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Using neuroimaging to help predict the onset of psychosis

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Abstract

The aim of this review is to assess the potential for neuroimaging measures to facilitate prediction of the onset of psychosis. Research in this field has mainly involved people at 'ultra-high risk' (UHR) of psychosis, who have a very high risk of developing a psychotic disorder within a few years of presentation to mental health services.

The review details the key findings and developments in this area to date, and examines the methodological and logistical challenges associated with making

predictions in an individual subject in a clinical setting.

Key words

Psychosis prediction; Ultra High-Risk of psychosis; machine learning; Support Vector Machines; multimodal neuroimaging; multicentre neuroimaging studies; graph analysis

Psychosis prediction and the ultra high-risk state

Psychosis describes a syndrome that includes symptoms such as hallucinations, delusions, disorganised thought, and catatonia [1 2]. Psychotic disorders are disorders that include symptoms of psychosis. The most common psychotic disorder is schizophrenia, however psychotic symptoms can occur in other disorders, for example in mood disorders such as bipolar and depression [3].

Before the onset of symptoms that are severe enough to meet the clinical thresholds of a psychotic disorder, those affected experience subclinical psychotic symptoms and a decline in social / occupational functioning [4]. Recognising the value of detecting and treating psychosis early [5], researchers and clinicians have developed the Ultra High-Risk (UHR) of psychosis criteria [6]. UHR criteria are the most commonly used criteria for indicating risk of developing a psychotic disorder [7].

Criteria for UHR status include attenuated psychotic symptoms and / or a brief limited intermittent psychotic episode and / or a genetically determined vulnerability, alongside deterioration in social and occupational functioning [7 8]. UHR status comes

with the caveat that those who meet UHR status are selectively those who have come into contact with clinical services. This review uses the term UHR throughout.

The UHR population is strikingly heterogeneous in terms of clinical outcomes. Follow-up studies [9] [10] suggest that 7 years after clinical presentation, approximately a third of UHR subjects will have developed a psychotic disorder, with most transitions occurring in the first 2 years [11]. Most of those who do not develop a psychotic disorder will have persistent attenuated symptoms and / or have developed another mental health disorder, whilst 14% will have recovered (see figure 1).

Clinical intervention in the UHR group may reduce the likelihood of the onset of a psychotic disorder [12]. However, as most UHR subjects do not develop a psychotic disorder, providing preventative treatment to all of those at risk is clinically inefficient. Identifying biomarkers that could be used to stratify the UHR group according to clinical outcome would enable the selective delivery of preventative interventions to the subgroup that would benefit the most.

It is difficult to predict clinical outcomes in an UHR subject on the basis of their clinical features at presentation. Although the clinical assessment at presentation has good diagnostic validity for ruling out a future psychotic disorder (meta analytical sensitivity of UHR assessment = 0.96) [13], it has only a modest ability to rule in a future psychotic disorder (meta-analytical specificity of UHR assessment = 0.47) [13]. There is thus a need to find other forms of assessment that can improve the specificity of psychosis prediction.

