Neuroimaging defined psychosis spectrum phenotypes in the general population

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Introduction:
Machine learning techniques are increasingly used to identify neuroimaging patterns for the diagnosis and prognosis in schizophrenia. We have previously shown that multivariate patterns of brain structural data (biosignatures) can successfully classify individuals at clinical high risk (CHR) for psychosis into those with good or poor prognosis. Converging evidence across studies implicates alterations in prefrontal and temporal cortical volume and surface area as well as changes in subcortical volumes. The ultimate purpose of this line of research is to develop a neuroimaging biosignature of risk to schizophrenia that could be used for the early identification of individuals likely to develop psychosis. As these models have been developed within the context of research settings, their applicability to identify vulnerable individuals in general population samples is currently unknown.

Aim:
To address this gap, we applied a multivariate biosignature previously used to predict functional outcome distinctions in CHR to two independent representative samples of healthy individuals. Here, we sought to test whether this biosignature can be identified in these general population samples.

Methods:
Samples: We used structural MRI (sMRI) from 2 representative healthy adults samples derived from the Human Connectome Project (HCP; N = 1113, mean age: 28.8 years, 54.5% female), and Cambridge Centre for Ageing and Neuroscience (CamCAN; N = 594, mean age: 54.3 years, 51.4% female).
Structural preprocessing: The open-source CAT12 toolbox (version r1155, http://dbm.neuro.uni-jena.de/cat12), was used to segment T1 structural images into gray matter (GM), white matter, and cerebrospinal fluid maps, and then to high-dimensionally register them to the stereotactic space of the Montreal Neurological Institute (MNI-152 space) using methods described by Koutsouleri and colleagues.
Model application: We used a multivariate brain structural pattern (biosignature) shown to predict poor outcomes in CHR individuals (Fig 1A). We applied this model without any in-between retraining to the HCP and CamCAN samples to obtain individual predicted class probabilities using the CAT12 preprocessed GM images.
Statistical Analyses: We first tested for group effects in cognition and demographic characteristics between individuals predicted to have good versus poor prognosis based on model application to the two healthy cohorts using independent samples t-tests for continuous variables and chi-square tests for categorical variables. Further, we examined prognostic profiles between the groups using increasingly greater cutoffs from the decision boundary. We compared individuals at different cutoffs using independent t-tests and calculating effect sizes (Cohen’s d) to assess differences in cognition between individuals with poor and good prognosis.

Results:
Biosignature: Applying the prognosticator to the HCP sample, we obtained two groups with 508 individuals predicted to have good outcome (mean [SD] age = 28.99 [3.67], 257 [50.59%] female, Fig. 1B) and 605 individuals predicted to have poor outcome (mean [SD] age = 28.65 [3.72], 349 [57.69%] female). Applying the prognosticator in the CamCAN sample, we obtained two groups with 339 individuals with predicted “good” outcome (mean [SD] age = 55.82 [17.14], 163 [48.08%] female) and 255 individuals with “poor” outcome (mean [SD] age = 47.41 [17.47], 142 [55.69%] female; Fig. 1C). Both samples showed increased GM density in the lateral frontal lobes and decreased GM density in the temporal lobes in those predicted to have poor outcome.
Cognition - HCP: χ2 analyses revealed that the two groups differed significantly in terms of sex (P = 0.019). Independent-samples t-tests showed worse cognitive performance in the poor group compared to the good group in: Penn Line Orientation Test median reaction time (T = 2.94, P = 0.003) and total number correct (T = 3.09, P = 0.002), List Sorting Working Memory Test (T = 2.20, P = 0.028), Pattern Completion Processing Speed (T = 2.52, P = 0.012), and Cognition Fluid Composite (T = 2.16, P = 0.031). Cognitive profiles are shown in Fig. 2. Effect size differences between groups at increasing cutoffs ranged from -0.13 to -0.70, with increasingly worse performance in poor at extremes. CamCAN: Independent-samples t-tests revealed significant differences between the groups in age (T = -5.8, P < 0.001).

There were no significant differences in cognition based on prognostic predictions. Effect size differences in cognition between groups are shown in Fig. 3 at various cutoffs.

Discussion:
These results suggest that biosignatures relevant to poor outcome for psychosis can also identify individuals with suboptimal cognitive functioning in young healthy individuals, which is consistent with the clinical profile of patients. The lack of significant findings in the CamCAN sample may result from a smaller sample size, or increased age range. Future studies should investigate differences prognostic biosignatures’ applicability based on the onset of the disorder. Further studies are needed to discover mechanisms that may translate this state of vulnerability to syndromal clinical expression.

References:

Figure 1: Biosignature used to predict prognosis in CHR in A. the original model. Through external validation of the model, effect size differences in brain volume between the predicted ‘good’ versus ‘poor’ outcome individuals are shown in B. the HCP sample and C. the CamCAN sample.

![Figure 1](image1.jpg)

Figure 2: Cognitive profiles of the two predicted outcome groups in the HCP sample based on increasing standard deviation cutoffs from the decision boundary. Cognitive Function Composite score is derived by averaging the normalized scores of each of the Fluid and Crystallized cognitive measures: Procedural Speed = Pattern Completion Processing Speed; VSPLUT; TO = Penn Line Orientation; Total Number Correct; ListSort = List Sorting Working Memory Test.

![Figure 2](image2.jpg)

Figure 3: Effect size (Cohen’s d) of differences in 2 cognitive measures in the CamCAN sample between the poor versus good predicted outcomes based on increasing SD cutoffs from the decision boundary. Negative effect sizes denote worse performance in poor compared to good groups.

![Figure 3](image3.jpg)