NeuroImage: Clinical 34 (2022) 102983

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Neuroanatomical markers of psychotic experiences in adolescents: A machine-learning approach in a longitudinal population-based sample

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ARTICLE INFO

Keywords:
Machine learning
Psychotic experiences
Adolescents
Neuroanatomy
Structural MRI
Diffusion MRI

ABSTRACT

It is important to identify accurate markers of psychiatric illness to aid early prediction of disease course. Subclinical psychotic experiences (PEs) are important risk factors for later mental ill-health and suicidal behaviour. This study used machine learning to investigate neuroanatomical markers of PEs in early and later stages of adolescence.

Machine learning using logistic regression using Elastic Net regularization was applied to T1-weighted and diffusion MRI data to classify adolescents with subclinical psychotic experiences vs. controls across 3 timepoints (Time 1:11–13 years, n = 77; Time 2:14–16 years, n = 56; Time 3:18–20 years, n = 40). Neuroimaging data classified adolescents aged 11–13 years with current PEs vs. controls returning an AROC of 0.62, significantly better than a null model, $p = 1.73^{e-29}$. Neuroimaging data also classified those with PEs at 18–20 years (AROC = 0.59;$P = 7.19^{e-10}$) but performance was at chance level at 14–16 years (AROC = 0.50).

Left hemisphere frontal regions were top discriminant classifiers for 11–13 years-old adolescents with PEs, particularly pars opercularis. Those with future PEs at 18–20 years-old were best distinguished from controls based on left frontal regions, right-hemisphere medial lemniscus, cingulum bundle, precuneus and genu of the corpus callosum (CC).

Deviations from normal adolescent brain development in young people with PEs included an acceleration in the typical pattern of reduction in left frontal thickness and right parietal curvature, and accelerated progression of microstructural changes in right white matter and corpus callosum. These results emphasise the importance of multi-modal analysis for understanding adolescent PEs and provide important new insights into early phenotypes for psychotic experiences.

1. Introduction

Adolescence is a uniquely vulnerable time for the emergence of mental health disorders (Rutter et al., 2006). The prevalence of psychotic disorders in the general population have been reported to be around 1–3.5% (2, 3) however, recent research has shown that psychotic experiences (PEs) in the general population, including hallucinatory and delusional experiences, occur at a significantly higher rate: approximately 17% of children, 8% of adolescents and 5% of adults report these experiences (Di Biase et al., 2020; Kelleher et al., 2012a; McGrath et al., 2015). A large body of research demonstrates that PE are clinically important phenomenon, especially when they occur in adolescence and early adulthood, when they predict a high rate of mental disorders, multimorbid psychopathology, suicidal behaviour, poorer cognitive

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https://doi.org/10.1016/j.nicl.2022.102983
Received 8 August 2021; Received in revised form 1 March 2022; Accepted 2 March 2022
Available online 4 March 2022

performance, and poorer psychosocial functioning (Carey et al., 2020; Healy et al., 2019; Kelleher et al., 2013, 2015, 2017)). Previous research has shown that around 80% of PEs are transitory in nature, with PEs that recur over time being more strongly associated with poor mental health outcomes (Kaymaz et al., 2012; Linscott & Os, 2013; Zammit et al., 2013). Psychotic experiences, especially recurring psychotic experiences, fit within a clinical staging model (Hickie et al., 2013; McGorry, 2012, 2013; McGorry et al., 2018) as markers of more severe and enduring psychopathology (Kelleher et al., 2012b; Wigman et al., 2012). Therefore models for predicting the recurrence of PE over the course of adolescence into early adulthood are valuable.

Machine learning is gaining popularity in attempts to characterize psychiatric conditions using neuroanatomical information (Dwyer et al., 2018; Janssen et al., 2018; Rutledge et al., 2019). Machine learning has the potential to identify complex neuroanatomical patterns in individuals with psychiatric disorders with the hope that this knowledge will enable prediction of illness. Importantly, machine learning can assist in generalizability and reproducibility of findings (Dubois & Adolphs, 2016) and identifying subtle changes in brain development of young people with psychotic experiences. Previous research on the current cohort of adolescents with psychotic experiences at 11–13 years reports neuroanatomical variations in the white matter microstructural organization of the striatum and uncinate fasciculus (O'Hanlon et al., 2015) and hippocampal volume (Calvo et al., 2020).

As PEs are associated with both concurrent (Calkins et al., 2014) and later mental disorders (6, (Dhossche et al., 2002) it is important to distinguish any differences between cross-sectional and longitudinal neuroanatomical changes and PEs. The cerebral cortex undergoes extensive changes over adolescence with cortical thinning being the most profound anatomical change in the cortex during this time, most clearly evident in the frontal lobe (Tamnes et al., 2017; Forde et al., 2017). Understanding the changes in the brain morphometry of adolescents with PEs that differ from normal brain development will increase our knowledge of the aetiology of PEs. This study addressed the following questions using machine learning:

1. What is the neuroanatomic signature associated with the current presence of psychotic experiences in early adolescents (PEs versus non-PEs)?
2. What is the early neuroanatomic signature associated with the recurrence/persistence of psychotic experiences in later adolescence/early adulthood (PEs versus non-PEs)?

