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Cortical gray matter reduction precedes transition to psychosis in individuals at clinical high-risk for psychosis: A voxel-based meta-analysis

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ABSTRACT

Gray matter and cortical thickness reductions have been documented in individuals at clinical high-risk for psychosis and may be more pronounced in those who transition to psychosis. However, these findings rely on small samples and are inconsistent across studies. In this review and meta-analysis we aimed to investigate neuroanatomical correlates of clinical high-risk for psychosis and potential predictors of transition, using a novel meta-analytic method (Seed-based *d* Mapping with Permutation of Subject Images) and cortical mask, combining data from surface-based and voxel-based morphometry studies. Individuals at clinical high-risk for psychosis who later transitioned to psychosis were compared to those who did not and to controls, and included three statistical maps. Overall, individuals at clinical high-risk for psychosis did not differ from controls, however, within the clinical high-risk for psychosis group, transition to psychosis was associated with less cortical gray matter in the right temporal lobe (Hedges' $g = -0.377$), anterior cingulate and paracingulate (Hedges' $g = -0.391$). These findings have the potential to help refine prognostic and etiopathological research in early psychosis.

1. Introduction

Individuals at Clinical High-Risk for Psychosis (CHR-P) – which encompasses those with "ultra-high risk" and/or "basic symptoms" (Fusar-Poli, 2017) – are characterized by the presence of subthreshold positive psychotic symptoms and functional impairments, which may precede the transition to full-blown psychosis (Fusar-Poli et al., 2020). Current CHR-P inclusion criteria include attenuated positive psychotic symptoms, brief limited intermittent psychotic symptoms and/or genetic vulnerability together with deterioration in global functioning

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ascertained in the context of a clinical assessment (Fusar-Poli et al., 2015a). Identification of these features is based on validated psychometric interviews which have a very good prognostic accuracy at group level (Fusar-Poli et al., 2015b), provided they are used in clinical samples who have undergone some risk enrichment (Fusar-Poli et al., 2016b). However, this prognostic accuracy is mostly driven by a good ability to rule out psychosis risk, as opposed to ruling in psychosis risk (Fusar-Poli et al., 2015b). Accordingly, the most recent meta-analysis has documented transition risk of 22% at 36 months follow-up (Fusar-Poli et al., 2020), therefore yielding a modest positive predictive value. Competing designations based on the DSM-5-Attenuated Psychosis Syndrome are characterized by comparable prognostic accuracy (Salazar de Pablo et al., 2019).

For the last two decades, numerous structural magnetic resonance imaging studies have attempted to identify brain-based biomarkers which predict transition to psychotic disorders, in order to improve the positive predictive value of current CHR-P instruments. Reduced gray matter volume in the temporo-parietal, prefrontal and limbic cortices, –including the anterior cingulate cortex– (Cannon et al., 2015; Mechelli et al., 2011; Pantelis et al., 2003) have been found in both cross-sectional and prospective CHR-P samples, with stronger effects in CHR-P individuals who later transition to psychosis (CHR-P-T) relative to those who do not (CHR-P-NT). However, structural neuroimaging findings have been conflicting and inconclusive at identifying reliable biomarkers, to the point that no neuroimaging biomarker is currently employed in CHR-P in clinical routine (Fusar-Poli and Meyer-Lindenberg, 2016). This is likely due to small sample sizes of individual studies, and is possibly also due to age-related effects influencing both CHR-P symptoms and structural measures, linked to different stages of brain development (Radua et al., 2012a; Schimmelmann et al., 2015). Furthermore, a large body of literature has suggested that the use of antipsychotics has an impact on brain structure (Smieskova et al., 2009) and has hampered interpretation of neuroimaging findings in patients with early psychosis.

The development of coordinate-based meta-analyses has made it possible to integrate data from individual imaging studies. Two previous structural imaging meta-analyses have been conducted in CHR-P samples (Ding et al., 2019; Fusar-Poli et al., 2011a), pooling studies using voxel-based morphometry (VBM) measures of gray matter volume. These studies yielded contradictory results, reporting for instance both decreased gray matter volume in the right superior temporal gyrus (Fusar-Poli et al., 2011a) and increased gray matter volume in the left superior temporal gyrus (Ding et al., 2019) in CHR-P compared to controls. Furthermore, these meta-analyses only reported on gray matter volume, excluding studies using surface-based metrics (Dale et al., 1999).