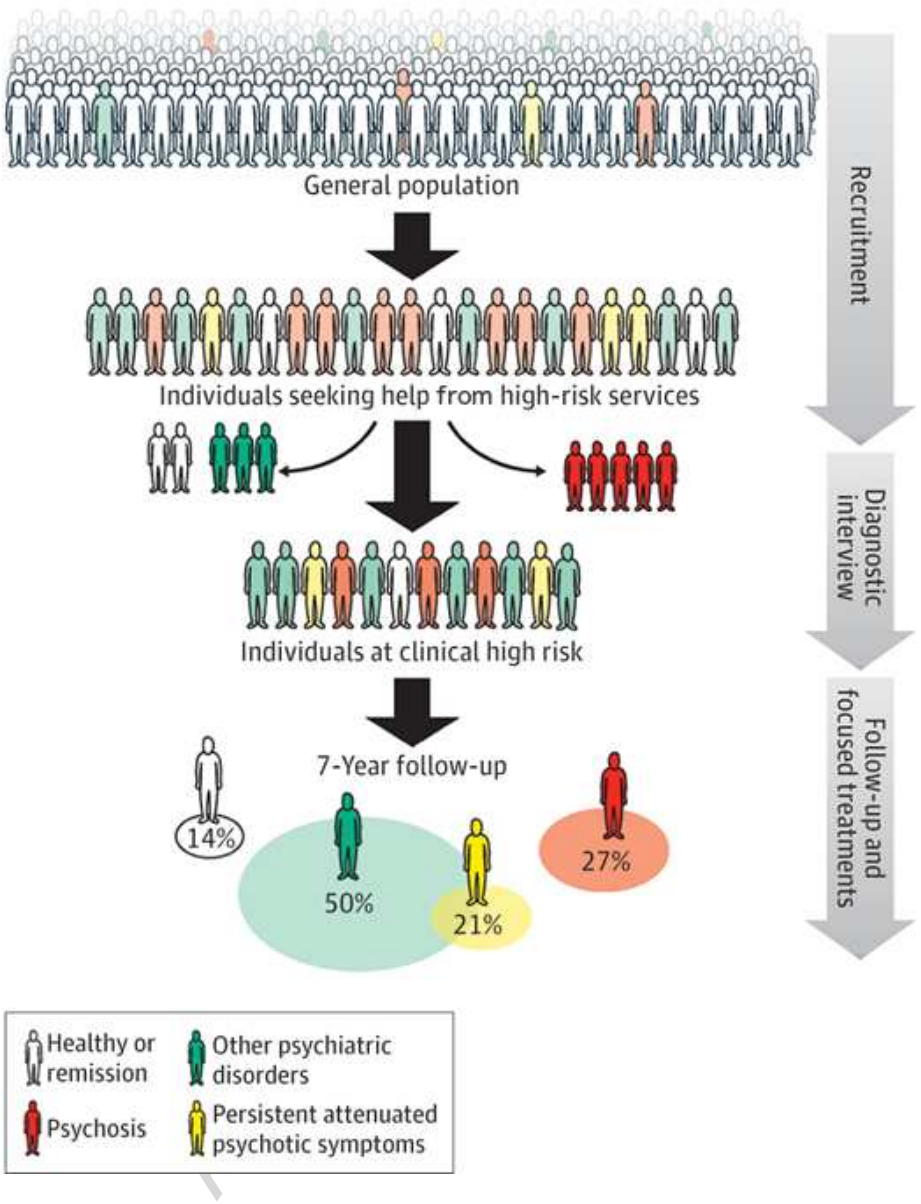


Figure 1. Colour intensifies as those with underlying vulnerability move closer towards disorder manifestation. Taken with permission from Fusar-Poli et al. (2015) [14] *and based on data by Lin et al. (2011)* [10]*.* [Single column fitting image]

Neuroimaging psychosis risk in the UHR population

Neuroimaging techniques have provided a wealth of new information about the

pathophysiology of psychiatric disorders [10]. Neuroimaging studies of the UHR population have implicated increased functional abnormalities in the prefrontal cortex (PFC), midbrain and medial temporal lobe (MTL) [15], structural abnormalities involving the PFC [16 17] and MTL [18], elevated dopaminergic activity in the striatum [19] and midbrain [15], and abnormalities in levels of glutamate [20] and GABA [21]. In general, these abnormalities are qualitatively similar but less severe than those seen in patients with psychotic disorders [5].

These findings represent the difference between the UHR population as a whole and healthy controls. However, the comparison that is relevant to the prediction of psychosis onset is between the minority of UHR subjects that subsequently develops a psychotic disorder and the majority that does not. Cross-sectional neuroimaging studies comparing these two subgroups at presentation have reported differences in activation in the PFC, MTL, midbrain and caudate [10 22], in the volume of the MTL, PFC, and cingulate cortex [23 24], in the integrity of white matter pathways [25], and in glutamate levels in the caudate nuclei [26]. Longitudinal studies with repeated measurements before and after the onset of a psychotic disorder have described progressive changes in MTL and PFC volume [14 27 28], in white matter volume [29] and integrity [30], and in striatal dopamine function [31]. These changes were not evident in UHR subjects who did not develop a psychotic disorder.