2. Method

2.1. Participants

Participants were drawn members of the Adolescent Brain Development (ABD) study who were assessed longitudinally over 3 timepoints from adolescence to early adulthood: Time 1: 11–13 years, Time 2: 14–16 years and Time 3: 18–20 years. Ethical approval for the study was received from the Beaumont Hospital, Dublin, Ireland medical ethics committee and the School of Psychology, Trinity College Dublin, Ireland and all subjects had given their written informed consent prior to the study in accordance with the Declaration of Helsinki. For further details on the recruitment and interviewing, refer to (Kelleher et al., 2008; Kelleher et al., 2012b) and Supplementary Material 1.

The original ABD sample consisted of 211 participants recruited from primary schools in North Dublin, and Kildare, Ireland between 2007 and 2011 (Time 1) - all received a clinical and cognitive assessment and 100 of these participants received an MRI scan (see (O'Hanlon et al., 2015)). At Time 2, 86 participants were re-recruited and 68 received an MRI scan. At Time 3, 53 were re-recruited with 41 receiving MRI scan. No significant difference was found at baseline between those who returned for follow-up and those who did not in terms of age (Time2: $F_{1,76} = 0.77$, $p = 0.39$; Time3: $F_{1,76} = 0.94$,$p = 0.34$), gender (Time 2: $\chi2 = 0.15$, $p = 0.70$; Time 3: $\chi2 = 0.044$, $p = 0.83$) or any past history of contact with psychiatric services (whether the participants had previous contact with child and adolescent services or child counselling services reported at the time of the interview or if any official diagnosis was received) (Time2: $\chi2 = 0.37$, $p = 0.54$; Time 3: $\chi2 = 1.76$, $p = 0.18$).

Psychotic experiences were assessed using the psychosis section of the Schedule for Affective disorders and Schizophrenia for School-Age Children (K-SADS) (Kaufman et al., 1997), and confirmed by a consensus committee (two psychiatrists and a psychologist) (further details in Supplementary Material 1). In line with previous studies [e.g., Avon Longitudinal Study of Parents and Children (ALSPAC) (Zammit et al., 2013) and Dunedin Multidisciplinary Health and Development Study (Fisher et al., 2013; Poulton et al., 2000)], PE were classified as absent, weak or strong at each time point. To ensure dichotomy of the target variables for the machine learning models, we did not include individuals with possible psychotic experiences (weak) in this analysis. The labels for targets variables for the machine learning models were "no PEs" or "strong PEs".

2.2. Diffusion-Weighted imaging acquisition and data analysis at Time 1 (11–13 years)

Whole-brain high-angular resolution diffusion-weighted imaging data with 61 gradient directions and $b = 1500$ s/mm^2 were acquired for each participant on a 3.0-T magnetic resonance system (Intera Achieva; Philips) equipped with an 8-channel head coil. A single $b = 0$ s/mm^2 image was also acquired for the purpose of registration. All imaging was performed on the same magnetic resonance system in Trinity College Institute of Neuroscience, Dublin. A parallel Sensitivity Encoding (SENSE) approach (Pruessmann 1999) with a reduction factor of 2 was utilised for all diffusion weighted image acquisitions. Single shot spin echo-planar imaging was used to acquire diffusion weighted data using the following parameters: echo time (TE) 79 ms, repetition time (TR) 20,122 ms, field of view 248 × 248 mm^2, matrix 128, isotropic voxel resolution 2 × 2 × 2 mm^3, 65 slices with 2 mm thickness with no gap between slices. Preprocessing and CSD based deterministic tractography were performed using a diffusion magnetic resonance imaging toolbox (*ExploreDTI*, RRID:SCR_001643) (https://www.Exploredti.com) (Leemans et al., 2009). Further description of the imaging methods can be found in O'Hanlon et al., (2015).

Automated atlas-based analysis was conducted using Explore DTI as previously implemented in (Kersbergen et al., 2014). The atlas template (ICBM DTI-81 atlas) was warped to each individual data set (motion distortion and eddy current corrected diffusion images) and white matter metrics (Fractional Anisotropy (FA), Medial Diffusivity (MD), Axial Diffusivity (AD) and Radial Diffusivity (RD)) were extracted for each region of interest selected. The ICBM atlas is a probabilistic white matter atlas that fuses diffusion tensor imaging (DTI) white matter information with an anatomical template ICBM-152 (Mori et al., 2008;

Table 1
Demographics for each model over the 3 timepoints. (N = sample size; PE = psychotic experiences; F = female; M = male).