We aim here to integrate all available naturalistic data so far by performing a mixed voxel and surface-based meta-analysis of CHR-P samples using Seed-based *d* Mapping with Permutation of Subject Images (SDM-PSI), a novel improvement of an established neuroimaging meta-analytical method (Albajes-Eizagirre et al., 2019c; Radua et al., 2012b, 2014), which allows to include surface-based metrics and directly tests for effects (rather than for convergence of findings as in the previous VBM meta-analyses (Albajes-Eizagirre and Radua, 2018) using a proper permutation of individual images. We hypothesized that individuals with CHR-P would present a) regional cortical gray matter reduction when compared to controls and b) that reduction in these cortical areas would characterize CHR-P who ended up developing a psychotic disorder at follow-up.

2. Material and methods

2.1. Literature search

This systematic review was undertaken in accordance with the MOOSE (Meta-analysis of Observational Studies in Epidemiology) reporting guidelines (Stroup et al., 2000) (MOOSE checklist available in Supplement, eTable 1). A computerized systematic literature search was carried out in MEDLINE/PubMed, PsycINFO and Scopus databases, for studies published up to 31 December 2019. The following search strategy was used: ("clinical high risk" OR "ultra-high risk" OR "at risk" OR "syndrome") AND ("psychosis" OR "schizophrenia") AND ("magnetic resonance imaging" OR "structural" OR "voxel-based morphometry" OR "cortical thickness" OR "volume"). Duplicates were deleted and the title and abstract of each article were scanned for relevance independently by two qualified researchers (AF, AB). Relevant data was extracted from the full text of selected articles meeting inclusion criteria. In addition, reference lists of relevant studies were searched for possible eligible studies, and authors with expertise in the topic were contacted for additional eligible data.

2.2. Inclusion and exclusion criteria

Studies meeting the following criteria were included: 1) original articles published in peer-review journals; 2) written in English; 3) including a CHR-P sample defined according to standardized psychometric instruments (Fusar-Poli et al., 2015a), compared to a healthy control group (HC) and/or CHR-P-T versus CHR-P-NT, in case-control studies with longitudinal follow-up; 4) employing a whole-brain approach; 5) measuring structural data using gray matter volume or cortical thickness metrics. Studies including individuals considered at risk for psychosis but not defined according to validated criteria, studies following a region of interest approach, not providing peak coordinates, or not investigating differences in either CHR-P versus HC or CHR-P-T versus CHR-P-NT contrasts were excluded. Authors from potentially eligible studies were contacted to ask for statistical t-maps; peak coordinates were also requested if these were not reported in the original article.

2.3. Voxel and surface-based morphometry meta-analysis via permutation of subject images

The meta-analysis was conducted using SDM-PSI (http://www.sdmproject.com), which is described in detail and validated elsewhere (Albajes-Eizagirre et al., 2019a,c; Radua et al., 2012b, 2014). Briefly, SDM-PSI uses the combination of statistical t-maps and peak coordinates from each study to estimate multiple times the map of effect sizes of each study based on MetaNSUE algorithms (Albajes-Eizagirre et al., 2019b). Next, each imputed dataset is meta-analyzed using standard random-effects models, and Rubin's rules are used to combine the multiple imputations. Rubin's rules are a set of formulas used to combine the estimates from the different imputation sets (Rubin, 1987). For instance, for effect size, the rule is to average the effect sizes of the meta-analyses derived from the different imputation sets; for the variance of the effect size, the rule also considers the variability between imputations.

In order to study measures of both cortical thickness and gray matter volume simultaneously, a validated cortical mask – instead of the gray matter mask implemented by default – was used (Li et al., 2019). This novel mask allows the combination of VBM and surface-based morphometry studies, increasing the number of studies included and thus the statistical power of the analyses. As already described (Li et al., 2019), the new cortical mask was created following the steps below: conversion of the FreeSurfer left and right hemisphere surface masks into volumes, combination of the two volumes (left and right hemisphere) into a single volume, registration of the volume from FreeSurfer space to MNI space, and narrow smoothing ($\sigma = 0.15$) so as to increase the thickness of the final mask.