Neuroimaging findings associated with the transition to psychosis have understandably been the focus of most studies to date, and most studies have subdivided UHR samples into groups who did or did not develop a psychotic

disorder. However, this subdivision is potentially misleading, as the subgroup that does not develop a psychotic disorder is not homogeneous: in some subjects, their presenting features resolve, such that they no longer meet the UHR criteria, whereas in others their symptoms persist. A further subgroup develop mental health disorders other than psychosis, particularly depression and anxiety (Figure 1) [9 10]. Identifying neuroimaging measures that predict these other outcomes is also of interest. For example, determining the factors that predict recovery may improve our understanding of what determines resilience to mental illness, and could allow clinicians to avoid giving unnecessary treatments to people who would be very likely to recover without any intervention. Recent studies have begun to examine predictors of recovery in the UHR population, but at present this literature is still relatively small [32 33].

Outcome can also be defined in terms of level of functioning, as opposed to clinical status. Long term follow up studies suggest that an UHR individual's level of social and vocational functioning can sometimes be more clinically meaningful than their diagnostic category [34]. Studies have also recently begun to examine the relationship between neuroimaging measures and functional outcomes [32 35 36].

Multi-centre studies

Although the results have been of great interest, to date most neuroimaging studies in UHR subjects have involved small sample sizes [37]. Traditionally, mental health services have not engaged people with psychotic symptoms until after development of a first episode of a psychotic disorder. The concept of clinical provision for UHR

individuals is relatively new, and specialised services for this group are still limited to a minority of psychiatric centres. As UHR subjects are usually ascertained through specialised clinical services, this constrains recruitment to research studies. This can lead to studies being underpowered, particularly if the hypotheses relate to a specific clinical outcome (such as the onset of a psychotic disorder) that is only evident in a subset of the total UHR sample. This issue can be addressed through the recruitment of UHR subjects from multiple different sites: a number of such multi-centre studies involving neuroimaging have recently been completed [15 19] and several others are on-going [38 39 40].

Although multi-centre studies can provide greater statistical power, there is a potential danger of introducing bias from between-centre differences in image acquisition and processing. For example, differences in scanning protocols [41 42] and scanning hardware [43] can cause significant variability in results, as can upgrades of software and hardware within centres [44]. These effects may be reduced through the harmonisation of scanning parameters and quality control across centres, and by the development of acquisition protocols that are specifically designed to minimise between centre variance, such as those used in the Alzheimer's Disease Neuroimaging Initiative (ADNI) [45 44].

Nevertheless, some between-centre variance is inevitable. Some studies quantify this by directly comparing neuroimaging data acquired from a group of volunteers [42 46 47 48] or identical phantoms at different sites [49]. Researchers have also used methods of post hoc statistical correction to adjust for between scanner variance [50].

However, if a predictive tool is to be employed at a variety of sites in a clinical setting, it may not be feasible to use phantoms or travelling subjects to control for between-site effects. In this case, the use of methods for post hoc correction may be more realistic.

