ETP, we used the traditional subscale constructs for the Interpersonal Relations (items 1-8, assessing relationships and level of social activity) and Instrumental Role (items 9-12, assessing level of occupational role functioning, accomplishment, underemployment, and satisfaction with occupational functioning) subscales to derive our variables for Social and Occupational Functioning, respectively.

Primary variables. Primary variables were selected based on previous findings that motivation, social cognition, cognition, negative symptoms and duration of untreated psychosis (DUP) are consistent predictors of functional outcome in schizophrenia (Fett et al., 2011; Milev et al., 2005; Nakagami et al., 2010; Penttilä et al., 2014; Robertson et al., 2014; Santesteban-Echarri et al., 2017).

Motivation was derived from three items from the Intrapsychic Foundations subscale of the QLS: item 13, "sense of purpose," item 14, "degree of motivation," and item 15, "curiosity." These items were originally derived as a measure of intrinsic

motivation (Nakagami, Xie, Hoe, & Brekke, 2008) and may also reflect a general trait-like motivation (Choi, Choi, Felice Reddy, & Fiszdon, 2014). They have been used extensively as a measure of motivation in schizophrenia with demonstrated convergent validity with interviewer-rated measures of motivation and laboratory measures of effort-based decision making (Fervaha, Foussias, Takeuchi, Agid, & Remington, 2015; Horan et al., 2015). A recent factor analysis found that these items loaded most strongly on the Intrapsychic Foundations/Motivation subscale (Mueser et al., 2017), and they predict cross-sectional and longitudinal functional outcomes in early and chronic schizophrenia (Choi et al., 2014; Fervaha, Foussias, Agid, & Remington, 2015; Saperstein, Fiszdon, & Bell, 2011).

Socio-affective capacity. As there are no measures of social cognition in RAISE-ETP, we derived the variable "socio-affective capacity" from the QLS as a proxy measure for higher order social cognitive abilities, such as social perception, theory of mind, and empathy. This measure consisted of item 20 "capacity for empathy" and item 21, "capacity for engagement and emotional with the interviewer" from the Intrapsychic Foundations subscale; they assess an individual's ability to perceive and respond to another person's perspective and affective state. Social perception, theory of mind, and empathy rely on partially shared neural circuitry and depend on intact functioning of the social brain (Green, Horan, & Lee, 2015; Shamay-Tsoory, 2011; Sparks, Mcdonald, Lino, O'donnell, & Green, 2010).

Cognition. A cognitive composite standardized Z-score was created from the Brief Assessment of Cognition using the average score of the six assessed cognitive domains (Keefe et al., 2004).

Negative symptoms were derived from the Positive and Negative Symptom Scale traditional three syndrome model composite score (Kay, Fiszbein, & Opler, 1987).

DUP, defined as time between onset of psychosis and initiation of antipsychotic medication, was measured in days at the time of study entry, and was log transformed due to skewness.

Secondary variables. Our analysis included psychopathology, substance use, psychological well-being (Browne et al., 2016), attitudes towards medications, age (log transformed) and treatment arm (Table 4.1) as additional variables which could influence functional outcomes and to identify more determinate edges among the primary variables (Ogarrio et al., 2016). Variable descriptions are included in the Supplemental Methods (Appendix C). Like the primary RAISE-ETP study, we did not include prescribed chlorpromazine equivalents in this analysis.

Study 2 Variables and Measures

Study 2 used the same variables as Study 1 for social functioning, occupational functioning, motivation, and socio-affective capacity and several of the same secondary variables, as detailed in Table 4.1.

Statistical Analysis

Independent sample t-tests for continuous variables and Pearson's chi-square tests for categorical variables tested for differences in demographic and clinical variables between 1) RAISE-ETP participants included and excluded from Study 1, and 2) participants in Study 1 and Study 2.

We used the Greedy Fast Causal Inference (GFCI) algorithm to estimate the causal relationships among baseline and six-month variables. GFCI searches the space of

all possible Partial Ancestral Graphs (PAGs) using a combination of goodness of fit statistics and conditional independence tests to identify the PAG that best models the causal process from which the data were sampled (Chickering, 2002; Ogarrio et al., 2016; Ramsey, 2015). In its first step, GFCI temporarily assumes that there are no unmeasured common causes of the observed variables and searches the space of all possible causal models to find the model which has the best penalized likelihood score. In its second step, it drops the assumption that there are no unmeasured common causes, and refines the graph produced by the first step by testing for all possible statistical inconsistencies that could have been induced by latent common causes. These inconsistencies are identified using conditional independence tests, and the graph is modified appropriately (Chickering, 2002; Ogarrio et al., 2016; Ramsey, 2015). In the resulting PAG, variables are represented as nodes in the graph. The type and orientation of an edge connecting two nodes specifies the nature of the modeled causal relationship (Figure 4.1). See the Supplementary Methods (Appendix C) and citations (Chickering, 2002; Ogarrio et al., 2016; Ramsey, 2015) for more detailed information on GFCI, including assumptions and proof of correctness. This process has been mathematically proven to be asymptotically correct, and has outperformed similar methods in simulations, where adjacencies and edge orientations in the output PAG have been shown to have high precision and recall on sample sizes comparable to the datasets studied here (Ogarrio et al., 2016).

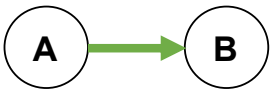
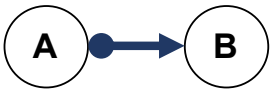
Edge Type	Meaning
	A is a direct cause of B. B is not the cause of A. There is no unmeasured confounder of A and B
	*A is a direct or indirect cause of B. B is not the cause of A. There is no unmeasured confounder of A and B
	A is a cause of B, OR there is a latent (unmeasured) variable that is a cause of A and B, OR both. B is not a cause of A
	One of the following is true: a) A is a cause of B, OR b) B is a cause of A, OR c) there is a latent (unmeasured) variable that is a cause of A and B, OR d) both a and c, OR e) both b and c

Figure 4.1. Greedy Fast Causal Inference Edge Types and Meaning.
*Note: When viewed in Tetrad 6.6.0, this edge type is represented as a thin green edge. We have used a blue edge here to distinguish the edge more easily from the thick green directed edge above.

The Tetrad software package version 6.6 was used for the GFCI analysis (https://cmu-phil.github.io/tetrad/manual/). Background knowledge included that the six-month variables could not cause baseline variables, and no variable could cause age. Model parameters include a Bayesian Information Criterion score, set to the standard penalty discount value of 1, and Fisher Z test, set to the default value of 0.01.

Effect Size Estimation and Model Fit Statistics

Raw and standardized effect sizes (ES) of the model-identified causal relationships were estimated by fitting a linear SEM to the PAG. Edges connecting to a possible latent variable were modeled as indirect covariations for the purposes of the SEM. The Comparative Fit Index (CFI) and Root Mean Square Error of Approximation (RMSEA) were inspected to assess model fit. The R package Lavaan 0.6.3 was used for

this analysis (Rosseel, 2012). Due to the prevalence of multiple possible latent variables in the CATIE validation study, model parameters were not estimated to avoid producing a SEM with low interpretability.

Graph Stability

The stability of the Study 1 and Study 2 PAGs were evaluated by running GFCI on 1000 jackknifed datasets containing 90% of the original dataset and 1000 bootstrapped datasets. The percentage of edges in the PAG that were confirmed in re-sampled graphs was calculated. Additional SEM comparison and sensitivity analyses were performed to assess for effects of measurement or construct overlap (see Supplementary Methods, Appendix C).

Results

Participants

After excluding 128 participants for missing data, study 1 included 276 participants from RAISE-ETP (Table 4.1). Excluded participants had higher scores on the Beliefs About Medications scale ($t=-2.16$, $p=0.03$). There were no statistically significant differences on any other baseline variables between participants included and excluded from the analysis (Supplementary Table 4.1, Appendix C).

Table 4.1

Study Sample Characteristics and Variable Descriptive Statistics

	Study 1 (N = 276)	**Study 2 (N = 187)**
	Mean (SD) or %	
Demographics		
Age (years)[a]	23 (4.9)	27.3 (6.1)
Gender: Male	74.3	80.2
Race		
American Indian or Alaskan Native	5.8	-
Asian	2.9	-
Black	35.1	-
Native Hawaiian or Pacific Islander	0.4	-
White	55.8	64.7
Ethnicity: Hispanic or Latino	18.5	-
Baseline Variables		
Treatment assignment to Coordinated Specialty Care	43.1	-
QLS social functioning	19.9 (8.6)	21.4 (10.5)
QLS occupational functioning	5.7 (6.7)	6.7 (5.3)
QLS motivation	7.7 (3.6)	8.4 (4.1)
QLS socio-affective capacity	8.0 (2.2)	8.0 (2.6)
Neurocognitive Composite Z score[b]	0.04 (1.0)	0.3 (0.9)
PANSS positive symptoms	18.9 (5.2)	18.0 (5.1)
PANSS negative symptoms	20.1 (5.2)	21.1 (6.7)
PANSS general symptoms	37.6 (7.7)	37.4 (8.8)
Calgary Depression Scale for Schizophrenia	4.4 (3.9)	4.5 (4.0)
Clinical Global Impressions-Severity	4.1 (0.8)	4.0 (1.0)
Duration of untreated psychosis (days)	185.7 (271.9)	-
Days of alcohol use in last month	1.9 (4.7)	-
Days of cannabis use in last month	3.2 (7.6)	-
Well-being scale total score	4.0 (0.9)	-
Mental Health Recovery Measure total score	73.3 (18.1)	-
Stigma Scale total score	4.0 (1.2)	-
Brief Evaluation of Medication Influences and Beliefs	4.9 (1.0)	-
Years of antipsychotic treatment	-	2.4 (1.6)
Face Emotion Discrimination Task correct responses	-	24.9 (3.7)
Six-Month Variables		
QLS social functioning	22.9 (9.8)	23.7 (10.7)
QLS occupational functioning[a]	9.0 (7.5)	7.5 (5.8)
QLS motivation	8.6 (3.6)	8.8 (4.0)
QLS socio-affective capacity	8.0 (2.4)	8.2 (2.6)

[a]Age $p = <0.001$, $t = -8.0$; QLS occupational functioning $p = <0.001$, $t = 4.0$

[b]Neurocognitive tests utilized differed between groups and means were not compared. Study 1 utilized the Brief Assessment of Cognition and Study 2 utilized a customized panel of neurocognitive tests. PANSS = Positive and Negative Symptom Scale, QLS = Quality of Life Scale; PANSS = Positive and Negative Symptom Scale

Blank cells indicate variable not available in dataset

Study 2 included 187 participants from CATIE (Table 4.1). Descriptive statistics were not compared between included and excluded CATIE participants because the included subset was selected to best match the RAISE-ETP cohort. Study 1 participants were significantly younger than Study 2 participants ($t = -8.0$, $p < 0.001$) and had better six-month occupational functioning ($t = 4.0$, $p < 0.001$) (Table 4.1).

Study 1 Primary Analysis

The full PAG for the RAISE-ETP cohort is shown in Figure 4.2a, and a functional outcome subgraph is shown in Figure 4.2b. The strength and sign of modeled causal relationships in the functional outcome subgraph are provided in Figure 4.3 and all effect sizes (raw and standardized) are provided in Supplementary Table 4.2 (Appendix C). The raw effect sizes are reported here. Fit statistics indicated an appropriate fit of the model to the data (CFI = 0.884; RMSEA = 0.066).