First, the meta-analysis was performed between all individuals with CHR-P versus HC. Then, CHR-P-T individuals were compared to CHR-P-NT to assess for cortical abnormalities related to transition to psychosis. Statistical maps provided by authors were preferred over peak coordinates, since their inclusion highly increase the power of the meta-analysis (Albajes-Eizagirre et al., 2019c). If a study reported both cortical

thickness and volume, the latter was preferred for the analysis, because it is the measure which the current meta-analytic method was initially designed for. Results are reported both using uncorrected $P < 0.005$ and voxel extent > 10, and using family-wise error rate (FWER) < 0.05. The use of two statistical thresholds is common in SDM meta-analyses. The "liberal" threshold (uncorrected $p < 0.005$) was proposed to balance false-positive and false-negative rates based on comparing the results of meta-analyses and mega-analyses of the same data (Radua et al., 2012b). The "conservative" threshold (FWER, $p < 0.05$) ensures the control of the false-positive rate. This balance between false positive and false negative rates has been included as one of the "ten simple rules for neuroimaging meta-analysis" (Müller et al., 2018). Hedges' *g* effect sizes were further extracted from relevant peaks. To assess heterogeneity, I^2 statistics were also reported (>50% is considered to indicate serious heterogeneity), and to assess potential publication bias, funnel plots and meta-regressions by standard error were reported.

2.4. Effects of antipsychotic medication and age

To assess the effect of antipsychotic medication, the analyses were repeated including only naïve or "quasi-nave" samples (with less than 10% of individuals receiving antipsychotic treatment). Meta-regression was performed to examine the effect of age on significant regions detected in the main analyses.

2.5. Quality assessment

The quality of all included studies was assessed using a modified version of the Newcastle-Ottawa Scale as reported in previous meta-analyses (Salazar de Pablo et al., 2019). (For detailed information see eTable 2 in the Supplement).

3. Results

Thirty-one studies were included in the meta-analysis. The CHR-P versus HC contrast included 28 studies (CHR-P: 1248 individuals, mean age = 22.33 years, %females = 43.21; HC: 1122, mean age = 22.87 years, %females = 44.96), with partial overlap in 5 samples. The CHR-P-T versus CHR-P-NT contrast included 8 studies (mean follow-up = 23.7 months; CHR-P-T: 153 individuals, mean age = 20.97 years, %females = 43.37; CHR-P-NT: 547 individuals, mean age = 20.90 years, %females = 44.81) with no overlapping samples. See flow-chart of study selection for details (Fig. 1) and Table 1, Table 2 and eTable 1 for detailed information about recruitment and methodology of these studies.