Machine learning for individual prediction of psychosis transition

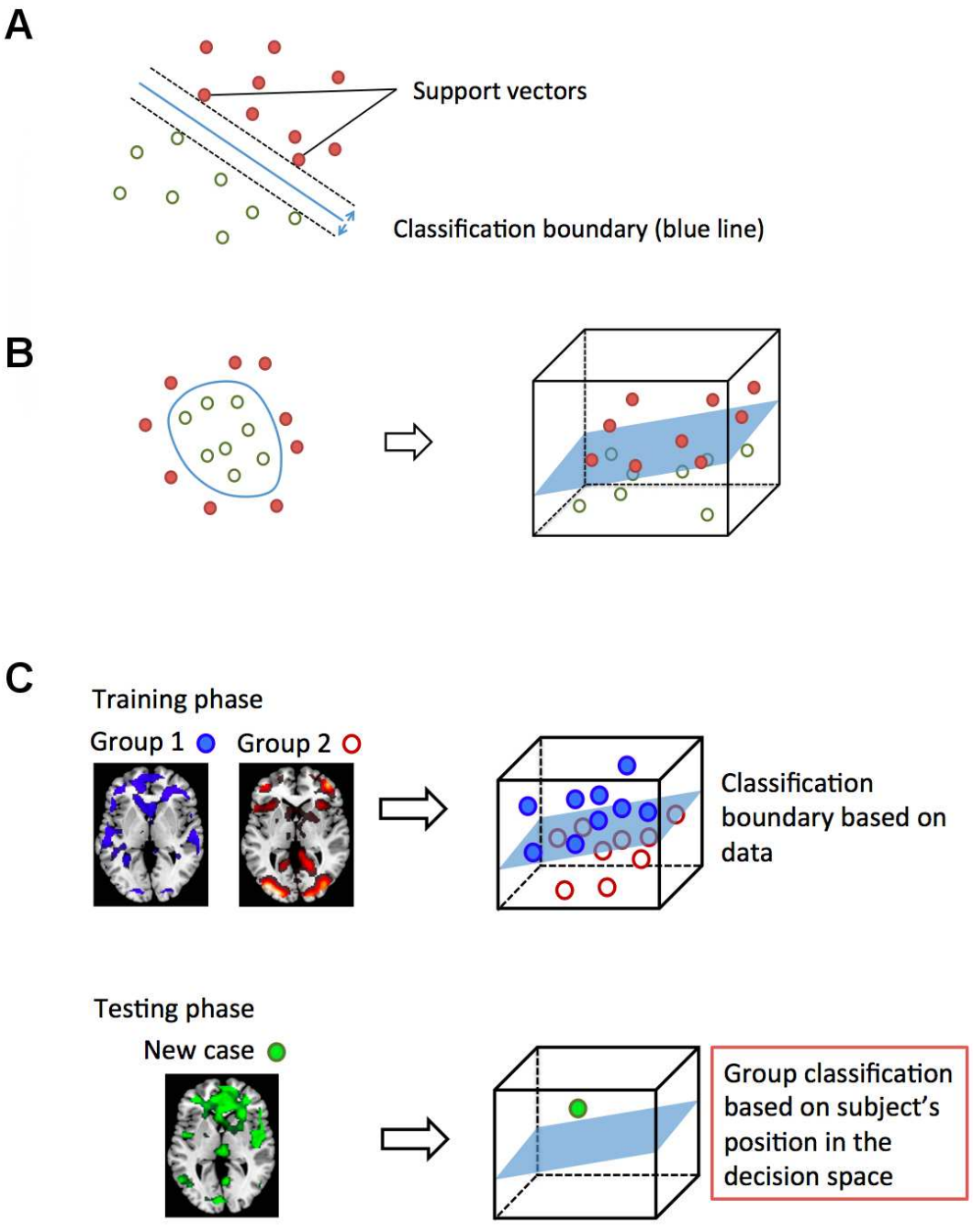
In clinical practice, predictions about the risk of psychosis need to be made using data from a single subject. However, most studies that have identified neuroimaging features that are associated with the onset of a psychotic disorder in UHR samples have described *average* differences between groups, which although statistically significant, describe two highly overlapping populations. In this context, individual inference has a limited utility. This has led to research on the application of statistical approaches that use multivariate patterns rather than group level differences, which are more suited to making individual level inferences. These approaches include machine-learning methods [51], such as Random Forests [52], Support Vector Machines (SVMs) [53], Linear Discriminant Analyses [54], and K-Nearest Neighbour algorithms [55]. Machine learning methods allow for individual classification and are sensitive to subtle effects that would go unnoticed using traditional univariate analyses [56].

The method that has been most widely applied to neuroimaging data is the SVM [57], which may reflect its comparatively better performance with highly dimensional data [58]. One reason for this is that SVMs base classification decisions on the most useful data points (see figure 2), which helps to overcome some of the difficulties

associated with modelling highly dimensional data [53].

The support vector machine (SVM) is a supervised classification algorithm that learns from an initial 'training' dataset to classify new cases into two or more groups [56]. For example, a SVM can be trained on a dataset of baseline neuroimaging measurements from UHR subjects defined by whether they subsequently developed a clinically defined outcome or not, and can then be applied to a new sample of UHR individuals [56] (see figure 2).