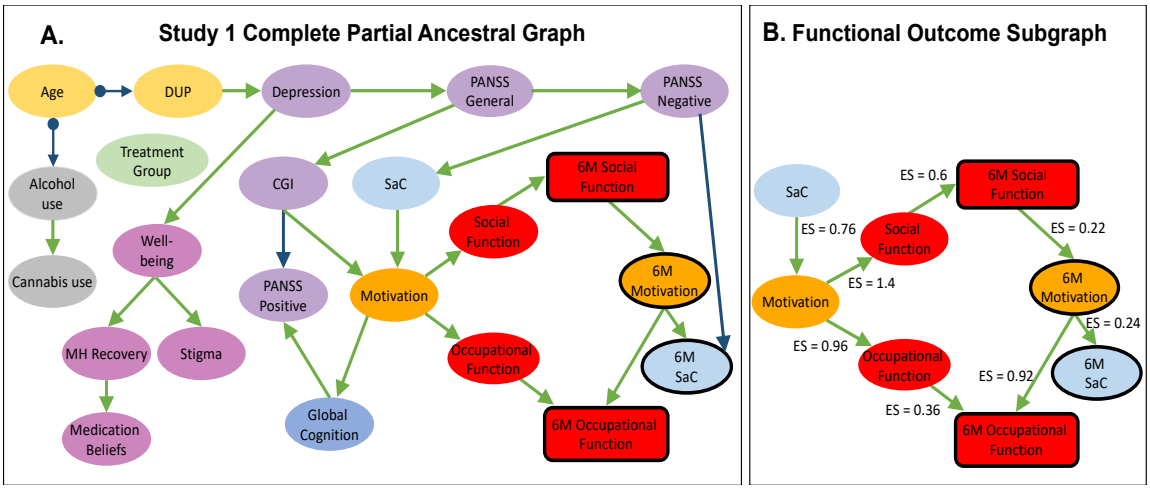


Figure 4.2. Study 1 Complete Partial Ancestral Graph and Functional Outcome Subgraph. All variables represent baseline unless specified as 6M (6 month). Alcohol use = days of alcohol use in previous month; Cannabis use = days of cannabis use in the past month; CGI = Clinical Global Impressions-Severity score; Depression = Calgary Depression Scale for Schizophrenia; DUP = duration of untreated psychosis (log transformed); Global Cognition = Brief Assessment of Cognition composite Z score; Medication Beliefs = Brief evaluation of medication influences and beliefs total score; MH Recovery = Mental Health Recovery Measure total score; PANSS = Positive and Negative Symptom Scale; SaC = Socio-affective capacity; Stigma = Stigma scale total score; Treatment Group = randomized into Coordinated Specialty Care versus Treatment as Usual. Wellbeing = Well-being scale total score.

Causal pathways to six-month social functioning. Our model contains one causal pathway leading to six-month social functioning: baseline socio-affective capacity is a cause of motivation (ES = 0.77), which is then a cause of baseline social functioning (ES = 1.5), which is then a cause of six-month social functioning (ES = 0.6).

Causal pathways to six-month occupational functioning. Our model contains two causal pathways leading to six-month occupational functioning. Path 1: baseline motivation is a cause of baseline occupational functioning (ES = 0.96), which then is a cause of six-month occupational functioning (ES = 0.36). Path 2: six-month social

functioning is a cause of motivation (ES = 0.21), which in turn is a cause of occupational functioning (ES = 0.92).

Causal effects of cognition, negative Symptoms, and DUP. Cognition is not included in a causal pathway to social or occupational functioning. Negative symptoms are a direct cause of socio-affective capacity at baseline (ES = -0.27), but their effect on social and occupational functioning is mediated by socio-affective capacity and motivation. DUP is upstream of the causal pathway to functional outcomes, and its effect is mediated by several variables including socio-affective capacity and motivation.

Six-month causal cycles. Our model contains several causal cycles which unfold over a period of six months, as shown in the augmented rolled graph (Figure 4.3). For example, socio-affective capacity causes motivation at baseline (ES = 0.76), and at six months, motivation causes socio-affective capacity (ES = 0.24). Similarly, motivation causes social functioning at baseline (ES = 1.4), and at six months, social functioning causes motivation (ES = 0.22). Thus, those with better socio-affective capacity at baseline have better motivation, and sustained improvements in motivation at six months lead to improved socio-affective capacity: a virtuous cycle. Motivation and social functioning also form a virtuous cycle: those with better motivation at baseline consequently enjoy better social functioning, which feeds forward to better motivation at six months.

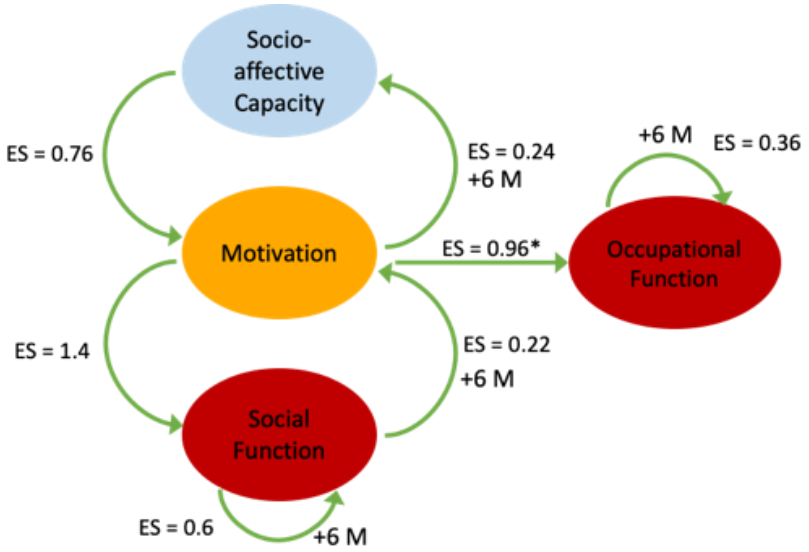


Figure 4.3. Study 1 Augmented Rolled Graph.
*Causal effect size for baseline motivation on baseline occupational functioning. The causal effect size from six-month motivation to six-month occupational functioning is 0.92. ES = effect size. +6 indicates a six-month time cycle over which the effect occurred.

Study 1 Graph Stability

The jackknife had 100% concordance with all graph features (i.e., edge presence, edge absence and edge orientation) in the functional outcome subgraph and the full PAG. The bootstrap had 100% concordance with all features in the functional outcomes subgraph (Supplementary Table 4.3, Appendix C). We also tested a model in which the motivation and socio-affective capacity variables covary instead of being separate variables with the causal relationships detailed above, however our original model had better fit ($p < 0.0001$, see Supplementary Methods, Appendix C). This is expected because GFCI is capable of modeling unmeasured common causes, therefore if motivation and socio-affective capacity are better represented by a single factor GFCI should indicate the possibility of a latent variable.

Study 2 Primary Analyses

The overall structure of the PAG for the functional outcome subgraph in Study 2 is similar to Study 1 (Figure 4.4). Relationships between baseline and six-month socio-affective capacity, motivation, and social and occupational functioning variables are maintained in the Study 2 PAG, supporting the findings from Study 1. Some edge orientations in this graph are less determinate, which permits but does not confirm the corresponding orientations found in Study 1.

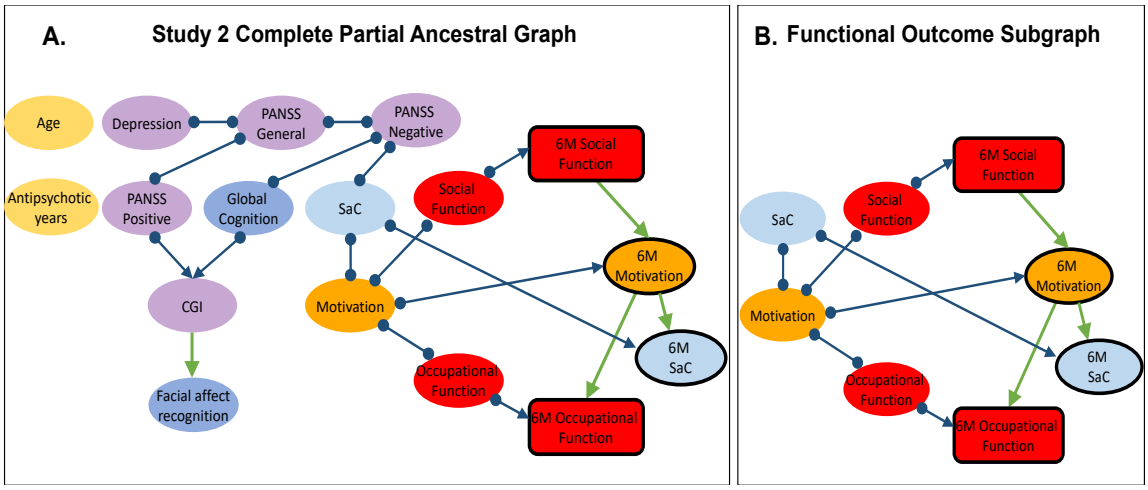


Figure 4.4. Study 2 Complete Partial Ancestral Graph and Functional Outcome Subgraph. All variables represent baseline unless specified as 6M (six-month). Antipsychotic years = years of antipsychotic use; CGI = Clinical Global Impressions-Severity score; Depression = Calgary Depression Scale for Schizophrenia; Facial Affect Recognition = Face emotion discrimination task correct responses; Global Cognition = Cognition composite Z score; PANSS = Positive and Negative Symptom Scale, SaC = Socio-affective capacity

Study 2 Graph Stability

The jackknife graph had 100% concordance with all graph features for the functional outcome subgraph. The bootstrap graph resulted in two dropped edges (connecting baseline to six-month socio-affective capacity and baseline motivation to six-

month socio-affective capacity), and had more determinate edge orientations for two edges (connecting baseline to six-month occupational functioning and baseline to six-month social functioning) when compared to the functional outcome subgraph in the primary PAG (Supplementary Table 4.3, Appendix C).

Discussion

Summary of Causal Pathway Findings

We used causal discovery modeling on a large sample of patients with first episode schizophrenia, to model which variables *plausibly cause* social and occupational functioning six months after entering treatment. We discovered a primary causal pathway in our model with large effect sizes from baseline socio-affective capacity to motivation, and from motivation to both social and occupational functioning at six months. Interestingly, cognition did not play a causal role; and DUP and negative symptoms indirectly influenced social and occupational functioning. These results may indicate the importance of vigorously and specifically targeting *socio-affective capacity and motivation* as soon as possible after a young individual enters care. Further, the discovered causal six-month cycle between socio-affective capacity and motivation suggests that early gains in these areas will be self-sustaining through a positive feedback loop. To the best of our knowledge, most evidence-based treatment programs do not explicitly identify these as critical targets of intervention nor directly assess them as part of patient outcome and program evaluation.

We also uncovered *a modeled causal cycle between social functioning and motivation*. At baseline, motivation was a cause of social functioning, and at six months social functioning was a cause of motivation. Higher motivation then led to higher

occupational functioning. A recent SEM study using RAISE data found that social functioning, but not occupational functioning, predicted later motivation (Fulford et al., 2017). Directly improving *social functioning* may be a third critical early treatment target for maintaining motivation and ultimately improving occupational functioning (Fulford et al., 2017).

Possible Mechanisms for the Causal Pathways and Cycles

Socio-affective capacity and motivation. Socio-affective capacity as measured in this study may capture aspects of social perception, theory of mind, and empathy during the QLS interview. As such, this measure may reflect social cognition abilities and the capacity to engage interpersonally. Shared neural mechanisms underlie social cognition and intact reward processing (necessary for adaptive motivated behavior), including important hubs in the ventromedial prefrontal cortex and the anterior cingulate (Fareri & Delgado, 2014); moreover, social stimuli are primary reinforcers for reward networks and activate frontal-striatal circuits (Fareri & Delgado, 2014). Deficits in perceiving and processing social stimuli and aberrant functioning of medial prefrontal circuitry can likely affect aspects of reward processing and motivated behavior. Consistently, we have found that social cognition training drives both adaptive changes in motivated behavior (Fisher et al., 2017; Miley et al., 2020) and medial prefrontal cortex neural activity (Subramaniam et al., 2012).

Motivation and social functioning. Individuals with psychotic disorders exhibit not only impaired social cognition (Fett et al., 2011), but reductions in social drive (Cornblatt et al., 2012; Tarbox & Pogue-Geile, 2008), and specific deficits in the valuation of social reward (Catalano, Heerey, & Gold, 2018). Poor motivation for social

rewards may therefore drive impairments in social functioning. At the same time, social inclusion and adaptive social functioning are critical developmental accomplishments during the adolescent and young adult years (Blakemore, 2008; Filia, Jackson, Cotton, & Killackey, 2019; Filia, Jackson, Cotton, Gardner, & Killackey, 2018; Gardner, Filia, Killackey, & Cotton, 2019), coinciding with the typical age of onset of psychosis. Social exclusion during this period may lead to the development of socially defeatist beliefs, further impeding motivated behavior for social participation (Campellone, Sanchez, & Kring, 2016). Thus, directly targeting social functioning may lead to enriched social environments that reinforce social rewards and improve the valuation of these rewards from continued exposure to positive social experiences, resulting in improved motivated behavior. Improved motivation may in turn promote engagement in goal setting and pursuit of occupational endeavors, and feedback to social cognitive functioning via the modulation of shared neural networks which underlie social cognitive and reward processes.

Causal Roles of Negative Symptoms, Cognitive Impairment, and DUP

The negative symptoms of schizophrenia are strongly associated with poor functional outcomes (Milev et al., 2005; Robertson et al., 2014). While negative symptoms were in the causal pathway to functional outcome in our model, their effect was at least partially mediated by socio-affective capacity and motivation. Socio-affective capacity and motivation share some, but not full, conceptual overlap with negative symptoms as measured by the PANSS subscale, which also includes measures of blunted affect and alogia. That the effect of negative symptoms in our model was at least partially mediated by socio-affective processing and motivation may suggest that

specifically targeting the *asociality* and *avolition* aspects of negative symptoms – which rely on intact socio-affective and motivation processes - may be most likely to drive improvements in both social and occupational functioning.