	N	Group (PE/Control, % PE)	Age (PE/Control)	F,p	Gender (F/M)	χ^2,p
11–13 years	77	25/52 (32.5%)	11.56 ± 0.71/11.73 ± 0.59	$F_{(1,76)} = 1.22$, $p = 0.27$	36F/41 M	$\chi^2 = 3.24$,$p = 0.07$
14–16 years	56	12/44 (27%)	15.62 ± 1.43/15.74 ± 1.24	$F_{(1,55)} = 0.09$, $p = 0.76$	28F/24 M	$\chi^2 = 3.23$,$p = 0.07$
18–20 years	40	10/30 (25%)	19.40 ± 1.43/18.9 ± 1.45	$F_{(1.38)} = 0.91$, $p = 0.35$	19F/21 M	$\chi^2 = 1.64$,$p = 0.20$

Oishi et al., 2008). A total of 186 white matter features from Time 1 were included in the models (see Supplementary Table 1 for list of features).

2.3Structural MRI Data Pre-processing and Data Analysis at Time 1 (11–13 years).

180 axial high-resolution T1-weighted anatomical images (TE = 3.8 ms, TR = 8.4 ms, FOV 230 × 230 mm ^{2}, 0.898 × 0.898 mm ^{2} in-plane resolution, slice thickness 0.9 mm, flip angle alpha = 8) were acquired. Scanning was conducted on the same scanner as the diffusion-weighted images at Trinity College Institute of Neuroscience, Dublin.

Cortical reconstruction and volume segmentation were performed with FreeSurfer 5.3, RRID:SCR_001847 (https://surfer.nmr.mgh.harvard.edu). Detailed descriptions of this method are found in Fischl, (2012). Cortical thickness, surface area, volume and gyrification of 34 cortical regions bilaterally were extracted. Subcortical volumes of 7 bilateral regions were also extracted. Brainstem, hippocampal and amygdala-nucleus accumbens subfields were calculated from the developmental version of FreeSurfer (v6.0 2017). A total of 381 grey matter features were included (See Supplementary Table 1 for features included). The ENIGMA Consortium Imaging Protocols (https://enigma.ini.usc.edu/protocols/imaging-protocols/) (Stein et al., 2012) were adopted to extract the data and control for outliers. Any values that were 3 standard deviations from the mean were replaced with the mean of that feature.

2.3. Machine learning analysis

Using machine learning, Time 1 neuroimaging data was used to classify the adolescents with subclinical psychotic experiences from controls over the course of adolescence at Time 1, Time 2 and Time 3 (see Fig. 1). A machine learning approach with penalized logistic regression regularised using the Elastic Net was utilized. The model included a total of 549 neuroanatomical features. The dataset was initially divided into 5 cross-validation (CV) folds in which 80% of the dataset (the training set) was used to create a regression model which was then tested on the remaining 20% of the data (the out-of-sample test, or holdout, set).

In each subfold (inner cross-validation), the data were z-scored and extreme values were replaced with a value of 3 (i.e., Winsorizing). The model was fitted with a range of hyperparameters using the elastic net (Friedman et al., 2010; Qian et al., 2013; Zou and Hastie, 2005), which is a regularization method for generalized linear models that includes l_1 regularization (i.e., lasso regularization - least absolute shrinkage and selection operator) and l_2 regularization (as in ridge regularization). Lasso regularization allows parameters to be 0, promoting parsimonious solutions; whereas ridge regularization allows parameters to be small but not to reach 0, avoiding overfitting (Murphy, 2012). In this model, the objective is to minimize the following equation:

$$\min\left[\frac{1}{2}\|Y - X\beta\|^2 + \lambda\alpha\|\beta\|_{l_1} + \frac{\lambda(1-\alpha)}{2}\|\beta\|_{l_2}^2\right]$$

where Y is the dependent variable (PEs vs controls), X the neuroimaging input data and covariates, β the regression coefficients, λ the penalization for complexity and α is weighting parameter between ridge and lasso regression (Friedman et al., 2010). The complexity and weighting parameters (λ andα, respectively) are not known *a priori*. Therefore, a range of values were explored: 15 linearly-spaced values of both hyperparameters in the range of 0.01 to 10 and all their possible combinations (i.e., a search grid of 225 parameter-pair values). The prediction accuracy of each parameter combination was assessed using the mean squared error. The parameter combination that yielded the lowest error was selected per subfold. The mode of α and the median of λ across subfolds were selected as parameters per main fold. These optimal parameters from the nested cross validation were used to fit a model using the training set of the main fold (outer cross-validation). The prediction of the model on the test set of each main fold was saved and pooled across main folds (Ruedo-Delgado et al., 2019).

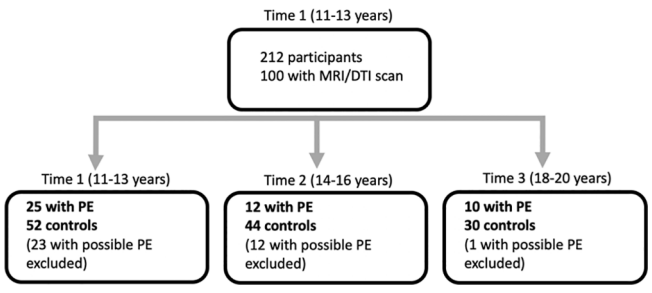

Fig. 1. Number of participants in the Adolescent Brain Development study over three timepoints (Time 1, Time 2 and Time 3). PE = psychotic experience.