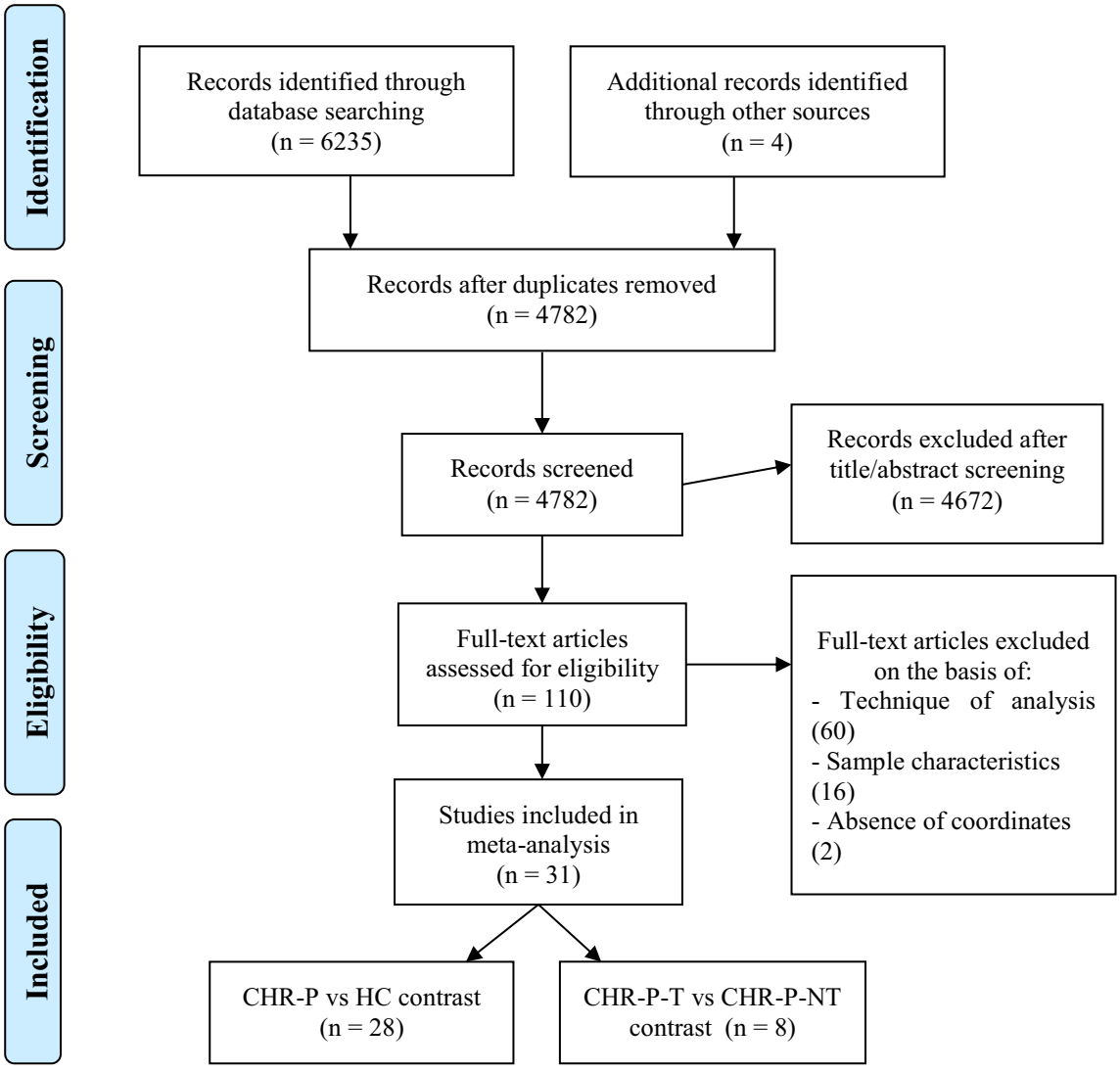

Fig. 1. Flow diagram of study selection and inclusion. Abbreviations: CHR-P, Clinical High Risk for Psychosis; HC, healthy controls; CHR-P-T, CHR-P with transition to psychosis; CHR-P-NT, CHR-P without transition to psychosis.

Table 1
Characteristics of the studies included in the contrast of individuals at Clinical High-Risk for Psychosis versus healthy controls.