Unexpectedly, baseline cognitive impairment was not found to be in the causal pathway to functional outcomes, despite the large body of evidence linking cognition to functional outcomes (Fett et al., 2011; Santesteban-Echarri et al., 2017). It is possible that significantly impaired cognition causes poor functional outcomes, but that this relationship does not hold with only mildly or moderately impaired cognition, leading to unstable or missed relationships in causal discovery analyses. It is also possible that the relationship between cognition and functional outcomes is mediated by variables not measured in this study, such as more specific measures of social cognition, reward processing, or other neural/neurocognitive operations (Bhagyavathi et al., 2015; Gard, Fisher, Garrett, Genevsky, & Vinogradov, 2009; Green, Hellemann, Horan, Lee, & Wynn, 2012). In our validation study drawn from the CATIE trial, cognition was possibly on a causal pathway to functional outcomes, however the direction of these relationships cannot be determined. RAISE-ETP used a less comprehensive cognitive assessment battery compared to CATIE, and it is possible that this resulted in the observed differences between the two datasets.

The association of DUP with functional outcomes in schizophrenia has also been strongly supported by previous research (Penttilä et al., 2014); however, DUP was upstream in the causal pathways to functional outcomes in our model. It remains largely unknown whether shortening DUP will lead to improved long-term outcomes (Penttilä et al., 2014), and the specific mechanisms through which DUP impacts functional outcomes

is unknown. Our model suggests that shortening DUP could impact functional recovery via its direct and downstream effects on several other clinical features, including depression, global disease severity, negative symptoms, motivation, and socio-affective capacity.

Unmet Treatment Needs in Early Schizophrenia

Our results point to critical unmet therapeutic needs in current coordinated specialty care (CSC) early intervention services, which are now the gold standard treatment for first episode schizophrenia. While CSC programs indirectly aim to improve social functioning, they currently lack explicit and consistently delivered interventions which robustly target social cognition or motivation as primary outcomes. Yet, deficits in social cognition and motivation are malleable to targeted interventions in early schizophrenia, such as social cognitive training, social skills groups, recovery focused goal setting and digitally delivered motivational coaching (Eack et al., 2009; Fernandez-Gonzalo et al., 2015; Fisher et al., 2017; Fulford, Piper, Meyer-Kalos, & Mueser, 2020; Roberts et al., 2014; Schlosser et al., 2018). Our results highlight the need for research on the integration of existing and novel social cognition and motivation interventions into CSC programs. Further, they suggest that specifically targeting social cognitive processes when individuals first enter treatment may exploit a positive feedback relationship between social cognition and motivation, thereby driving improved social and occupational functioning. Interventions specifically targeting social recovery have been shown to elicit improvements in social engagement when added to early intervention services (Fowler et al., 2018) and should continue to be evaluated as critical treatment components.

Validation and Limitations

Our validation study from the CATIE dataset did not contradict the results of our primary analysis and supported many of the findings. The overall structure of the functional outcome subgraph was very similar to the RAISE-ETP model even though many edge orientations in the graph were less definitive. The less definitive relationships could be due to differences in sample size, which can influence the ability of the GFCI algorithm to rule out alternative causal models. RAISE-ETP participants were younger and included individuals aged 15-17 who may have different supports and functional expectations than adult patients. CATIE participants had greater illness chronicity, longer duration of exposure to medications, and an established diagnosis of schizophrenia (versus one lifetime episode of psychosis), which could lead to more heterogeneity in symptoms and functioning. Temporally, enrollment dates for RAISE-ETP and CATIE were approximately a decade apart during a movement towards recovery-oriented care. It is likely that these differences could also impact results pertinent to longitudinal functional outcomes, including the directionality and/or strength of causal relationships among our primary variables. These differences may lend support to the value of our validation study, suggesting that our results could generalize beyond illness phase and contextual factors and are not simply attributed to specific features of the population studied.

Our study has several limitations. First, because RAISE-ETP did not include laboratory measures of social cognition, we relied on interviewer-rated proxy measures of socio-affective capacity and engagement with the interviewer, the construct validity of which is unknown. Until validated by future research, our interpretation of the

relationship between socio-affective capacity, motivation and functional outcomes should be considered in the context of this limitation. While our motivation measure has been validated in previous research, it is similarly an interviewer-rated item. Future prospective research must build on our analyses and include well-validated and robust social cognition and motivation measures to confirm the causal influence of these domains on functional outcomes. We focused our analysis on clinical predictors (i.e., symptoms, cognition) that could be treatment targets, and did not include variables reflecting treatment engagement or prescribed antipsychotic dose equivalents, which could also impact short-term functional outcomes. Some variables had non-Gaussian distributions which could affect model performance. The primary method of analysis, GFCI, was recently developed, and although some benchmarking has been done, its finite-sample performance has not been completely characterized. GFCI generates a model of the plausible causal relationships from which the data were sampled, and its correctness relies on some assumptions that cannot be directly tested but are plausible for the studied data. Statistical models can be wrong; however, they are highly useful if accurate. GFCI also cannot identify the presence of synchronous causal cycles, if there are any.

Conclusion

To our knowledge, this is the first study to model direct causal pathways between socio-affective abilities, motivation, and social and occupational functioning in an early schizophrenia sample, using a data-driven causal discovery analysis. These findings have high clinical relevance and underscore the importance of specifically and vigorously targeting social cognitive processes and motivation as early as possible in the course of

treatment to enhance social and occupational recovery. In addition, our findings suggest that promoting social functioning may have continued downstream effects on motivation, socio-affective capacities, and occupational functioning, and should also be a specific target of early intervention services.

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Conflicts of Interest

Drs. Ma and Kummerfeld and Ms. Miley report no financial relationships with commercial interests. Dr. Meyer-Kalos has received consulting fees from the NAVIGATE program for first episode psychosis and Happify.com. Dr. Bond has received consulting fees and/or research grants from Alkermes PLC, Myriad Genetics, and NuBiyota. Dr. Vinogradov serves on the Scientific Advisory Boards for the

following organizations: Mindstrong, Inc., Alkermes, Inc., and Psyberguide. She also has scientific collaborations with scientists at PositScience, Inc.

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Chapter 5: Discussion

The unifying goal of this dissertation is to advance the science of social functioning deficits in schizophrenia spectrum disorders to lead to better identification and treatment of those at risk for functional decline. Together the three manuscripts of this dissertation leverage translational data-driven approaches to explore the bio-behavioral determinants and risk factors for functional outcomes, inform individual prognostic models, and identify potential high impact treatment targets that, if modified, could improve social recovery rates. This final chapter highlights and synthesizes primary findings from this dissertation and offers a discussion of the implications of the results for research and practice.

Summary of Findings

Chapter 2 (Manuscript 1): Critical Review of Individual Prognostic Models

This critical review manuscript characterizes the state of the science of individual prognostic models for functional outcomes in schizophrenia spectrum disorders with a focus on model performance, salient model predictors, and methodological considerations. Results from this chapter may inform future individual prognostic research and improve the conceptualization of functional impairments by identifying themes in important model predictors across biological, clinical, cognitive, and functional domains. Twelve studies with machine learning models relying on a range of bio-behavioral predictor modalities were included and reviewed. The heterogeneity of methods and specific methodological concerns (i.e., small sample sizes, non-specific functional outcome measures with arbitrary dichotomization, and lack of stringent

validation procedures) present challenges for synthesis of results, and the following summary should be interpreted in this context.

Functional outcomes were predicted with a wide range of accuracies (43 – 87%). Models relying on neurobiological predictors tended to have small sample sizes with concerns for overfitting, and more heterogeneity in performance relative to models relying on clinical and functional predictors. Combining neurobiological and clinical or functional data modalities resulted in higher accuracies when compared to models relying on only one domain. Few studies directly compared the accuracies of models built with different modalities, hindering definitive assessment of whether the added costs of including neurobiological data is justified for incremental improvements in model accuracy. Results of this review do not indicate that any particular data modality should be included over others in future individual prognostic model research. This may suggest that less complex models using easily obtained clinical and functional data should be pursued to promote clinical translation, without concerns for substantially sacrificing model accuracy.

Common themes for important model predictors included psychosis and other psychiatric symptoms (i.e., depression, substance use disorders), baseline level of functioning, and structural brain measures in the fronto-temporal regions and occipital, cerebellar, and thalamic structures. Conflicting or sparse evidence exists about linkages between the commonly identified clinical predictors and functional outcome (Rabinowitz et al., 2012; Santesteban-Echarri et al., 2017), and therefore, these predictors should be further explored as potential risk markers and treatment targets for functional deficits. The identified brain regions are in line with existing evidence (Wojtalik, Smith,

Keshavan, & Eack, 2018) and thus may add to current conceptual models of social functioning which typically lack biological determinants.

Overall, this review indicates that development of clinically useful individual prediction models for functional outcomes in schizophrenia spectrum disorders is in a nascent stage. In addition to attention to gold-standard analytic methods and inclusion of well-defined outcome measures, results highlight a need to evaluate and directly compare predictive models which utilize different predictor modalities to understand how to optimally balance accuracy and clinical usability.

Chapter 3 (Manuscript 2): Individual Prediction of Functioning in Healthy Adults

In this study, we used bio-behavioral data from the Human Connectome Project Healthy Young Adult sample (age 22-35, N=1,101) (Van Essen et al., 2013) to build individual prediction models from comprehensive neuroanatomical, cognitive, psychological and other behavioral data, compare performance of models which utilize different combinations of predictor modalities, and identify which predictors are most salient to the social functioning models. To our knowledge, there are no comprehensive investigations of individual social functioning outcomes in healthy young adults, yet such research could inform the understanding of specific changes that occur as young individuals develop psychiatric illnesses such as schizophrenia.

Integrating bio-behavioral data and directly comparing models across data modalities allows for insights into the relative importance of specific domains to individual prediction of social functioning - a research gap identified in Chapter 2 (Manuscript 1). To avoid arbitrarily dichotomizing the social functioning outcome measure, we utilized a regression machine learning approach (Support Vector

regressions) to estimate social functioning from variable sets of increasing complexity consisting of: 1) a brain-only model, 2) a brain-cognition model, 3) a cognition-behavioral model, and 4) a combined brain-cognition-behavioral model. Only the combined and cognition-behavioral models significantly predicted individual social functioning scores, and these models performed equally well (R^2 =0.53, 95% CI [0.38, 0.62] for each model). Thus, adding neuroanatomical data to the cognition-behavioral models did not enhance model performance. The brain and brain-cognition models had poor performance (R^2 = 0.06, 95% CI [-0.07, 0.16] and R^2 = 0.11 95% CI [-0.05, 0.23], respectively) and were significantly worse at social functioning prediction than the combined and cognition behavioral models. These results overall align with the findings of Chapter 2 which suggested that prognostic models relying on behavioral data may promote clinical usability while maintaining predictive accuracy.

In the combined brain-cognition-behavioral model, negative affect, psychological wellbeing, withdrawn symptoms, extraversion, and cortical thickness in right and left rostral middle frontal gyri and left superior temporal gyrus were the most salient predictors. In addition to the psychological/behavioral variables of the combined model, agreeableness and aggression symptoms were identified as important variables in the cognition-behavioral model. No cognitive variables were identified as top predictors in any models, an unexpected finding. The neuroanatomical findings align with research linking brain to functional outcomes in schizophrenia (Wojtalik et al., 2018), bipolar disorder (Sartori et al., 2018), and depression (Koutsouleris et al., 2018). Thus, while the neuroanatomical models were not useful over and above the cognitive-behavioral models for prediction of outcomes, they may point to transdiagnostic neural markers of social

functioning. The behavioral variables identified may indicate potential risk markers and treatment targets for social functioning impairments to be explored in future research.

Chapter 4 (Manuscript 3): Causal Pathways to Social & Occupational Functioning

Chapter 4 presents a published manuscript titled, "Causal Pathways to Social and Occupational Functioning in the First Episode of Schizophrenia: Uncovering Unmet Treatment Needs" (Miley et al., 2021). In this chapter, we shifted the focus from prognostic models and identifying *predictors* of social functioning to identifying *potential causes* of functional outcomes that could be high impact treatment targets in first episode schizophrenia. We obtained a rich set of measures spanning demographic, clinical, cognitive, and psychosocial domains for 276 participants in the Recovery After an Initial Schizophrenia Episode Early Treatment Program (RAISE-ETP) trial (Kane et al., 2016). We used a novel causal discovery algorithm, Greedy Fast Causal Inference, to model causal relationships across the 22 baseline measures and social and occupational functioning at six-month follow up. Results were validated in an independent dataset drawn from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study (Stroup et al., 2003).