In each nested CV fold each feature of the dataset was individually evaluated to assess its utility in classifying the groups (PEs versus non-PEs). This was done by applying a simple logistic regression model to the nested training set (64% of the data) and applying the resulting model to the nested test set (16% of the data), to estimate each feature's utility as predictor. A set of thresholds was created to define subsets of features that met varying minimum cut-off scores for their individual prediction ability and stability across subsets of the sample.

Within each CV fold nested cross-validation was used to set the Elastic Net (Zou & Hastie, 2005) hyperparameters and thresholds. Finally, the combination of model hyperparameters and thresholds that resulted in the model with the maximum the area under the curve of the receiver operating characteristic (AROC) was identified for each nested CV partition. The optimal model hyperparameters and thresholds from each nested CV partition were used to create the final prediction model in each main CV fold. This analysis was carried out five times, using different CV fold allocations each time (i.e., a different out-of-sample test set). The entire analysis was repeated 100 times to attenuate idiosyncrasies of any given model (note: each iteration had 5 folds). Results are mean values across all iterations of the analysis. The performance of each model was further validated by creating null models, which were generated by a random-label permutation (i.e., randomly assigning the outcome variable across subjects). Using this permuted outcome variable, the entire analysis was performed again 100 times. The accuracy achieved using the real data (i.e., actual model) by ranking against the accuracy of the 100 null models. This comparison was done for the area under the curve of the receiver operating characteristic (AROC), true positive rate and true negative rate, and provides an estimate of how likely the result was by chance. Other metrics are also listed including F1 score, area under the curve of precision vs. false positive rate (APR) and logarithmic loss (log loss). The accuracy of the actual model was deemed to be successful if it performed better than the null model based on a *t*-test ($p < 0.016$, 0.05/3 models). As recommended by (Jollans et al., 2019) we did not preselect regions of interest to conduct analyses to include variables not previously linked to the outcome of interest.

The Elastic Net can assign a beta weight of zero to non-informative features. To identify the most predictive features in successful models, we computed the Elastic Net's 'selection frequency' of each individual feature (cf. (Rueda-Delgado et al., 2019)). Selection frequency was calculated by summing each feature's non-zero count in each main fold (i.e., the number of times that feature was selected in the model) and then averaging this value across the 100 repetitions. Features selected in 99% of models were deemed to be robustly predictive. The scripts were run on Matlab V2015a (RRID:SCR_001622).

3. Results

3.1. Demographic information

Table 1 summarises demographic information for the two groups (adolescents with subclinical psychotic experiences (PEs) and controls) at the 3 timepoints over adolescence. One-way between groups analysis

of variance (ANOVA) was used for group comparisons. Sex differences between groups was assessed using chi-squared test. There were no significant group differences in age or sex between adolescents with PEs compared to controls over the 3 timepoints (Table 1). Data were analysed using SPSS statistics (Version 25) (IBM SPSS Statistics, RRID: SCR_019096).

0.2. Longitudinal Results: Classification results for neuroimaging model at 11–13 years over 3 time points.

Using the 11–13 years brain model to classify adolescents with PEs from a control group (adolescents without PEs) at this age returned an AROC of 0.62 (sensitivity = 66.28%, specificity 60.48%). Thirty features exceeded the 99th percentile derived from the null distribution. Features with over 50% selection frequency included the left pars opercularis (84.4% frequency) and the left precentral thickness (57.8% frequency) (see Fig. 4). Classification results for the longitudinal target at 14–16 years returned an AROC of 0.49 (sensitivity = 80.17%, specificity = 26.53%) and 0.59 at 18–20 years (sensitivity = 67.8, specificity = 59.27%). At, 18–20 years, 101 features survived the 99th percentile from the null distribution. There were 8 top discriminant features with over 50% selection frequency which included increased right cingulum (hippocampus) (AD – 86.4% of models) and (MD – 80.4% of models) and right medial lemniscus (52.4% frequency). Reductions in thickness also feature highly in frontal regions, such as left superior frontal (79.2% frequency), left pars opercularis (73% frequency) and left medialorbitofrontal (64.2% frequency) with a reduction in right precuneus curvature (62.8% frequency) (see Fig. 5). The genu of the corpus callosum had 51.8% selection frequency. For further statistical results see Figs. 2 & 3and Supplementary Tables 2 & 3 for classification results.