Figure 2. A. A classification boundary is created based on the maximum margin space between the two distributions of data points. Only data points near the margin (the support vectors) affect the classification boundary, facilitating a good generalization of the classification model. B. If it is not possible to create a linear classification boundary, a kernel function can be used to transform the data into higher dimensional space where classes become linearly separable. C. Schematic of SVM training and testing with neuroimaging data. In training, information from the two groups, or classes, is used to make a classification algorithm based on the predictive differences of the two groups. In testing, the algorithm is applied to data from a new subject to classify them as belonging to either group. [1.5 column fitting image]



A SVM is validated by demonstrating that it can classify individuals in a sample independent of the dataset it was originally trained on. Ideally this is done using a second dataset that has been acquired separately from the original [56]. Validation

can also be attempted without a second dataset, for example by splitting the original sample (repeatedly), with one portion being used as the training dataset and other portions being used for cross-validation (e.g. k-fold cross-validation [59]). However, any overlap between the training and test datasets will result in the model over-fitting [60]. This issue can be addressed by using methods that ensure separation between the training and test data, such as repeated double cross-validation [61]. Nevertheless, splitting a single sample for training and validation will include sampling error in the classification, and there is a risk that the original sample is atypically easy or difficult to classify, particularly when the sample is small.

Preliminary results from the application of SVMs in UHR samples have been promising. A SVM trained on volumetric MRI data was able to distinguish between UHR subjects who later transitioned and a combined group of non-transitioning UHR subjects and healthy controls with an accuracy of 88%, and between UHR who did not transition and a combined group of healthy controls and UHR who did transition with an accuracy of 86% [62]. A subsequent study used voxel-level MRI measures of grey matter volume to distinguish between UHR participants who did or did not go on to develop a psychotic disorder with an accuracy of 84.2% [63].

To date, applications of SVMs to UHR samples have used cross-validation methods within a single sample [63 64] rather then the ideal validation method of using a second independent dataset. This partly reflects the fact that it is logistically difficult to ascertain large samples of UHR subjects with neuroimaging data and initial studies did not have access to another large dataset with comparable neuroimaging

measures. One study has used a SVM on two small datasets from different centres, although these employed different UHR criteria and MRI protocols. This reported an accuracy of classification of UHR transition outcomes of 80% [65], and also suggested that between centre effects could be minimised by using a sample pooled across both centres for training and testing [65].

The use of larger UHR samples would reduce (though not completely eliminate [66]) the risk of models over-fitting the data [67]. A model that over-fits the data is one that has been influenced by random error and noise in the training data to the extent that it does not accurately reflect the underlying phenomenon being studied [68]. Over-fitting is a particular concern in models where the number of dimensions greatly outweighs the sample size and in highly complex models.

In addition to ensuring a sufficient sample size, over-fitting can be reduced by limiting the analysis to the most predictive features, using dimensionality reduction or subset selection techniques [69]. It is also possible to use the results of previous research to limit predictive models to regions of interest [70], although this relies on the assumption that findings from mass univariate approaches are applicable to a multi-variate analyses.

The size of the sample studied also impacts on the generalizability of the findings. Small samples may result in higher fluctuations of accuracy estimates when using neuroimaging data in SVMs, suggesting poor model generalizability [71]. In addition, larger sample sizes are less affected by sampling effects and capture more of the population's heterogeneity, making them more likely to be representative of the

population being studied [72]. The numerous advantages of studying large samples has led to a wave of multicentre neuroimaging studies that are recruiting UHR subjects from several different centres, often using standardised image acquisition protocols [38 39 40]. A further development has been the HARMONY initiative, which is designed to standardise neuroimaging, clinical, and electrophysiological assessments across these different multi-centre UHR consortia [73]. As well as the opportunity to pool data to create even larger datasets, this will allow a SVM developed using one large sample to be validated on large independent datasets collected by other consortia.

There is also scope for the modification and optimisation of the machine learning methods that have been used in UHR subjects. For instance, SVMs can be modified to incorporate different statistical components. This includes the application of Bayesian probability and 'fuzzy logic' to SVMs, which have been used to create Relevance vector machines (RVM) [74] and Fuzzy SVMs [75] respectively. Both of these methods can be used to minimise the effect of outliers on the training phase of a machine [74 75].