Our primary finding was a modeled causal pathway from baseline socio-affective capacity to motivation, and from motivation to both social and occupational functioning at six months. We found large effect sizes for the relationships of socio-affective capacity on motivation and motivation on social and occupational functioning, suggesting that intervening on either of these targets could have significant effects on functional outcomes. A second modeled causal pathway to occupational functioning was identified: at six-months, social functioning was a cause of motivation, which was then a cause of

occupational functioning. Finally, we discovered two causal cycles over the six-month period, which may serve as positive feedback loops: one between socio-affective capacity and motivation, and the second between motivation and social functioning. These findings suggest that 1) early improvements in socio-affective capacity and motivation may be self-sustaining through positive feedback, and 2) targeted interventions for social functioning could be important for maintaining motivation, ultimately leading to gains in occupational functioning. Current gold-standard treatment models for first episode schizophrenia do not include components specifically targeting socio-affective capacity (i.e., social cognition) and motivation, yet effective interventions do exist. Integration of existing and novel interventions into care may be a critical component of enhancing social and occupational functioning in early schizophrenia.

Synthesis

The work of this dissertation comes together through two unifying questions. First, how can we better identify individuals at risk for poor social functioning, with a focus on schizophrenia spectrum disorders? And secondly, once we identify such individuals, how can we improve treatment to promote their robust recovery in social and occupational functioning? Accurate identification will require individual-level prediction and an understanding of the risk factors and determinants of social functioning outcomes, while improving treatment will require understanding the causal processes that contribute to functional decline. Schizophrenia and other psychotic disorders are multifaceted and heterogeneous psychiatric syndromes involving a complex interplay of biological, clinical, and social/environmental factors (Brown, 2011; Moran et al., 2016; Owen, Sawa, & Mortensen, 2016). Integrating information across these domains may be

necessary to understand and intervene on the day-to-day sequalae of these disorders, including social functioning impairments. This synthesis addresses these unifying questions in the context of results from the three manuscripts discussed above.

Individual Prognostic Models

Results from Chapters 2 (Manuscript 1) and 3 (Manuscript 2) generally did not support inclusion of biological measures in individual prognostic models. In our analysis of the Human Connectome Project sample of healthy young adults, the brain-only model had poor performance, and adding brain measures to the combined model did not increase model performance. In the critical review of 12 studies reporting on individual prognostic models for functional outcomes in schizophrenia spectrum disorders, studies which relied on brain measures demonstrated more heterogeneity in performance, and overall did not outperform models built on other data modalities. Yet, some studies found that combined brain-behavioral models offered better accuracy by margins of 6-9% (de Wit et al., 2017; Koutsouleris et al., 2018), with a particular role of combined models in clinically ambiguous cases (Koutsouleris et al., 2018). The limited variance in brain structure likely present in the healthy adult Human Connectome Project sample could have influenced performance of the brain-only models. Nonetheless, results from these studies may point towards focusing prognostic model development on utilizing less costly and more readily available clinical data. Results from Chapter 4 (Manuscript 3) suggest that inclusion of motivation, social cognition, and baseline functioning measures may especially enhance model performance due to their role as potential causes of functional outcomes.

Bio-behavioral Conceptualization and Treatment Targets

Results of this dissertation advance a bio-behavioral conceptualization of risk-markers and determinants of functional impairments. At the biological level, results from Chapters 2 (Manuscript 1) and 3 (Manuscript 2) both point to frontal-temporal brain structures as potentially important for social functioning outcomes, which is largely consistent with previous research in schizophrenia (Wojtalik et al., 2018), bipolar disorder (Sartori et al., 2018) and depression (Koutsouleris et al., 2018). It is a significant finding that similar brain regions were identified across the varied schizophrenia spectrum and healthy populations included across these two manuscripts, pointing to potential transdiagnostic biomarkers to be further explored in future research. Fronto-temporal brain networks have been broadly implicated in the pathophysiology of schizophrenia, and aberrations have been linked to a number of clinical and social cognitive symptoms which could impact social functioning.

In terms of clinical symptoms, results from the critical review in Chapter 2 (Manuscript 1) suggest positive symptoms (i.e., hallucinations, delusions), negative symptoms (i.e., diminished emotional and verbal expressiveness, asociality, avolition, and anhedonia), depression, and substance use may be relevant to functional outcomes across clinical high risk, first episode, and chronic schizophrenia samples. Some similar constructs were identified as important to individual prediction models in a healthy young adult sample in Chapter 3 (Manuscript 2), including negative affect, withdrawn symptoms, and aggression – which have conceptual overlap with negative and depression symptoms.

Additionally, in the analysis for Chapter 4 (Manuscript 3), negative symptoms were in the primary pathway to social and occupational functioning outcomes, although their effect was mediated by socio-affective capacity and motivation. Socio-affective capacity and motivation do share conceptual overlap with the broader negative symptom construct, which may suggest the asociality and avolition negative symptoms are most relevant to social functioning impairments and thus should be the focus of treatment efforts. Indeed, results from Manuscript 4 indicate that improving social and occupational recovery rates may rely on explicitly targeting motivation and socio-affective capacity as early as possible for individuals experiencing schizophrenia, providing guidance for future intervention development and implementation studies.

Predictive analytics, such as those employed in Chapter 3, can be powerful tools to parse large and diverse datasets to identify risk factors and candidate treatment targets, however such models do not provide information about the direction of causation, and thus provide limited inference to guide clinical research and practice. If the ultimate goal is to improve a health outcome, researchers must go beyond prediction to identifying the potential causes of an outcome, that if remediated, could result to clinical improvement. A strength of this dissertation is the integration of both predictive and causal analytics to not only expand the conceptualization of social functioning impairments, but to also identify plausible critical intervention points.

Limitations

There are a number of limitations to consider when interpreting the results of this dissertation. A primary limitation is the lack of a cohesive psychotic disorder sample (i.e., first episode schizophrenia or chronic schizophrenia) across the three manuscripts.

Although understanding relationships between bio-behavioral measures and social functioning in healthy adults can establish a baseline and inform the understanding of changes that occur in the development of psychiatric illness, results may not necessarily translate to schizophrenia spectrum disorders. For example, limited variance across brain and cognitive measures in a healthy sample (relative to a schizophrenia sample) could have impacted the ability of the machine learning algorithm to discriminately use these measures for prediction of functioning, even with a relatively large sample size (Avinun, Israel, Knodt, & Hariri, 2020; Masouleh, Eickhoff, Hoffstaedter, Genon, & Alzheimer's Disease Neuroimaging Initiative, 2019). This dissertation relied on secondary data analysis and the machine learning methods required large datasets – to our knowledge, no datasets of similar magnitude of samples and depth of measures in psychotic disorders exist for accessible utilization.

Similarly, the social functioning outcome measures and measures used for varied clinical constructs (i.e., symptoms and cognition) differed across manuscripts, making direct comparison of results difficult and potentially leading to some of the notable heterogeneity in results that characterizes studies reviewed in Chapter 2 (Manuscript 1). Data-sharing consortiums with harmonized data elements and large sample sizes are imperative to driving forward data-driven research for the many pressing schizophrenia research priorities.

Limitations for each manuscript are further reviewed in their respective chapters; primary limitations are reviewed here. In Chapter 2 (Manuscript 1), a number of methodological concerns for reviewed studies resulted in significant challenges to interpreting results of the body of work. A structured risk of bias assessment, which

could aid in further identifying methodological strengths and weaknesses of the studies, was not performed.

In Chapter 3 (Manuscript 2), primary limitations included limited diversity in the sample, use of cross-sectional data, and lack of external validation. Future research must extend these results to diverse populations and prediction of longitudinal outcomes. Predictive models do not provide information regarding causality, limiting the interpretation of the relationships between identified top predictors and social functioning, and we did not model potential causal relationships with causal discovery methods.

Finally, in Chapter 4 (Manuscript 3), due to limitations of the dataset, our measure of socio-affective capacity was created from an interviewer-rated scale not explicitly designed to measure social cognitive abilities, the construct validity of which must be confirmed in future research. The methods employed in this chapter produce causal *models* – modeled relationships should be tested experimentally to confirm the causal relationships.

Implications for Nursing Research and Practice

This research was undertaken due to an identified need in the literature (Miley, Hadidi, Kaas, & Yu, 2020), but perhaps more importantly, due to my personal experiences caring for individuals with psychotic disorders as a psychiatric nurse practitioner. A diagnosis of schizophrenia or other psychosis is devastating and life-altering for patients and families, and too often leads to an unravelling of personal and professional goals. With onset in the late adolescent to young adult years, this occurs at a critical time in a young person's life course when they are developing their unique sense

of purpose (Arnett, 2000; Damon, Menon, & Cotton Bronk, 2003; Gardner, Filia, Killackey, & Cotton, 2019). As I partner with patients and families, I see that first and foremost, they want cures for mental illnesses that will quickly and completely treat the underlying disorder. While cures are likely not on the immediate horizon for schizophrenia, we must strive to move clinical science and practice forward in a way that promotes recovery and centers what individuals experiencing this mental illness want for themselves: full and personally meaningful lives, connected relationships, and work that brings purpose.

Implications for Research

Prognostic tools for functional outcomes. As we enter an era of precision healthcare, there is great promise for machine learning and other data-driven methods to improve the dominant models of diagnosis, prognosis, and treatment (Dwyer, Falkai, & Koutsouleris, 2018), including for patient-centered outcomes like social functioning. Our results highlight, however, that to advance towards clinically useful individual prognostic tools for functional outcomes, several methodological considerations must be systematically addressed. It is critical that the research community prioritizes building collaborative data consortiums that will allow for the necessary sample sizes to rigorously develop and externally validate individual prediction models (Sanfelici, Dwyer, Antonucci, & Koutsouleris, 2020). This will require harmonization of data elements (i.e., symptom and functional outcome measures) and sufficient geographical diversity to ensure representative samples. To promote clinical translation, research teams must include both clinical domain experts and artificial intelligence experts to avoid common

design and analysis methods pitfalls that limit research implementation (Sanfelici et al., 2020; Wolff et al., 2019).

To impact patient outcomes, future research must be designed with clinical translation and implementation as the ultimate goal. The current and dominant paradigm in mental health research focuses on identifying novel biological markers and treatment targets that are proximal to hypothesized psychopathology (Carpenter, 2020). This focus is important and necessary to understand the pathophysiology of psychiatric diseases in sufficient detail to foster mechanistic research into potential cures and novel interventions. Yet, this paradigm has scarcely led to clinically useful tools or treatments. A more holistic and less reductionist approach to understanding the sequalae of psychiatric disorders – such as impairments in social functioning – may require a shift of focus to clinical, behavioral, and social factors that more directly influence outcomes and can be specifically targeted for intervention. Such a shift could be critical for promoting translation of predictive tools by relying on easily obtainable metrics that are available in everyday clinical practice. Nursing science, which historically and uniquely balances biological symptom science and a holistic and contextual perspective to understanding illnesses and their impacts on patient-centered outcomes (National Institute of Nursing Research Strategic Plan Working Group, 2022) can fill a critical gap in mental health research.

Importantly, we found in Chapters 2 and 3 that inclusion of neurobiological data did not consistently and robustly improve prognostic accuracy for functional outcomes. Additionally, our literature review revealed that, to date, clinical applications from prognostic models are absent. Future next research steps should evaluate how to best

collect and utilize clinical data to build predictive models for functional outcomes that can support clinical decision making in real-world settings. Results from Chapter 4 suggest that clinical data related to social cognition and motivation may be especially important to measure and track, and future research is needed to evaluate whether systematically measuring these informs clinical care and patient outcomes. Studies that leverage causal discovery methods to build individual-level models may be especially informative to patients and clinicians; to date, they have not been investigated in psychosis domains. Finally, the synergistic effect of integrating biological and behavioral data – as shown by key studies in the critical review (de Wit et al., 2017; Koutsouleris et al., 2018) – should be further explored for usefulness in improving prognostication for select cases.

More broadly, clinical translation and implementation of predictive tools will not only rely on a better alignment of the data inputs and the outcome of interest, but also on an integration of clinical domain and analysis experts. Implementation of predictive tools is often hindered by complexities of existing clinical environments and workflows which prevent even highly accurate predictive models from supporting clinical care, such as ease of data acquisition, clinician capacity, and perceived value of the tool at the level of patient, clinician, and health system (Jung et al., 2020). Emphasizing the role of key stakeholders in the design of prognostic tool research – including clinicians, informaticians, and administrators who are responsible for resource allocation – is critical to ensuring a match between the research methods and eventual clinical application.