4. Discussion

Applying machine learning using logistic regression regularized using the Elastic Net, we conducted a multi-modal neuroimaging investigation in adolescents with psychotic experiences (PEs) to examine baseline structural neuroimaging measures associated with current and later PEs. We found that neuroimaging data has some utility at classifying the presence of PEs at 11–13 years though less accurately predicted the recurrence of PEs over time. Reduced cortical thickness in left hemisphere frontal regions discriminate adolescents with psychotic experiences (PEs) from controls at the earliest time point (11–13 years) and are also robust brain classifiers for future PEs at 18–20 years. In addition, reduced right precuneus curvature and microstructural changes in the right cingulum bundle, right medial lemniscus and genu of the corpus callosum were top brain classifiers predicting recurrent PEs 7 years later at 18–20 years. Neuroimaging data was poor at predicting PEs at 14–16 years.

Cortical morphological measurements such as accelerated left frontal cortical thinning could be an early phenotype in psychotic experiences as evident from top discriminatory features in the models, with a reduction of cortical thickness being identified in several left hemisphere frontal cortical regions when predicting current and future PE, in particular, the pars-opercularis, a region in the inferior frontal gyrus strongly involved in language (Costafreda et al., 2006). Significant impairments in receptive language scores and microstructural changes in the arcuate fasciculus, a language-related white matter tract connecting the inferior frontal gyrus, were previously reported in this cohort of adolescents with PEs at 11–13 years (Blanchard et al., 2010; Dooley et al., 2020). Accelerated frontal lobe cortical thinning has been observed in adolescents who developed depressive symptoms (Bos et al., 2018), in externalising behaviours in adolescents (Tanzer et al., 2020) and in adolescents at chronic high risk of psychosis (Cannon et al., 2015; ENIGMA Clinical High Risk for Psychosis Working Group et al., 2021; Jung et al., 2011). Other robust frontal cortical regions classifying the 18–20 year old group included the left superior frontal cortex and left orbitofrontal cortex. The genetic process controlling frontal cortical development may contribute to current and later PEs (Woolf, 1997; Wyatt, 1996).

Increased axial diffusivity (AD) and medial diffusivity (MD) of the right cingulum (section adjoining the hippocampus) was a top discriminator in predicting future PEs at 18–20 years. The parahippocampal (temporal) cingulum has been closely linked to learning and episodic memory (Beckmann et al., 2009). Previously, reduced hippocampal volume has been reported in our PE group (Calvo et al., 2020), which may consequently impact on the cingulum. Increases in MD in the cingulum are implicated in depression (Benedetti et al., 2011), schizophrenia (Takei et al., 2009), autism spectrum disorder (Shukla et al., 2011) OCD (Koch et al., 2014) and ADHD (Amico et al., 2011; Makris et al., 2008). The maturation of the cingulum extends through adolescents and beyond, often not reaching full maturation until mid-twenties or later (Lebel et al., 2019; Lebel & Beaulieu, 2011). The long period of development has significant implications for cognitive and emotional development during adolescence.

Motor-related regions may be a core neuroanatomical marker in the development of current and persistence of recurrent PEs. A reduction of the left precentral thickness was a robust classifier of current PEs at 11–13 year, a region involved in controlling voluntary motor movement with a role in motor speech production (Itabashi et al., 2016) and high functional connectivity with the pars opercularis (Du et al., 2020). A reduction in right medial lemniscus radial diffusivity (RD) in early adolescence classified those with recurrent PEs longitudinally at 18–20 years. The medial lemniscus plays a critical role in sensory function, fine motor coordination and skillful movement (Yang et al., 2009) and is a major somato-sensory pathway. Fine motor deficits have been reported in this adolescent cohort with PEs at 11–13 years, which extend into later adolescence and early adulthood (Carey et al., 2019, 2020). Functional hypo-connectivity of the motor network has previously been reported in this cohort of adolescents with PEs at 11–13 years (O'Neill et al., 2020).

It is important to consider networks of the brain in relation to the development of PEs. In the current study, several brain classifiers predicting future PEs have been identified as nodes in the default mode network. (DMN). The DMN encompasses temporal, parietal and frontal regions that are connected via the cingulum (Greicius et al., 2009) (Alves et al., 2019; Catani et al., 2002, 2012) with the precuneus acting

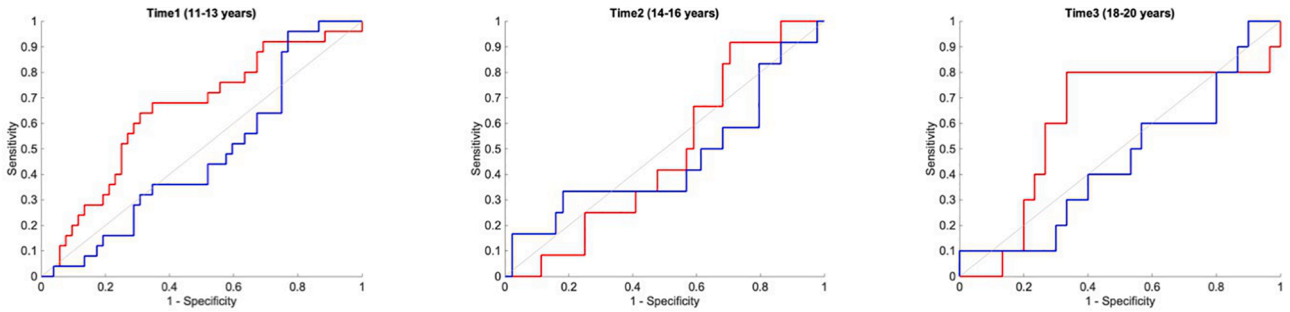

Fig. 2. Receiver operating characteristic curve (ROC) of Time 1 (11–13 years) brain model classifying groups at 11–13 years, 14–16 years and18-20 years.