By introducing a different loss function [76] support / relevance vector algorithms can also be used in regression (Support Vector Regression: SVR [77]; Relevance Vector Regression: RVR [74]), which allows for classification in terms of a continuous, as opposed to a categorical outcome. Tognin et al. (2014) used this approach to show that symptom progression in UHR subjects could be predicted using a RVR applied to cortical thickness at presentation [78]. Regression-based machine learning has also

been applied to neuroimaging data to predict 'brain age', whereby individual brains are characterised according to indices of maturity [79 80]. Such examples show high accuracy in predicting age based on MRI-derived brain descriptors in large-scale cohorts of healthy adolescents and adults [81]. In patient populations, Koutsouleris et al. (2013 [79], 2015 [82]) demonstrated 'accelerated aging effects' using volumetric MRI data in different patients groups, including UHR participants. In a longitudinal study, Schnack et al. (2016) showed that aging of the brain continues to accelerate during the first five years after onset of a psychotic disorder [83]. Brain age estimation has also been conducted with resting state fMRI data in a large sample of children, suggesting delayed maturation to predict the presence of mental health problems [84].

These findings suggest that machine learning-based biomarkers for psychosis prediction could be improved by taking account of the potential impact of neurodevelopmental changes on neuroimaging data. For example, predictors trained on UHR samples that are limited to subjects of a narrow age range may not be generalizable to samples that include subjects outside that range, who are at different stages of development. This issue may be particularly relevant to prediction in UHR samples, as these can include subjects within a wide age window (14-40 years), but there can be marked differences in the age of those enrolled at different centres, reflecting variations in the way that UHR subjects are recruited. For example, the mean age in UHR subjects recruited through adolescent or youth mental health services is significantly lower than in subjects enrolled through adult early detection services, and age therefore varies across studies [85]. Large-scale collaborative efforts that include samples with different age ranges such as

HARMONY [73] may help to address the issue of 'neurodevelopmental heterogeneity' in the UHR state.

Multimodal prediction of psychosis onset

A feature of machine learning methods that has yet to be fully exploited in the UHR field is that their use is not restricted to neuroimaging data: they can be applied to multiple data modalities [86]. The integration of data from different modalities may be particularly useful in predicting the onset of psychosis, as it is the result of interactions between a diversity of genetic, environmental and neurobiological factors [87]. Moreover, multimodal neuroimaging studies in UHR subjects indicate that the normal relationships between glutamate and grey matter volume (MRS and sMRI) [88], glutamate and functional activity (MRS and fMRI) [89 90 91], glutamate and dopamine (MRS and PET) [92] and dopamine and functional activity (PET and fMRI) [15 93] are perturbed. These observations are consistent with animal models of psychosis, which also implicate interactions between the medial temporal cortex and the striatum and midbrain, and dopaminergic, glutaminergic and GABAergic dysfunction [94].

To date, most SVM studies in UHR subjects have involved data from a single neuroimaging modality (MRI), although the impact of introducing additional data modalities has recently been explored [86]. This partly reflects the logistical demands associated with acquiring multi-modal neuroimaging data in samples that are large enough to permit comparison of subgroups with different clinical outcomes [95]. However, ongoing multi-centre studies in this field involve a range of different

neuroimaging modalities, as well as genetic, clinical and cognitive data, and will be able to recruit samples large enough to assess predictors of outcomes.

There is some evidence that combining modalities may improve the prediction accuracy of machine learning classifiers. In predicting the onset of Alzheimer's disease from mild cognitive impairment, combining neuroimaging and neurocognitive measures increased the accuracy of SVMs beyond that of a single modality SVM [96 97]. Conversely, a study of UHR, FEP and healthy control subjects found that prediction in some comparisons was more accurate when using a single neuroimaging modality compared to multiple modalities [86]. The authors suggest that this may have been a result of an absence of complementary information in the additional modalities [86].

A further consideration in the use of multiple data modalities is practicality and cost. Data collection with some imaging modalities, such as PET, is expensive, can involve long acquisition times or may require specialist equipment and technical support [44]. On the other hand, the collection of volumetric MRI, blood samples, and behavioural measures is feasible in many centres, making them the most viable options for wider clinical use. However, if predictive findings identified using relatively sophisticated neuroimaging techniques were closely correlated with measures in other domains, the latter could then serve as more accessible and less expensive proxy measures for a neuroimaging gold standard. For example, in the prediction of the onset of Alzheimer's disease, the level of past education and occupational functioning are putative proxy measures for PET data on brain glucose

metabolism [98].