Study	Method	Scan	Groups (no. of participants)	Mean age		%Female		AP%
				CHR-P	HC	CHR-P	HC	
Tomyshev et al., 2019	SBM (V)	3 T	CHR-P (30); HC (30)	20	21	0	0	93
Shan et al., 2019	VBM (V)	3 T	CHR-P (74); HC (76)	22	22	42	49	0
Kwak et al., 2019	SBM (CT)	3 T	CHR-P (74); HC (34)	21	20	27	37	0
Sakuma et al., 2018	VBM (V)	1.5 T	CHR-P (45); HC (33)	21	24	60	67	36
Gisselgård et al., 2018	SBM (CT)	1.5 T	CHR-P (41); HC (37)	17	17	51	61	0
Lian et al., 2018	VBM (V)	3 T	CHR-P (19); HC (30)	20	21	32	47	NA
Zhao et al., 2018	VBM (V)	3 T	CHR-P (26); HC (39)	21	22	31	51	0
Dukart et al., 2017[a]	VBM (V, CT)	3 T	CHR-P (59); HC (26)	25	28	27	54	0
Bakker et al., 2016	SBM (CT)	3 T	CHR-P (18); HC (24)	23	23	56	42	0
Iwashiro et al., 2016	VBM (V)	3 T	CHR-P (23); HC (16)	21	24	43	38	NA
Valli et al., 2016	VBM (V)	1.5 T	CHR-P (25); HC (25)	29	25	28	44	0
Klauser et al., 2015[a]	VBM (V); SBM (CT)	3 T	CHR-P (69); HC (32)	22	23	32	47	0
Nenadic et al., 2015	VBM (V)	3 T	CHR-P (43); HC (49)	24	24	51	47	0
Bernasconi et al., 2015	VBM (V)	3 T	CHR-P (49); HC (24)	24	28	22	58	0
Lincoln and Hooker, 2014	VBM (V)	3 T	CHR-P (22); HC (21)	22	22	NA	NA	NA
Roman-Urrestarazu et al., 2014	VBM (V)	1.5 T	CHR-P (39); HC (73)	22	22	74	59	NA
Nakamura et al., 2013	VBM (V)	1.5 T	CHR-P (14); HC (51)	22	24	29	41	21
Jung et al., 2012	VBM (V)	1.5 T	CHR-P (16); HC (23)	22	23	44	43	19
Smieskova et al., 2012	VBM (V)	3 T	CHR-P (31); HC (19)	25	27	71	53	3
Whitford et al., 2012	VBM (V)	3 T	CHR-P (58); HC (19)	19	21	45	63	0
Fusar-Poli et al., 2011b	VBM (V)	1.5 T	CHR-P (39); HC (41)	24	23	38	20	46
Fusar-Poli et al., 2011c	VBM (V)	1.5 T	CHR-P (15); HC (15)	24	25	47	40	0
Mechelli et al., 2011	VBM (V)	1.5/3 T	CHR-P (182); HC (167)	23	24	64	38	8
Koutsouleris et al., 2009	VBM (V)	1.5 T	CHR-P (46); HC (75)	26	25	37	39	0
Stone et al., 2009	VBM (V)	3 T	CHR-P (27); HC (27)	25	25	48	52	19
Ziermans et al., 2009	VBM (V)	1.5 T	CHR-P (54); HC (54)	16	16	39	50	22
Meisenzahl et al., 2008	VBM (V)	1.5 T	CHR-P (75); HC (40)	25	25	39	38	0
Borgwardt et al., 2007	VBM (V)	1.5 T	CHR-P (35); HC (22)	24	23	37	41	9

Abbreviations: %AP, percentage of individuals treated with antipsychotics in the clinical high-risk group; CHR-P, Clinical High-Risk for Psychosis; HC, healthy control; SBM, surface-based morphometry, VBM, voxel-based morphometry; CT (cortical thickness); V (volume); T, Tesla; NA, not applicable.
[a] Available statistical maps provided by authors.

3.1. Differences in cortical gray matter in CHR-P individuals relative to HC

No significant areas of decreased or increased cortical gray matter were found in individuals with CHR-P compared to HC ($P < 0.005$).

3.2. Differences in cortical gray matter in CHR-P individuals according to transition to psychosis

CHR-P-T individuals showed a large cluster of decreased cortical gray matter in the right temporal lobe and superior and middle temporal gyrus; and a second cluster in the right anterior cingulate cortex and paracingulate gyrus ($P = 0.0005$ and 0.0008; Hedges' $g = -0.377 \pm 0.232$ and -0.391 ± 0.232; FWER > 0.05) (Table 3, Fig. 2, eFigure 1), compared to CHR-P-NT. No areas of increased cortical gray matter were found in CHR-P-T relative to CHR-P-NT. The analysis did not show relevant heterogeneity or potential publication bias (Table 3, eFigures 2–3). These analyses were repeated selecting thickness over volume in studies reporting both measures, and yielded overlapping results (see Supplementary analysis).

3.3. Effect of antipsychotics and age

More than 50% of the studies included in the CHR-P versus HC contrast were antipsychotic naïve, and a further 10.7% were quasi-naïve. Seven studies reported rates of over 10% of antipsychotic treatment, and four failed to report psychopharmacological data (see Table 1 for more information). Repeating the meta-analyses including only naïve or quasi-naïve samples yielded unchanged results, revealing no significant clusters of gray matter differences.