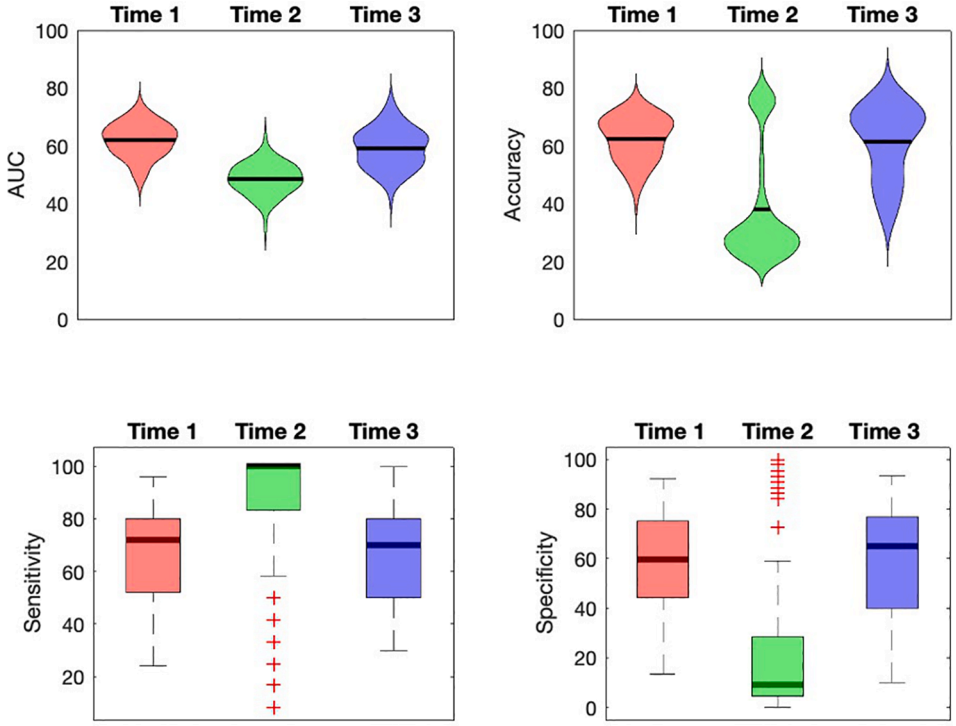

Fig. 3. Area Under the Curve (AUC), Accuracy, Sensitivity and Specificity results across the 3 timepoints over 100 iterations.