Consortium recruiting large samples of UHR participants will collect a range of imaging, blood-based (bio-marker and genetic), and questionnaire based data [38 39 40]. This is a benefit both due to the range of data-types available for predictive modelling and because it allows for an understanding of the interactions between different biological systems, which may be crucial to predicting the onset of psychosis. For example, it has been suggested that the hypothalamic-pituitary-adrenal axis acts as the mediating system for the influence of stress on psychotic symptoms, a system involving both hormones / inflammatory markers, brain areas, and psychological stress [99 100 101 102].

Another possibility is that less expensive measures may provide predictive models without the need for imaging. Promising preliminary results have been found using machine learning methods on blood-based biomarkers (mainly hormones and inflammatory markers) for the prediction of a future psychotic disorder [103 104]. These early studies used around 15-30 blood-based markers [103 104], which gives an appropriate number of degrees of freedom for a predictive model, a benefit over models based on highly dimensional neuroimaging or genetic data. Given that blood-based biomarkers would likely reflect psychosis risk due to their interface with the brain however, predictive models using both imaging and blood-based biomarkers could perform better than each modality alone.

Graph analysis

Psychosis can be conceptualised as disorder of brain dysconnectivity [105] [106] [107], and neuroimaging studies suggest that both functional and structural connectivity are altered in people at UHR. Moreover, differences in connectivity have also been identified between UHR subjects who later develop a psychotic disorder and those who do not [108] [109], suggesting that measures of connectivity may be useful in predicting the onset of psychosis [110].

There are several methods that can be used to assess connectivity, but one of the most promising involves the application of network modelling approaches such as graph theory (GT), which forms graphs representing patterns of connectivity between brain areas [111]. Brain graphs are conceptualised as comprising nodes (neuroanatomical regions) that are connected by edges (structural/functional connections) [112]. This allows for connectivity to be characterised in terms of functional segregation (e.g. modularity), functional integration (e.g. shortest path length (see figure 3), global efficiency), small world, network motifs, centrality (e.g. degree), and network resilience (e.g. degree distribution) [113]. Graph analysis thus provides information on the integrative features of brain networks.

Brain graphs in healthy participants suggest that the brain is normally organised in a way that maximises the integration of the whole network, while allowing for the segregation of specific brain regions. Brain graphs typically show a modular organization, such that the network can be broken down into smaller sub networks [111], with modules specialized for specific computational processes [114]

Within brain networks, certain nodes, termed hubs, are much more connected than others [111], and form 'rich clubs' [115] (see figure 3). Hubs have more long distance connections and higher metabolic demands than regular nodes [116 117], and because of their strategic position in the network are thought to have an important role in brain functioning [118 119].