Improving treatment to promote social recovery. There may be little benefit in identifying individuals at risk for poor functional outcomes if treatments which result in

substantial restoration of functioning are not available. Results from Chapter 4 suggest that interventions which improve social cognition and motivation are critical to restoring social and occupational functioning. Further, our results suggest that improvements in these domains may be self-sustaining through a positive feedback loop. Early research shows that social cognition training may be able to exploit the relationship between social cognition and motivation with promising results (Fisher et al., 2017; Miley et al., 2020). Future research should seek to delineate the specific mechanisms that contribute to this relationship, including an understanding of how aberrations in social cognition may impact social motivation and response to social rewards (Catalano, Heerey, & Gold, 2018) – and vice versa – and whether interventions targeting these domains will result in improved social functioning.

In addition to intervention development, research which focuses on the implementation of existing evidenced-based practices that target social cognition and motivation, with demonstrated (if heterogenous) effects on functional outcomes, into routine clinical care is needed. Such interventions include social cognition training, social skills groups, and digitally delivered motivational coaching (Eack, Hogarty, Greenwald, Hogarty, & Keshavan, 2011; Fulford, Piper, Meyer-Kalos, & Mueser, 2020; Kurtz & Richardson, 2012; Schlosser et al., 2018; Vita et al., 2021). Unfortunately, few of these clinical interventions are commonly available and treatment effects in real-world clinical settings are largely unknown. To this end, research which evaluates provider, service-user, and systems level barriers to implementation of evidenced based interventions for functional recovery is critical.

Implications for Nursing and Clinical Practice

Psychiatric nurses and other clinicians have a vital role to play in providing recovery-focused care to individuals experiencing psychotic disorders and other serious mental illnesses. Clinicians must be vigilant about assessing social functioning for their patients - including individuals' social participation and connectedness, sense of purpose, and family and community supports – and must partner with patients' and families to formulate specific plans to prevent social decline or restore functioning as a primary treatment goal. The need to incorporate explicit screening for social functioning impairments has become more pressing in the context of the COVID-19 pandemic, which has brought with it a "double pandemic of social isolation" (Holt-Lunstad, 2020). As social isolation is a known risk factor for medical morbidity and early mortality (Holt-Lunstad, Smith, Baker, Harris, & Stephenson, 2015; Valtorta, Kanaan, Gilbody, Ronzi, & Hanratty, 2016), assessing social functioning should be a priority in medical as well as mental-health practices.

As noted above, our results suggest that specifically targeting domains of socio-affective processing and motivation may be critical to functional outcomes. However, typical evidenced-based treatment programs do not include focused interventions for these areas or measure them as important treatment outcomes. When working with individuals experiencing social functioning deficits, clinicians should evaluate these domains and incorporate them into treatment planning. Some interventions – such as motivational interviewing and goal setting (Fulford et al., 2020) - are readily implementable by nurses. Nurses and other clinicians must also advocate for other evidenced based interventions for functional outcomes to become more accessible to

patients in standard community care, such as through expanded funding and insurance reimbursement of psychosocial interventions.

Conclusion

Schizophrenia and other psychotic disorders are characterized by devasting impairments in social functioning, which require rapid identification and early intervention with effective treatments. This dissertation leverages data-driven approaches to provide fundamental knowledge for developing individual prognostic models for social functioning and to guide clinical research seeking to fill critical unmet treatment needs for the remediation of functional impairments. Remediation of these impairments is a treatment priority for individuals living with schizophrenia. Research and clinical agendas must continue to advance the science toward ensuring that social recovery is the expectation of mental health treatment through early identification of individuals at risk for functional decline and innovative treatments which enhance their functioning.

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Appendix A. Institutional Review Board Approval

The research for Chapters 3 and 4 was deemed "Not Human Research" by the University of Minnesota Institutional Review Board (IRB). The respective IRB correspondence for the research studies for each chapter are included in this Appendix.

Chapter 3 IRB Approval

UNIVERSITY OF MINNESOTA

Twin Cities Campus

Human Research Protection Program
Office of the Vice President for Research

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NOT HUMAN RESEARCH

November 11, 2020

Connie Delaney

612-626-3039
delaney@umn.edu

Dear Connie Delaney:

On 11/11/2020, the IRB reviewed the following submission:

Type of Review:	Initial Study
Title of Study:	A data-driven approach to identify the neural and cognitive basis of social functioning in health and first episode psychosis
Investigator:	Connie Delaney
IRB ID:	STUDY00011404
Sponsored Funding:	None
Grant ID:	None
Internal UMN Funding:	None
Fund Management Outside University:	None
IND, IDE, or HDE:	None
Documents Reviewed with this Submission:	• Human Research Determination form, Category: IRB Protocol;

The IRB determined that the proposed activity is not research involving human subjects as defined by DHHS and FDA regulations. To arrive at this determination, the IRB used "WORKSHEET: Human Research (HRP-310)." If you have any questions about this determination, please review that Worksheet in the HRPP Toolkit Library and contact the IRB office if needed.

Ongoing IRB review and approval for this activity is not required; however, this determination applies only to the activities described in the IRB submission and does not apply should any changes be made. If changes are made and there are questions about whether IRB review is required, please submit a Modification to the IRB for a determination.

Sincerely,

Jeffery Perkey, CIP, MLS
Senior IRB Analyst

Chapter 4 IRB Approval

UNIVERSITY OF MINNESOTA

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NOT HUMAN RESEARCH

July 17, 2020

Erich Kummerfeld

612-626-3348
erichk@umn.edu

Dear Erich Kummerfeld:

On 7/17/2020, the IRB reviewed the following submission:

Type of Review:	Initial Study
Title of Study:	Causal Discovery Modeling to Identify Unmet Treatment Needs in Schizophrenia
Investigator:	Erich Kummerfeld
IRB ID:	STUDY00010222
Sponsored Funding:	None
Grant ID:	None
Internal UMN Funding:	None
Fund Management Outside University:	None
IND, IDE, or HDE:	None
Documents Reviewed with this Submission:	• Causal Discovery Modeling in Schizophrenia, Category: IRB Protocol; • Data Use Certification , Category: Other;

The IRB determined that the proposed activity is not research involving human subjects as defined by DHHS and FDA regulations. To arrive at this determination, the IRB used "WORKSHEET: Human Research (HRP-310)." If you have any questions about this determination, please review that Worksheet in the HRPP Toolkit Library and contact the IRB office if needed.

Ongoing IRB review and approval for this activity is not required; however, this determination applies only to the activities described in the IRB submission and does not apply should any changes be made. If changes are made and there are questions about whether IRB review is required, please submit a Modification to the IRB for a determination.

Sincerely,

Driven to Discover℠

Andrew Allen, CIP
IRB Analyst

"We strive to provide clear, consistent and timely service to maintain a culture of respect, beneficence and justice in research. Complete a brief survey about your experience."

Appendix B. Chapter 3 Supplementary Methods and Results

Exploratory Analysis of Mis-predicted Cases

To identify demographic groups or individual profiles for whom the model may not generalize well, we examined trends in the performance of the combined model by examining individual cases in the test dataset. The absolute value of the residual of the predicted versus observed SF score was calculated and the residuals were standardized as Z-scores. We defined mis-predicted cases as those with a standardized residual (absolute value) greater than 1. We first examined whether cases that were mis-predicted differed from correctly predicted cases on any demographic variables with independent sample t-test for continuous variables and Chi-square tests for categorical variables. Secondly, we completed a qualitative analysis of the top mis-predicted cases, i.e., those with the biggest disagreements between the actual and predicted SF scores, (absolute value of z-score > 2, N= 7) to examine trends in the data.

We found that in the testing sample (N = 111), twenty-one (18.9%) cases were determined to be mis-predicted by the combined model. There were no differences in demographic variables or mean values of any model features between the mis-predicted and correctly predicted groups (Table S2.3). In the qualitative analysis of the top mis-predicted cases, five of the seven cases were found to have high observed social functioning scores (10.7 – 14). For these cases, an unexpected pattern was found for their scores on the negative affect and psychological wellbeing scales, such that there was a mismatch between the expected patterns of associations between these variables. For example, for individuals with high social functioning, it would be expected that their

negative affect score would be low, and their psychological wellbeing score would be high. In the top mis-predicted cases, this expected pattern did not occur.

As we found that the mis-predicted cases were not driven by differences in the mis-predicted and correctly predicted groups, this indicates that the model may generalize across demographic populations. Instead, we observed that the model was unable to accurately predict an individual's social functioning score if there was a mismatch between social functioning, negative affect, and psychological well-being scores. These are derived from the NIH-Emotion toolbox and are self-report measures. While they have been validated and have demonstrated convergent validity with objective measures (Salsman et al. 2013), it may be that inconsistent self-reporting resulted in poor prediction accuracy for a subset of our sample, and highlight a need for an objective, gold-standard measure of social functioning which may improve prediction accuracies in future research (Dunning, Heath, and Suls 2004; Harvey 2016; Kruger and Dunning 1999).

Chapter 3 Supplemental Tables

Table S3.1

Descriptive Statistics for NIH-ETB Social Functioning Individual Scales

Scale	Minimum value	Maximum value	Mean (SD)
Friendship	20.8	66.5	50.4 (9.0)
Loneliness	37.6	82.9	51.0 (8.6)
Emotional support	15.9	62.5	51.4 (9.6)
Instrumental support	22.1	62.9	48.0 (9.0)
Perceived rejection	35.9	85.3	48.5 (8.7)

Note. NIH-ETB = National Institutes of Health Emotion Toolbox, SD = standard deviation

Table S3.2

Descriptive Statistics for Model Features (N = 1,101)

	Mean (SD) or %
Social Cognition & Cognition	
Penn Emotion Recognition Task Correct Responses	35.6 (2.5)
Penn Emotion Recognition Task Reaction Time (seconds)	1830.7 (330.6)
HCP Theory of Mind Task	
Random Stimuli percent correct	85.3 (19.7)
Random Stimuli-correct reaction time (seconds)	1038.1 (366.8)
Social Stimuli percent correct	94.1 (12.7)
Social Stimuli-correct reaction time (seconds)	1000.1 (283.2)
HCP Emotion Processing Task Accuracy (percent correct)	97.5 (3.5)
HCP Emotion Processing Reaction Time (seconds)	777.5 (116.4)
Mini-Mental State Exam	29.0 (1.0)
Attention – Short Penn Continuous Performance Test Sensitivity	0.95 (0.08)
Attention – Short Penn Continuous Performance Test Specificity	0.95 (0.04)
Episodic memory – Picture Sequence Memory Test	105.0 (16.6)
Episodic memory – Penn Word Memory Test	35.6 (2.9)
Working memory – List sorting	103.2 (13.3)
Language – Oral Reading Recognition	106.8 (14.9)
Language – Picture Vocabulary	109.1 (15.4)
Executive Functioning – Card Sort Test	102.3 (9.9)
Executive Functioning – Flanker Task	101.7 (10.1)
Processing Speed – Pattern Comparison test	103.7 (20)
Affective, Psychiatric and Behavioral	
NEO-FFI Neuroticism	16.6 (7.4)
NEO-FFI Extroversion	30.7 (6.0)
NEO-FFI Openness	28.3 (6.2)
NEO-FFI Agreeableness	33.5 (5.8)
NEO-FFI Conscientiousness	34.5 (5.9)
ASR Anxious/Depressed	53.9 (6.2)
ASR Withdrawn	53.6 (5.8)
ASR Somatic Complaints	54.0 (6.0)
ASR Thought Problems	53.7 (5.7)
ASR Attention Problems	54.9 (5.5)
ASR Aggression Problems	52.6 (4.2)
ASR Rule Breaking Problems	53.9 (5.3)
NIH Emotion Toolbox Negative Affect composite	38.1 (5.3)
NIH Emotion Toolbox Psychological Well-being composite	40.9 (5.6)
Delay Discounting Task – Area Under of the Curve for $200	0.26 (0.20)
Delay Discounting Task – Area Under of the Curve for $40,000	0.51 (0.28)
Substance Use	
Number of alcohol drinks in last 7 days	4.9 (7.1)
Number of drinks per day in the last 12 months	2.3 (1.6)

Table S3.2

Descriptive Statistics for Model Features (N = 1,101)

	Mean (SD) or %
Lifetime Cannabis use amount (%)	
Never used	45.1
1-5 times	20.3
6-10 times	7.4
11-100 times	11.4
101-999 times	6.4
1000 or more times	9.1
Physical Functioning	
NIH Toolbox endurance	107.8 (14.0)
NIH Toolbox gait speed	1.3 (0.2)
NIH Toolbox dexterity	100.2 (9.8)
NIH Toolbox strength	103.6 (20.0)
Pittsburg Sleep Quality Questionnaire	4.8 (2.8)
Body Mass Index	26.5 (5.2)
Sensory Functioning	
Words in Noise test	4.4 (1.5)
Odor Identification test	97.8 (11.1)
Regional Taste Intensity Test	93.9 (14.7)
Pain interference	45.7 (7.6)
Mars Contrast Sensitivity	1.8 (0.57)