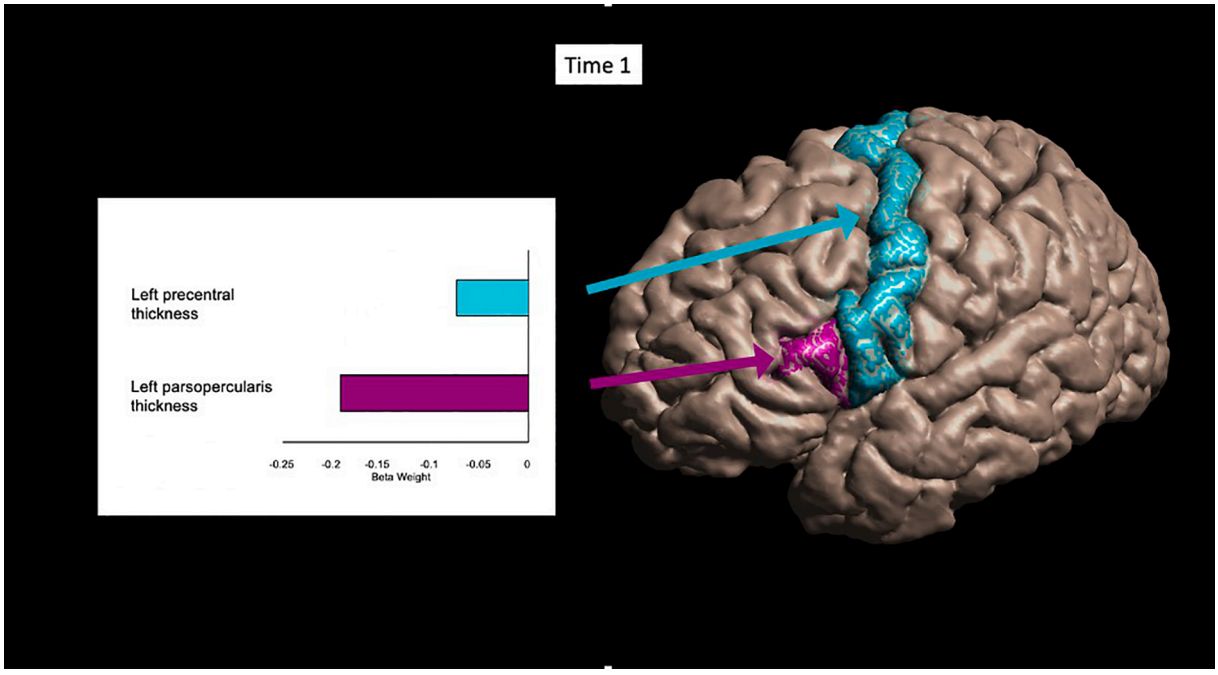

Fig. 4. Top discriminant features with over 50% frequency in all models classifying adolescents with PEs from controls at 11–13 years.

as a functional core of the network (Utevsky et al., 2014). The precueneus, a region involved in self-processing is strongly interconnected with the prefrontal cortex, with the interaction playing a role of in theory of mind and reflective self-awareness (Cavanna & Trimble, 2006). Early childhood adversity has been linked to variations found in the DMN in adulthood, particularly in connections between the medial prefrontal cortex and posterior cingulate cortex/precuneus - a connection that is known to be affected by chronic stress (Dauvermann et al., 2021). A recent study of the current cohort of adolescents with auditory verbal hallucinations reported functional connectivity anomalies related to the DMN (Amico et al., 2017).

Normative developmental maturation processes in the adolescent brain are associated with increased white matter and decreased grey matter in the frontal and parietal cortex (Blakemore, 2012; Lebel & Beaulieu, 2011). The current study reports that adolescents with PEs show an acceleration in typical pattern of reduction in left hemisphere frontal thickness and right parietal curvature, and accelerated progression of microstructural changes in right hemisphere white matter

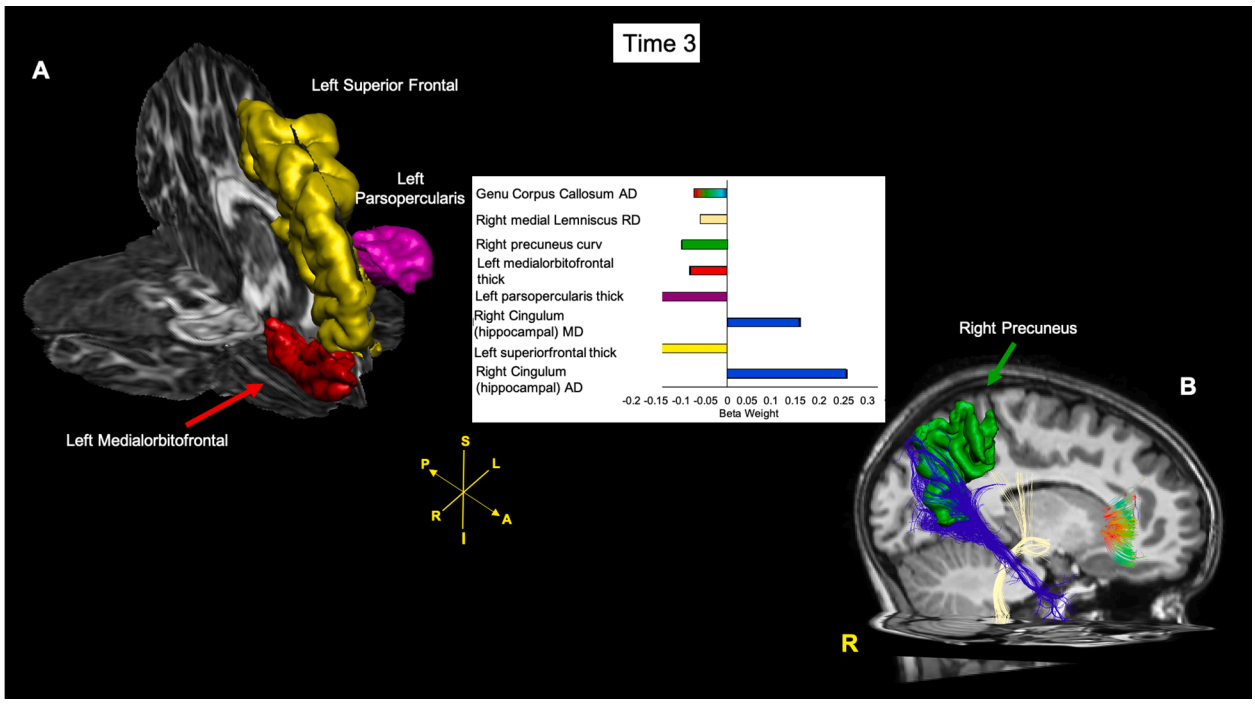

Fig. 5. a & 5b: Top discriminant features with over 50% frequency in all models classifying PEs longitudinally at 18–20 years based on neuroanatomy at 11–13 years.

regions and genu of the corpus callosum. Such deviations in early neurodevelopment trajectories may contribute to the development of current and future PEs.