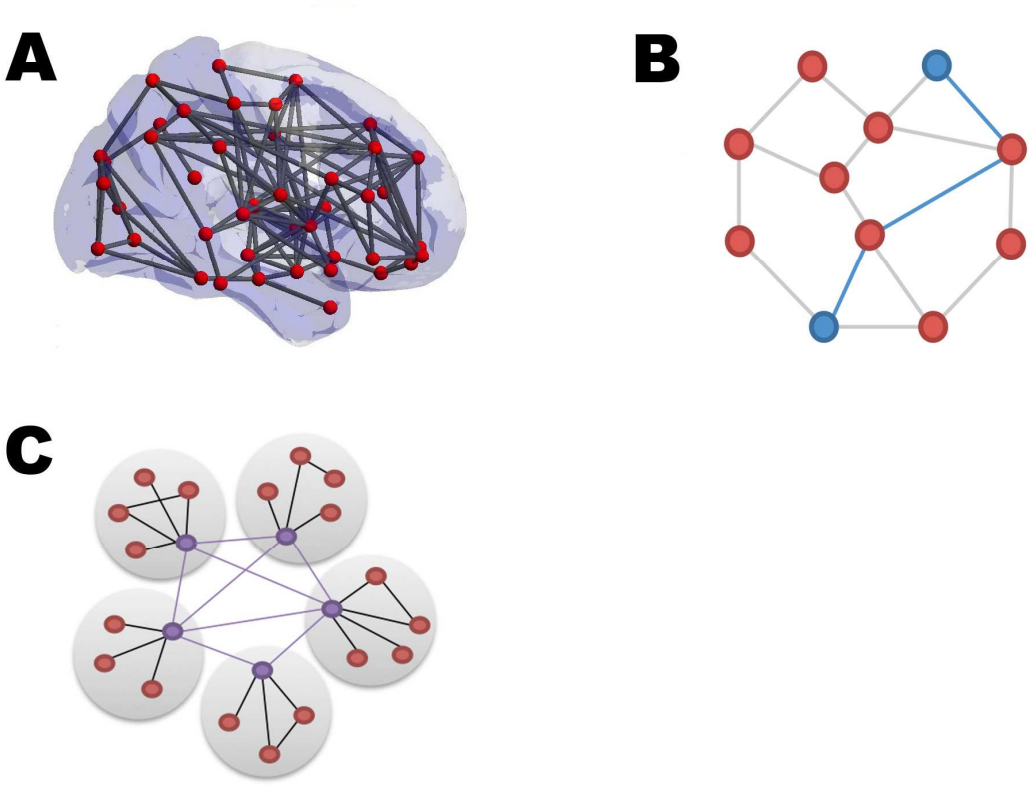


Figure 3. A. Visualisation of a brain graph with 90 defined nodes, parcellated according to the Automatic Anatomical Labelling atlas [120]. B. Simple example of shortest path length. Shortest path between the two blue nodes highlighted by blue edges. C. Example of a network that shows community structure (sub-networks highlighted in grey) with hubs (purple nodes) connected in a rich club (purple edges). [Single column fitting image]

Graph analysis of neuroimaging data in patients with schizophrenia suggests that the disorder is associated with decreased efficiency [121], clustering and small worldness [122], and MRI abnormalities in psychotic disorders appear to be preferentially concentrated in hub regions [123] [124]. Abnormal GT measures have also been associated with elevated psychotic symptomatology in a sample of UHR participants [125].

The mathematical functions of machine learning cannot easily be applied to graphs however [126]. To date, studies that have used graph analysis metrics for machine learning have used whole brain graph theory metrics rather than representing the characteristics of individual nodes and / or edges [127] [128]. In answer to this, methods for transforming graph data in to real vector space have been proposed, allowing for the application of machine learning classification and pattern recognition methods to graph data [126] [129]. For instance, techniques such as graph embedding allow for vector representation of nodes or edges, which can additionally incorporate graph topological features [130]. Additionally, graph kernels carry the possibility of applying graphs to kernel based machines such as SVMs [126]. Developments in this area are on-going [131] but these methods have not yet been validated in brain graphs, and it remains to be seen whether the complex and noisy graphs that are derived from neuroimaging data can be adequately represented [130].

Conclusions

Because it is difficult to predict whether a UHR subject will develop a psychotic disorder on the basis of a clinical assessment, there is a need for biomarkers that

can help to predict outcomes in this group. Neuroimaging measures have the potential to facilitate the prediction of outcomes in UHR subjects. Further progress in their application requires the development of methods that permit prediction using data from an individual subject, and their validation in large independent samples. The extent to which the accuracy of prediction is enhanced by using more than one type of imaging data, or incorporating non-imaging data remains to be determined. Many of these issues are currently being addressed in multi-centre neuroimaging studies in UHR subjects.

The on-going effort to use neuroimaging to facilitate prediction of the onset of psychosis provides a good example of a recent shift in the focus of psychiatric neuroimaging research, from descriptive studies to investigations with an explicitly translational objective.

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Highights

- Machine learning methods allow for prediction of psychosis outcomes in individuals.
- Current multicentre studies seek to recruit sufficient samples for ML prediction.
- Multiple modalities can be incorporated into ML predictive models.
- ML methods can be used to predict continuous outcomes.
- ML can incorporate graph analysis if data is transformed into vector space.

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