Note. HCP = Human Connectome Project; NEO-FFI = Neuroticism, Extraversion, Openness Five Factor Inventory; ASR = Achenbach Adult Self Report scale

Table S3.3

Comparison of Mis-Predicted and Correctly Predicted Cases for Combined Brain-Behavioral Model in Test Sample

	Mis-predicted (N = 21) Mean (SD) or %	**Correctly predicted (N = 90) Mean (SD) or %**	**t or X^2 value (p-value)**
Demographics			
Age	27.95 (3.8)	28.89 (3.66)	-1.05 (0.30)
Gender: female	42.86	60.00	2.04 (0.15)
Education (years)	15.14 (2.03)	14.99 (1.80)	0.35 (0.73)
Race			2.28 (0.68)
Asian, Native Hawaiian, Other Pacific Islander	4.77	6.66	
Black or African American	19.05	10.00	
White	71.43	78.89	
More than one	0.00	2.22	
Unknown	4.77	2.22	
Ethnicity: Hispanic or Latino	19.05	7.78	2.42 (0.12)
Currently married or in live-in relationship	47.62	47.78	0.00 (0.99)
Currently employed	80.95	91.11	1.8 (1.18)
Income level			0.02 (0.90)
$0 – 39,999 yearly	35.00	65.00	
> $40,000 yearly	36.67	63.33	
Model Features[a]			
Negative Affect	38.66 (6.07)	37.78 (5.28)	0.67 (0.51)
Psychological Wellbeing	40.97 (5.47)	41.09 (5.15)	-0.10 (0.92)
ASR Withdrawn Symptoms	54.52 (5.54)	53.19 (5.61)	0.99 (0.33)
NEO-FFI Agreeableness	30.67 (9.56)	33.64 (5.76)	-1.86 (0.07)
NEO-FFI Extraversion	31.00 (5.45)	31.12 (5.37)	-0.10 (0.93)
R Inferior parietal thickness	2.63 (0.10)	2.64 (0.11)	-0.49 (0.63)
R Rostral middle frontal thickness	2.58 (0.14)	2.58 (0.11)	0.04 (0.97)
L Rostral middle frontal thickness	2.59 (0.13)	2.57 (0.11)	0.62 (0.53)
L Supramarginal thickness	2.65 (0.10)	2.65 (0.11)	-0.32 (0.75)
R Superior parietal area	0.003 (0.00)	0.003 (0.00)	-0.89 (0.38)
L Superior temporal thickness	2.91 (0.12)	2.88 (0.11)	1.18 (0.24)
L Temporal pole area	0.0003 (0.00)	0.0003 (0.00)	-2.03 (0.05)

Note. Abbreviations: ASR = Achenbach Adult Self Report scale; L = left; NEO-FFI = Neuroticism, Extraversion, Openness Five Factor Inventory; R = right

[a]Cortical thicknesses are measured in mm. Surface areas (mm^2) have been corrected for total intracranial volume.

Appendix C. Chapter 4 Supplementary Methods and Results

1. Additional Description of Included Variables

The following secondary variables were included in our analysis for Study 1:

Psychopathology: The Positive and Negative Symptom Scale (PANSS) traditional three syndrome model scale scores were used for positive, negative, and general symptoms variables (Kay, Fiszbein, & Opler, 1987). Depression was measured with the Calgary Depression Scale for Schizophrenia (Addington, Addington, & Maticka-Tyndale, 1993). Overall illness severity was measured with the Clinical Global Impressions-Severity scale (Guy, 1976).

Substance use: Alcohol and cannabis use was measured by self-report of the number of days in the preceding month that each substance was used.

Psychological well-being: Three self-report measures of psychological well-being were used in Study 1. The well-being variable represents the total score from an 18-item subset of the modified version of the Scales of Psychological Well-being developed by Carol Ryff. The 18-item version was used in the RAISE-ETP study and measures six areas of self-perceived psychological well-being including environmental mastery, autonomy, personal growth, positive relationships, purpose in life, and self-acceptance (Browne et al., 2016; Ryff, 1989). The mental health recovery measure used in RAISE-ETP and our analysis is a modified version of the Young, Ensing & Bullock's Mental Health Recovery Measure (MHRM). The RAISE-ETP modified scale uses 15 of the original 30 items, and converted from a 5 item Likert scale to a 7 item Likert scale (Browne et al., 2016; Ralph, Kidder, & Phillips, 2000; Young, Ensing, & Bullock, 1999). Perceived stigma was measured in RAISE-ETP and our analysis from a modified version

of the Stigma Scale (King et al., 2007). Seven of the original 28 items were used in the modified scale which represent perceived prejudice and discrimination related to mental illness (Mueser et al., 2019).

Beliefs about medications: The total score for the Brief Evaluation of Medication Influences and Beliefs (BEMIB) scale was used as a measure of participant attitudes regarding adhering to antipsychotic medications. This measure has been found to correlate with objective medication adherence assessments (Dolder et al., 2004). Four items from the eight item BEMIB scale were used in RAISE-ETP and in our analysis.

2. Causal Discovery and Greedy Fast Causal Inference[1]

Like all statistical methods that aim to make deeper inferences from data, rather than simply describing data, causal discovery analysis makes some assumptions. The primary and most general assumption is that the observed data come from a causal process that can be accurately described with a causal model. More precisely, we assume that the data is generated by one of the models among a set of explicitly defined possible models. In this way, causal discovery analysis is similar to structural equation modeling (SEM), with the main difference being that while the SEM approach asks an expert to stipulate a small number of candidate model structures at this step, causal discovery modeling considers all possible model structures that meet some very broad criteria, e.g. all structures that contain no feedback loops, or all structures that have no unmeasured common causes, or all structures that meet both criteria. This is the primary, and perhaps only, distinction between SEM analysis and causal discovery analysis, and so causal discovery does not stand on ground any less firm than SEMs do generally.

[1] Section 2 of this Supplement, Causal Discovery and Greedy Fast Causal Inference, was written by Erich Kummerfeld, PhD, senior author on published manuscript.

It must also be emphasized that there is a large difference between the SEM approach and causal discovery, stemming from the fact that the space of all models meeting causal discovery's weak restrictions is extremely large. In fact, the space of models that causal discovery considers grows at a super exponential rate with the number of variables in the data set. If x is the number of variables, then the number of models typically considered by causal discovery grows at a rate proportional to 2^(x^2). As an example, with only 5 variables there are 29,281 possible directed acyclic graphs (DAGs), graphical structures which contain directed edges connecting nodes that represent observed variables, with no feedback loops formed by the edges. These DAGs correspond to the different structures that many causal discovery algorithms consider might have generated the data. With 10 variables, the number of DAGs has already grown to 4,175,098,976,430,598,143. For many data sets, the number of possible DAGs is too many to fit a SEM to each one of them and compare fit statistics.

Causal discovery analysis attempts to resolve this problem by using advanced computing strategies to compute these statistics more efficiently, and/or by rapidly removing large numbers of models from consideration without testing them individually. Greedy Fast Causal Inference (GFCI), the causal discovery analysis method used in this paper, uses the latter approach. It first uses an intelligent search procedure to selectively fit models as SEMs, iteratively modifying each SEM to optimize model fit statistics, until it cannot improve the fit statistics any further. Our implementation of GFCI for this project used the Bayesian Information Criterion (BIC) fit statistic for linear Gaussian models. The BIC score is a penalized likelihood score defined by:

$$BIC = -2 \ln(L) + k \ln(n)$$

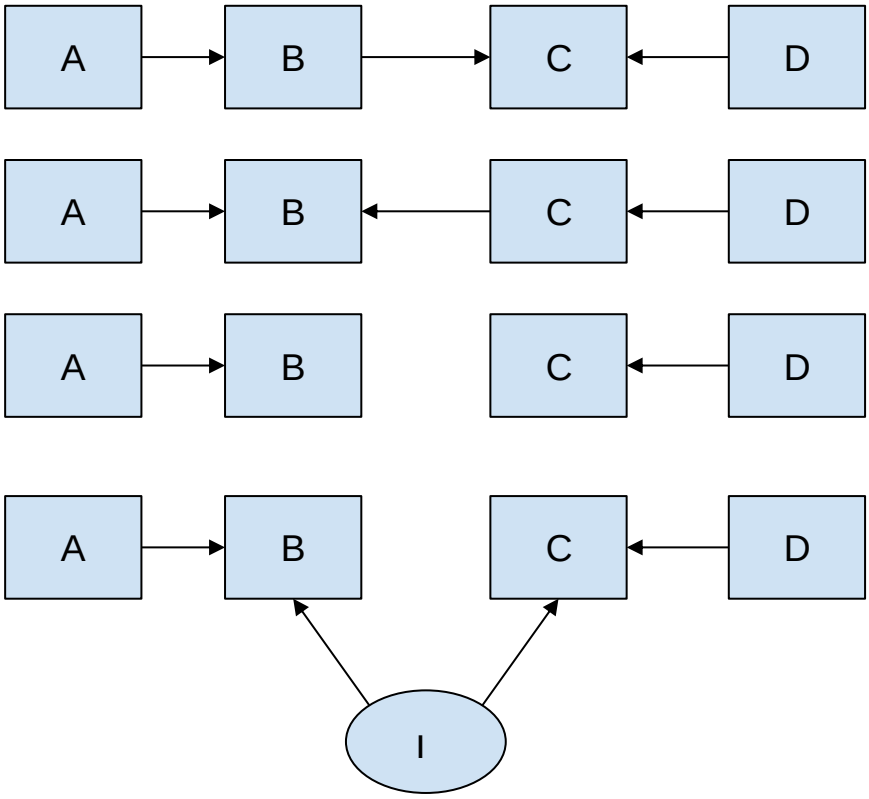
k is the number of free parameters in the model, for linear Gaussian SEMs this is the number of variables plus the number of edges. n is the sample size. The likelihood, L, is the probability of the data given the model, after fitting the model's free parameters to the data. Lower BIC scores are preferred to higher BIC scores, forcing a trade-off between the model's ability to plausibly generate the observed data and the model's complexity.

For each model structure tested, the algorithm fits an appropriate multivariate Gaussian distribution to the data. Since this is a distribution over different possible values the data could take, it calculates a specific probability value for our actual data set (the likelihood). The BIC transforms the likelihood by taking its natural log, and then adds a penalty term to prevent overfitting with unnecessarily complex models. This process is repeated while the algorithm systematically searches through the space of possible models by adding and removing individual edges, until it identifies a model structure that appears to have the best BIC.

After identifying a model structure that optimizes the BIC, GFCI then goes a step further by considering that there may be unmeasured common causes. Unmeasured common causes can be explicitly modeled with individual SEMs, but again the space of models being considered is too large for this. At present, the primary approach to unmeasured common causes among the many causal discovery analysis methods is to use hypothesis testing rather than model fitting. Underlying theoretical work has been done identifying an exhaustive collection of statistical signals that indicate the presence or absence of unmeasured common causes.

For example, consider the models in the figure below. These models all have 4 measured hypothetical variables, A, B, C, and D, and model 4 also has one unmeasured

variable, L. There is always an edge from A to B, and from D to C, but the relationship between B and C is different in each model.



Let's consider how a causal discovery analysis algorithm would use tests to determine what is the most plausible causal model. If the algorithm sees in the data that B and C are significantly correlated, then it can drop model 3. Since in model 3 there is no causal pathway that connects B and C, that model would not be able to explain why B and C are correlated. Models 1, 2, and 4, can explain this correlation, so they are retained for consideration. If the algorithm then finds that B and D are significantly correlated conditional on C, or in other words that the partial correlation of B and D given C is significant, then it can drop model 2. In model 2, conditioning on C will separate B from

D, implying that B and D should be uncorrelated given C, but that contradicts what we found in the data. That leaves the algorithm with models 1 and 4 still under consideration. It can then test whether A and C are correlated after conditioning on B. If it finds that A and C are correlated after conditioning on B, then it drops model 1 from consideration, as B blocks the path from A to C in model 1. This leaves only model 4, where B and C both have two arrowheads pointing at them, which can explain the above-mentioned conditional dependencies found in the hypothetical data.