Strengths of the research include the implementation of state-of-the-art machine learning analysis techniques, which enable prediction on an individual basis. The use of a treatment-naïve, community-based sample rather than a hospital or clinic-based sample increases the generalizability of these results to other adolescent groups. The 3-wave longitudinal design is also a strength. Few papers using machine learning incorporate a follow-up assessment for long-term outcome. Although the accuracy of the neuroimaging model for identifying current and future PEs is below the 80% clinical relevant accuracy threshold, future developments in MRI methodology could improve the sensitivity of this approach. Furthermore, the utility of MRI as a predictor could likely be augmented by the sophisticated integration of other relevant clinical, psychological, demographic and cognitive data (e.g., within a deep learning approach). This is in line with the Research Domain Criteria Initiative at the National Institute of Mental Health who aim to integrate biological and psychological science in understanding the nature of mental health and illness. It is important to note some limitations of the study. Concerns have been raised around the use of the atlas template (ICBM DTI-81 atlas) in terms of the correctness of spatial orientation and correctness of white matter labels (Rohlfing, 2013). However, other studies have utilised this atlas in cohorts of similar age groups as the current study (Lebel et al., 2019). There is a risk of overfitting, due to the small sample size and large feature set used in the prediction models and low signal-to-noise that are characteristic of neuroimaging data (Jollans et al., 2019); therefore, replication studies with larger sample sizes will be valuable. However, given smaller sample sizes, inclusion of larger feature sets may improve model performance as the Elastic Net, when applied to neuroimaging data, has been shown to generally perform better as more features are added, even at lower sample sizes (Jollans et al., 2019).

5. Conclusion

Psychotic experiences, especially recurrent psychotic experiences, fit within a clinical staging model as markers of more severe and enduring psychopathology. Therefore, models for predicting PE and their recurrence over time are valuable. This study aimed to identify underlying neuroanatomical markers of the earliest clinical stages of emerging mental disorders, thereby contributing to preventative and personalised psychiatry. Clinical staging requires widespread investment in novel systems of care to provide timely access to large cohorts of help-seeking youths offering stepwise and evidence-informed care.

Our results provide important new insights into early markers of PEs. The current research highlights that at pre-clinical stages of psychosis, machine learning can discriminate adolescents with PEs from controls based on accelerated reductions in left hemisphere frontal thickness and right parietal curvature, and accelerated progression of microstructural changes in right hemisphere white matter regions and genu of the corpus callosum.

Key Points:

Questions

- Can neuroanatomical markers classify young adolescents with psychotic experiences from controls?
- Can early neuroanatomical markers be used to predict the recurrence of psychotic experiences over the course of adolescents?

Findings

- Neuroimaging data show some utility at predicting the presence of psychotic experiences in adolescents though are less accurate at predicting the recurrence of psychotic experiences over 7 years. Neuroimaging data predicted current psychotic experiences with an AROC of 0.62 and future outcomes of recurrent PEs with an AROC of 0.59.
- Top brain classifiers for current PEs at 11–13 years included a reduction of thickness in left hemisphere frontal regions, particularly pas opercularis.
- Early adolescent brain classifiers for longitudinal PEs at 18–20 years included reduced thickness in left hemisphere frontal regions, reduced right precuneus curvature and accelerated progression of microstructural changes of right hemisphere medial lemniscus, cingulum bundle and genu of the corpus callosum.

- This research makes a significant contribution to preventative and precision psychiatry by identifying individual-level biological markers at the earliest clinical staging of emerging mental disorders.

CRediT authorship contribution statement

Joanne P.M. Kenney: Conceptualization, Data curation, Investigation, Project administration, Formal analysis, Writing – original draft, Visualization. **Laura Milena Rueda-Delgado:** Software. **Erik O. Hanlon:** Software, Visualization. **Lee Jollans:** Software. **Ian Kelleher:** Data curation, Writing – review & editing. **Colm Healy:** Data curation. **Niamh Dooley:** Data curation. **Conor McCandless:** Data curation. **Thomas Frodl:** Software. **Alexander Leemans:** Software. **Catherine Lebel:** Software. **Robert Whelan:** Writing – review & editing, Supervision. **Mary Cannon:** Supervision, Funding acquisition, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This project was funded by a European Research Council Consolidator Award to MC (iHear 724809). JPMK was supported by the European Research Council and Irish Research Council (project number: GOIPD/2019/708). The funding sources had no role in the design or conduct of the study: collection, management, data analysis, interpretation, preparation, review, approval of the manuscript, or decision to submit for publication.

A poster of this research was presented at British Neuroscience Association Conference 2019 and Federation of European Neuroscience Conference 2020.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.102983.

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