In fact, this combination of testable statistical features descriptively found in the data cannot be explained by any DAG that does not have an unmeasured common cause of B and C. This sort of logical inference has been encoded into a collection of structural inference rules that can be iteratively applied, guiding a sequence of hypothesis tests that continuously refines the model by considering possible ways that unmeasured variables, like L in the above example, might influence the descriptive statistics found in the data. For a detailed list of these rules see citations (Spirtes, Glymour, & Scheines, 2000; Zhang, 2008). GFCI applies these rules in its second step, refining the initial graph learned in its first step by making adjustments based on hypothesis tests checking for specific interactions from unmeasured common causes, like that in the example given previously. The final product is a graph representing a collection of DAGs, which may include unmeasured variables in them. It is a collection, rather than a single DAG, because even with all of the above, some models can still be indistinguishable from each other when using linear Gaussian model fit and conditional independence tests on the observed variables. This collection is then graphically represented as a Partial Ancestral Graph (PAG), which has a variety of different edges that capture the potentially multiple

possible relationships that two connected variables have across the different DAGs in the collection. For example, if the DAGs in the collection include a graph where A causes B, a graph where A doesn't cause B but there is an unmeasured common cause of A and B, and a graph where A causes B and there is also an unmeasured common cause of A and B, then the PAG would use a specific edge to represent this collection of possible relationships between A and B which is typically visualized as A o--> B (see Figure 1 in the main text for a description of edge types and their interpretations).

3. SEM Comparison and Sensitivity Analyses (Study 1)

SEM comparison. A previous factor analysis found that the items on the Quality of Life scale that comprise the motivation and socio-affective capacity variables used in this study load together during factor analysis (Mueser et al., 2017). Factor analysis does not necessarily indicate that motivation and socio-affective capacity are the same entity and separating them may have clinical relevance.

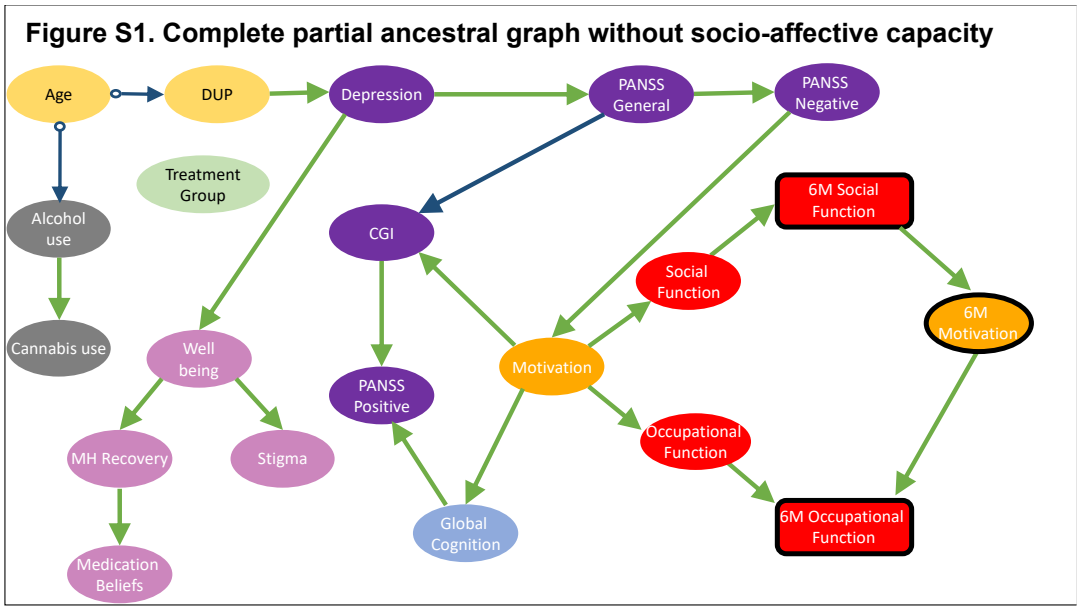
If there is an unmeasured common cause between motivation and socio-affective capacity due to redundancy of measurement or overlapping traits, GFCI should identify this as the best fit in the model search. To ensure that our results are not due to overlapping traits represented by the motivation and socio-affective capacity variables we directly tested the separateness of these variables (i.e., that the observed relationship between motivation and socio-affective capacity in our graph was not better explained by a shared latent trait) by comparing model fit statistics from our original SEM to a SEM in which the relationship between motivation and socio-affective capacity at baseline and six-months is modeled as a latent variable. Model comparisons were performed using

hypothesis tests for non-nested models described in Vuong using the "nonnest2" package in R (Vuong, 1989).

Results of this analysis indicated that our original model had significantly better fit than the alternative model ($z = 5.97$, $p = 1.2e\text{-}0.9$). The Comparative Fit Index (CFI) and Root Mean Square Error (RMSEA) of both models are provided below.

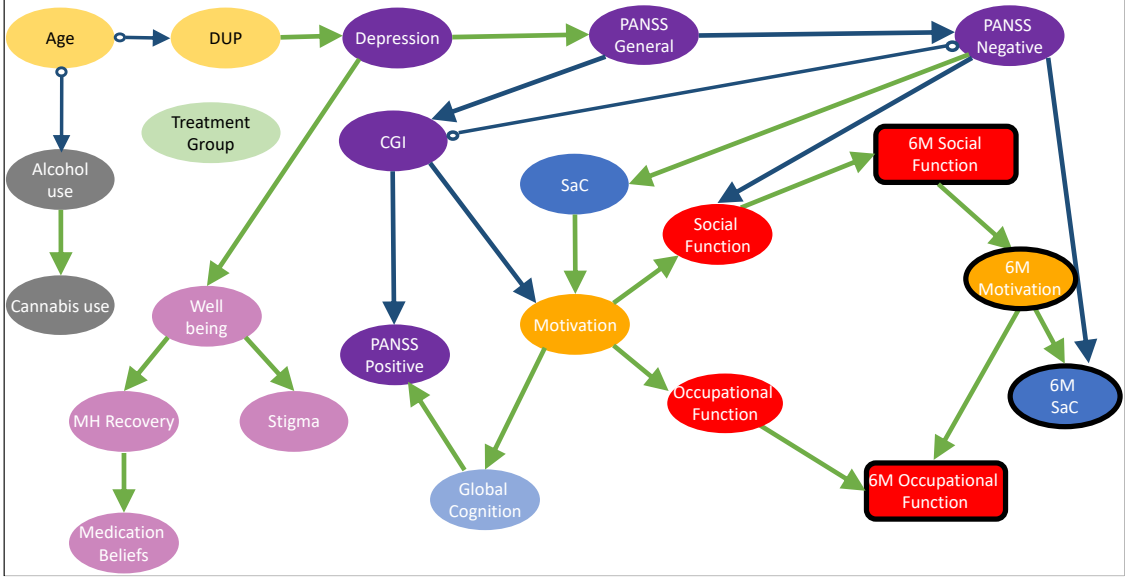
	Original model	Alternative model
CFI	0.884	0.848
RMSEA	0.066	0.076

Sensitivity Analysis. We completed two sensitivity analyses to ensure our results are not driven by measurement overlap. First, we excluded the socio-affective capacity variable from the model to assess whether the remaining structure of the functional outcomes subgraph was dependent on socio-affective capacity. We found that dropping socio-affective capacity did not impact the relationships in the graph, except for a change in the edge orientation between baseline motivation and Clinical Global Impressions (Figure S1). This edge did not survive the bootstrap and jackknife assessment for graph stability, indicating that it is a weak and unstable relationship in the alternative graph.



Second, we dropped PANSS item N3 measuring engagement with the interviewer from the PANSS negative symptom composite score due to measurement overlap with the socio-affective capacity variable. The original relationships were largely maintained in the resulting graph (Figure S2). In the alternative graph there is an added edge indicating that baseline negative symptoms are a direct or indirect cause of baseline social functioning. This edge did not survive the bootstrap and jackknife assessment for graph stability, indicating that it is a weak and unstable relationship.

Figure S2. Complete partial ancestral graph with modified PANSS negative



4. Supplemental Tables

Table S4.1

Demographic and Variable Descriptive Statistics for Included and Excluded RAISE-ETP Participants

	Included (N=276) Mean (SD) or %		Excluded (N=128) Mean (SD) or %	
Demographics				
Age (years)	23	(4.9)	23	(5.4)
Gender: male	74.3		68.8	
Race				
American Indian or Alaskan Native	5.8		3.9	
Asian	2.9		3.1	
Black	35.1		43.0	
Native Hawaiian or Pacific Islander	0.4		0.0	
White	55.8		50.0	
Ethnicity: Hispanic or Latino	18.5		17.2	
Baseline Variables				
Treatment Assignment to Coordinated Specialty Care	43.1		48.4	
QLS social functioning	19.9	(8.6)	19.5	(8.9)
QLS occupational functioning	5.7	(6.7)	5.3	(6.1)
QLS motivation	7.7	(3.6)	7.4	(3.5)
QLS socio-affective capacity	8.0	(2.2)	7.6	(2.1)
Neurocognitive Composite Z score[a]	0.04	(1.0)	0.0	(1.0)
PANSS positive symptoms	18.9	(5.2)	18.4	(5.2)
PANSS negative symptoms	20.1	(5.2)	20.4	(5.5)
PANSS general symptoms	37.6	(7.7)	37.8	(8.8)
Calgary Depression Scale for Schizophrenia	4.4	(3.9)	5.3	(4.8)
Clinical global impressions of severity	4.1	(0.8)	4.0	(0.8)
Duration of untreated psychosis (days)	195.7	(271.9)	187.3	(240.4)
Days of alcohol use in last month	1.9	(4.7)	1.8	(4.1)
Days of cannabis use in last month	3.2	(7.6)	2.7	(7.0)
Well-being scale total score	4.0	(0.9)	3.9	(1.0)
Mental health recovery measure total score	73.3	(18.1)	73.4	(19.6)
Stigma scale total score	4.0	(1.2)	3.9	(1.3)
Brief evaluation of medication influences and beliefs total score[b]	4.9	(1.0)	5.1	(1.0)

Note. PANSS = Positive and Negative Symptom Scale; QLS = Quality of Life Scale
[a]Neurocognitive composite from the Brief Assessment of Cognition
[b]p=0.03, t=-2.2

Table S4.2

Study 1 RAISE-ETP Sample Causal Effect Sizes

Edge Type in PAG	Nodes		Raw Effect Size (Standard Error)		95% Confidence interval	Standardized effect size (Standard Error)		95% Confidence interval	Z-score	p-Value
	Node 1	**Node 2**								
o→	[a]Age (years)	Days alcohol use in last month	0.07	(0.02)	0.03, 0.12	0.18	(0.06)	0.07, 0.29	3.1	0.002
	[a]Age (years)	DUP	0.02	(0.004)	0.01, 0.03	0.28	(0.06)	0.16, 0.39	4.5	0
→	CGI	PANSS Positive	4.57	(0.28)	4.03, 5.11	0.71	(0.04)	0.63, 0.80	16.6	0
	PANSS Negative	Socio-affective Capacity 6 Month	-0.17	(0.02)	-0.21, -0.13	-0.38	(0.05)	-0.47, -0.3	-8.1	0
→	CGI	Motivation	-1.41	(0.21)	-1.82, -1.0	-0.32	(0.05)	-0.42, -0.23	-6.74	0
	Days alcohol use in last month	Days cannabis use in last month	0.34	(0.09)	0.16, 0.53	0.21	(0.06)	0.10, 0.33	3.6	0
	Depression	PANSS General	0.89	(0.10)	0.69, 1.1	0.46	(0.05)	0.36, 0.57	8.7	0
	Depression	Well-being scale total score	-0.08	(0.01)	-0.10, -0.06	-0.37	(0.06)	-0.48, -0.26	-6.7	0
	DUP	Depression	1.2	(0.27)	0.70, 1.76	0.26	(0.06)	0.15, 0.38	4.5	0
	Global Cognition	PANSS Positive	1.09	(0.24)	0.63, 1.55	0.2	(0.04)	0.12, 0.28	4.65	0
	Mental Health Recovery Measure total score	Medication Beliefs	0.01	(.003)	.007, .002	0.25	(0.06)	0.13, 0.36	4.27	0
	Motivation	Global Cognition	0.08	(0.02)	0.05, 0.12	0.32	(0.06)	0.20, 0.43	5.5	0

Edge Type in PAG	Nodes		Raw Effect Size (Standard Error)		95% Confidence interval	Standardized effect size (Standard Error)		95% Confidence interval	Z-score	p-Value
	Motivation	Occupational Functioning	0.96	(0.10)	0.77, 1.15	0.51	(0.05)	0.41, 0.61	9.7	0
	Motivation	Social Functioning	1.45	(0.12)	1.22, 1.68	0.6	(0.05)	0.50, 0.70	12.3	0
	Motivation 6 Month	Socio-affective Capacity 6 Month	0.24	(0.03)	0.18, 0.3	0.37	(0.05)	0.28, 0.46	7.8	0
	Motivation 6 Month	Occupational Functioning 6 Month	0.92	(0.10)	0.73, 1.12	0.45	(0.05)	0.35, 0.54	9.3	0
	Occupational Functioning	Occupational Functioning 6 Month	0.36	(0.05)	0.26, 0.47	0.33	(0.05)	0.23, 0.42	6.8	0
	PANSS General	PANSS Negative	0.35	(0.04)	0.28, 0.42	0.51	(0.05)	0.41, 0.61	9.9	0
	PANSS General	CGI	0.07	(.007)	0.06. 0.08	0.68	(0.04)	0.59, 0.76	15.3	0
	PANSS Negative	Socio-affective Capacity	-0.27	(0.02)	-0.31, -0.23	-0.65	(0.05)	-0.74, -0.56	-14.2	0
	Social Functioning	Social Functioning 6 Month	0.60	(0.06)	0.49, 0.71	0.53	(0.05)	0.43, 0.63	10.3	0
	Social Functioning 6 Month	Motivation 6 Month	0.22	(0.02)	0.18, 0.25	0.6	(0.05)	0.49, 0.68	12.1	0
	Socio-affective Capacity	Motivation	0.76	(0.08)	0.60, 0.91	0.46	(0.05)	0.37, 0.55	9.65	0
	Well-being Scale total score	Mental Health Recovery Measure total score	16.07	(0.83)	14.45, 17.7	0.76	(0.04)	0.68, 0.84	19.4	0
	Well-being Scale total score	Stigma scale total score	-0.52	(0.08)	-0.67, -0.38	-0.38	(0.06)	-0.49, -0.27	-6.9	0

Note. CGI = Clinical Global Impressions of Severity; DUP = duration of untreated psychosis, measured in days (log transformed); Depression = Calgary Depression Scale for Schizophrenia; Medication Beliefs = Brief Evaluation of Medication Influences and Beliefs total score; PANSS General = Positive and Negative Symptom Scale General Symptoms total score; PANSS Negative = Positive and Negative Symptom Scale Negative Symptoms total score; PANSS Positive = Positive and Negative Symptom Scale Positive Symptoms total score

[a]Age is log transformed.

Table S4.3

Re-sampling Analyses for Study 1 (RAISE-ETP) and Study 2 (CATIE) Samples

Jack-knife Re-sampling Analysis for Study 1 RAISE-ETP Sample									
Edge Type in PAG	**Nodes**		**Proportion of 1,000 jack-knife resamples with edge type**						
o→	Node 1	Node 2	→	←	o→	←o	o--o	←→	No edge
	Age	Days Alcohol Use	0	0	**0.666**	0	0	0	0.334
	Age	DUP	0	0	**0.999**	0	0	0	0.001
→	CGI	Motivation	**0.949**	0.019	0.004	0.001	0	0	.027
	CGI	PANSS Positive	**0.837**	0.094	0.002	0.047	0.012	.008	0
	Days Alcohol Use	Days Cannabis Use	**0.388**	0	0	0	0.256	0	0.356
	Depression	PANSS General	**0.942**	0.055	0	0	0.003	0	0
	Depression	Well-being Score	**0.931**	0.06	0	0	0.003	0	0.006
	DUP	Depression	**0.886**	0.012	0	0	0	0	0.102
	Global Cognition	PANNS Positive	**0.668**	0	0.005	0	0	0	0.327
	Mental Health Recovery Measure	Medication Beliefs	**0.568**	0	0	0	0	0	0.432
	Motivation	Global Cognition	**0.973**	0	0	0	0.005	0	0.022
	Motivation	Occupational Functioning	**0.995**	0	0	0	0.005	0	0
	Motivation	Social Functioning	**0.995**	0	0	0	0.005	0	0
	Motivation 6 Month	Socio-affective capacity 6 Month	**0.836**	0.163	0	0	0	0	0.001
	Motivation 6 Month	Occupational Functioning 6 Month	**1**	0	0	0	0	0	0
	Occupational Functioning	Occupational Functioning 6 Month	**0.995**	0	0.005	0	0	0	0
	PANSS General	PANSS Negative	**0.799**	0.002	0	0.09	0	0.006	0.103
	PANSS General	CGI	**0.87**	0.045	0.001	0	0.004	0	0.08

	PANSS Negative	Socio-affective capacity	**0.862**	0.002	0.001	0.001	0.134	0	0
	PANSS Negative	Socio-affective capacity 6 Month	**0.864**	0	0.135	0	0	0	0.001
	Social Functioning	Social Functioning 6 Months	**0.995**	0	0.005	0	0	0	0
	Social Functioning 6 Month	Motivation 6 Month	**0.875**	0.125	0	0	0	0	0
	Socio-affective capacity	Motivation	**0.85**	0.014	0.131	0.001	0.004	0	0
	Well-being Scale	Mental Health Recovery Measure	**0.991**	0.006	0	0	0.003	0	0
	Well-being Scale	Stigma Scale	**0.997**	0	0	0	0.003	0	0

Bootstrap Re-sampling Analysis for Study 1 RAISE-ETP Sample

Edge Type in PAG	**Nodes**		**Proportion of 1,000 bootstrap resamples with edge type**						
o→	Node 1	Node 2	→	←	o→	←o	o--o	←→	No edge
	Age	Days Alcohol Use	0	0	**0.553**	0	0	0	0.467
	Age	DUP	0	0	**0.857**	0	0	0	0.143
→	CGI	Motivation	**0.412**	0.054	0.045	0.003	0.009	0.002	0.475
	CGI	PANSS Positive	**0.443**	0.204	0.089	0.111	0.052	0.101	0
	Days Alcohol Use	Days Cannabis Use	0.277	0.031	0	0.014	0.222	0	**0.456**
	Depression	PANSS General	**0.491**	0.442	0.022	0.012	0.033	0	0
	Depression	Well-being Scale	**0.596**	0.169	0.01	0.004	0.033	0	0.188
	DUP	Depression	0.287	0.141	0	0.009	0.005	0	**0.558**
	Global Cognition	PANNS Positive	0.301	0.015	0.072	0.003	0	0	**0.609**
	Mental Health Recovery Measure	Medication Beliefs	0.396	0.004	0.001	0	0.016	0	**0.583**
	Motivation	Global Cognition	**0.55**	0.002	0.003	0.054	0.08	0.001	0.31
	Motivation	Occupational Functioning	**0.807**	0.031	0.013	0.041	0.107	0.001	0
	Motivation	Social Functioning	**0.762**	0.104	0.027	0.008	0.098	0	0.001
	Motivation 6 Month	Socio-affective capacity 6 Month	**0.5**	0.367	0	0	0	0	0.133

	Motivation 6 Month	Occupational Functioning 6 Month	**0.973**	0.023	0	0	0	0	0.004
	Occupational Functioning	Occupational Functioning 6 Month	**0.838**	0	0.147	0	0	0	0.015
	PANSS General	CGI	**0.52**	0.219	0.01	0.012	0.047	0.002	0.19
	PANSS General	PANSS Negative	**0.333**	0.176	0.002	0.176	0.026	0.019	0.268
	PANSS Negative	Socio-affective capacity	**0.426**	0.246	0.036	0.027	0.264	0.001	0
	PANSS Negative	Socio-affective capacity 6 Month	**0.65**	0	0.288	0	0	0.002	0.06
	Social Functioning	Social Functioning 6 Month	**0.889**	0	0.108	0	0	0	0.003
	Social Functioning 6 Month	Motivation 6 Month	**0.726**	0.273	0	0	0	0.001	0
	Socio-affective capacity	Motivation	**0.368**	0.239	0.196	0.03	0.082	0.016	0.069
	Well-being Scale total score	Mental Health Recovery	**0.791**	0.157	0.001	0.003	0.048	0	0
	Well-being Scale	Stigma Scale	**0.818**	0.065	0.008	0.002	0.039	0	0.068

Jack-knife Re-sampling Analysis for Study 2 CATIE Sample

Edge Type in PAG	**Nodes**		**Proportion of 1,000 jack-knife resamples with edge type**						
o--o	Node 1	Node 2	→	←	o→	←o	o--o	←→	No edge
	Depression	PANSS General	0.002	0.042	0.052	0	**0.904**	0	0
	Motivation	Occupational Functioning	0.062	0	0	0	**0.938**	0	0
	Motivation	Social Functioning	0.028	0.034	0.218	0	**0.72**	0	0
	PANSS General	PANSS Negative	0	0.034	0	0.062	**0.904**	0	0
	PANSS General	PANSS Positive	0.086	0	0	0.01	**0.904**	0	0
	PANSS Negative	Socio-affective capacity	0	0.034	0	0	**0.955**	0	0.011
	PANSS Negative	Global Cognition	0.034	0	0	0	**0.94**	0	0.026

	Socio-affective capacity	Motivation	0	0.044	0.018	0	**0.938**	0	0
o→	Global Cognition	CGI	0.02	0.022	**0.599**	0	0	0	0.359
	Motivation	Motivation 6 Months	0.038	0	**0.593**	0	0	0	0.369
	PANSS Positive	CGI	0.084	0	**0.903**	0	0.007	0	0.006
	Occupational Functioning	Occupational Functioning 6 Month	0.062	0	**0.938**	0	0	0	0
	Social Functioning	Social Functioning 6 Month	0.28	0	**0.72**	0	0	0	0
	Socio-affective capacity	Socio-affective capacity 6 Month	0.038	0	**0.789**	0	0	0	0.173
→	CGI	Facial Affect Recognition	**0.641**	0	0	0.005	0.008	0	0.346
	Motivation 6 Month	Socio-affective capacity 6 Month	**0.809**	0.163	0	0	0.002	0	0.026
	Motivation 6 Month	Occupational Functioning 6 Month	**0.897**	0.103	0	0	0	0	0
	Social Functioning 6 Month	Motivation 6 Month	**0.843**	0.012	0	0	0	0	0.145
No edge	Age (years)	Age at first antipsychotic use	0	0.001	0.171	0.011	**0.817**	0	0

Bootstrap Re-sampling Analysis for Study 2 CATIE Sample

Edge Type in PAG	Nodes		Proportion of 1,000 bootstrap resamples with edge type						
o--o	Node 1	Node 2	→	←	o→	←o	o--o	←→	No edge
	Depression	PANSS General	0.11	**0.342**	0.182	0.009	0.27	0	0.087
	Motivation	Occupational Functioning	0.419	0.008	0.025	0.014	**0.501**	0	0.033
	Motivation	Social Functioning	0.212	0.238	0.151	0.007	**0.392**	0	0
	PANSS General	PANSS Negative	0.066	**0.333**	0.028	0.271	0.296	0.006	0
	PANSS General	PANSS Positive	**0.384**	0.069	0.003	0.218	0.32	0.006	0

	PANSS Negative	Socio-affective capacity	0.054	0.186	0.034	0.113	**0.396**	0	0.217
	PANSS Negative	Global Cognition	0.267	0.03	0.017	0.012	**0.389**	0	0.285
	Socio-affective capacity	Motivation	0.061	0.31	0.077	0.02	**0.521**	0	0.011
o→	Global Cognition	CGI	0.074	0.092	0.16	0.002	0.03	0	**0.642**
	Motivation	Motivation 6 Months	0.229	0	0.272	0	0	0.001	**0.498**
	PANSS Positive	CGI	**0.324**	0.067	**0.324**	0.011	0.12	0	0.154
	Occupational Functioning	Occupational Functioning 6 Month	0.456	0	**0.492**	0	0	0	0.052
	Social Functioning	Social Functioning 6 Month	**0.599**	0	0.398	0	0	0.003	0
	Socio-affective capacity	Socio-affective capacity 6 Month	0.229	0	0.347	0	0	0	**0.424**
→	CGI	Facial Affect Recognition	0.268	0.02	0.003	0.031	0.063	0	**0.615**
	Motivation 6 Month	Socio-affective capacity 6 Month	**0.546**	0.206	0	0	0.005	0	0.243
	Motivation 6 Month	Occupational Functioning 6 Month	**0.636**	0.34	0.001	0	0.001	0	0.022
	Social Functioning 6 Month	Motivation 6 Month	**0.509**	0.131	0	0	0	0.001	0.359
No edge	Age (years)	Age at first antipsychotic use	0	0.138	0.31	0.11	**0.43**	0.012	0

Note. CGI = Clinical Global Impressions of Severity; DUP = duration of untreated psychosis, measured in days (log transformed); Depression = Calgary Depression Scale for Schizophrenia; Medication Beliefs = Brief Evaluation of Medication Influences and Beliefs total score; PANSS General = Positive and Negative Symptom Scale General Symptoms total score; PANSS Negative = Positive and Negative Symptom Scale Negative Symptoms total score; PANSS Positive = Positive and Negative Symptom Scale Positive Symptoms total score
Age is log transformed in RAISE sample.