Table 2
Characteristics of the studies included in the contrast of individuals at Clinical High-Risk for Psychosis according to transition to psychosis.

Study	Method	Scan	Groups (no. of participants)	Mean age		%Female		AP%
				CHR-P-T	CHR-P-NT	CHR-P-T	CHR-P-NT	
Klauser et al., 2015[a]	VBM (V); SBM (CT)	3 T	CHR-P-T (7); CHR-P-NT (56)	NA	NA	NA	NA	0%
Cannon et al., 2015	SBM (CT)	3 T	CHR-P-T (35); CHR-P-NT (239)	19	20	29%	39%	NA
Ziermans et al., 2012	VBM (V); SBM (CT)	1.5 T	CHR-P-T (8); CHR-P-NT (35)	17	15	32%	50%	23%
Fusar-Poli et al., 2011a	VBM (V)	1.5 T	CHR-P-T (5); CHR-P-NT (17)	NA	NA	NA	NA	46%
Mechelli et al., 2011	VBM (V)	1.5/3 T	CHR-P-T (48); CHR-P-NT (134)	23	23	64%	38%	8%
Koutsouleris et al., 2009	VBM (V)	1.5 T	CHR-P-T (15); CHR-P-NT (18)	22	26	27%	39%	0%
Borgwardt et al., 2007	VBM (V)	1.5 T	CHR-P-T (12); CHR-P-NT (23)	25	23	25%	24%	9%
Pantelis et al., 2003	VBM (V)	1.5 T	CHR-P-T (23); CHR-P-NT (25)	19	22	43%	42%	7%

Abbreviations: CHR-P-T, Clinical High-Risk for Psychosis with transition to psychosis; CHR-P-NT, Clinical High-Risk for Psychosis without transition to psychosis; AP%, percentage of individuals treated with antipsychotics in both Clinical High-Risk for Psychosis (with and without transition) groups; SBM, surface-based morphometry, VBM, voxel-based morphometry; CT (cortical thickness); V (volume); T, Tesla; NA, not applicable.
[a] Available statistical maps provided by authors.

Table 3
Cortical abnormalities in individuals at Clinical High-Risk for Psychosis relative to controls and according to transition to psychosis.

	MNI coordinates	Hedges' *g*	*P* value	FWER	No. of voxels	Heterogeneity (I^2)	Breakdown (no. of voxels)[a]
CHR-P < HC (none)							
CHR-P > HC (none)							
CHR-P-T < CHR-P-NT							
Right anterior cingulate/paracingulate gyri and median cingulate	6, 34, 28	−0.391	0.0005	>0.05	90	4.7%	Right BA 32 (87)
Right superior temporal gyrus/temporal pole	56, 0, −4	−0.377	0.0008	>0.05	133	0.7%	Right BA 48 (31) Right BA 38 (30) Right BA 21 (26)
CHR-P-T > CHR-P-NT (none)							

Abbreviations: MNI, Montreal Neurological Institute; FWER, family-wise error rate; CHR-P, Clinical High-Risk for Psychosis; CHR-P-T, Clinical High-Risk for Psychosis with transition to psychosis; CHR-P-NT, Clinical High-Risk for Psychosis without transition to psychosis; BA, Brodmann area.
[a] Cluster extent threshold = 10 voxels.

For the CHR-P-T versus CHR-P-NT contrast, 5 out of 8 studies were antipsychotic naïve ($n = 2$) or quasi-naïve ($n = 3$). Two studies reported a higher rate –in one of them both groups were receiving antipsychotics, while in the other only individuals in the non-transition group were taking antipsychotics –and one further study did not report data relative to antipsychotic treatment (see Table 2 for more information). Repeating the meta-analyses including only naïve or quasi-naïve samples revealed two comparable clusters located in the right temporal pole and superior temporal gyrus and in the median/anterior cingulate and paracingulate gyrus ($P < 0.005$) (see eTable 2 and eFigure 4 in the Supplement).

Meta-regression found no effects of age in regions showing significant effects in the CHR-P-T versus CHR-P-NT contrast.

3.4. Quality assessment

The Newcastle-Ottawa Scale scores ranged from 4 to 8. For detailed results see eTables 5–6.

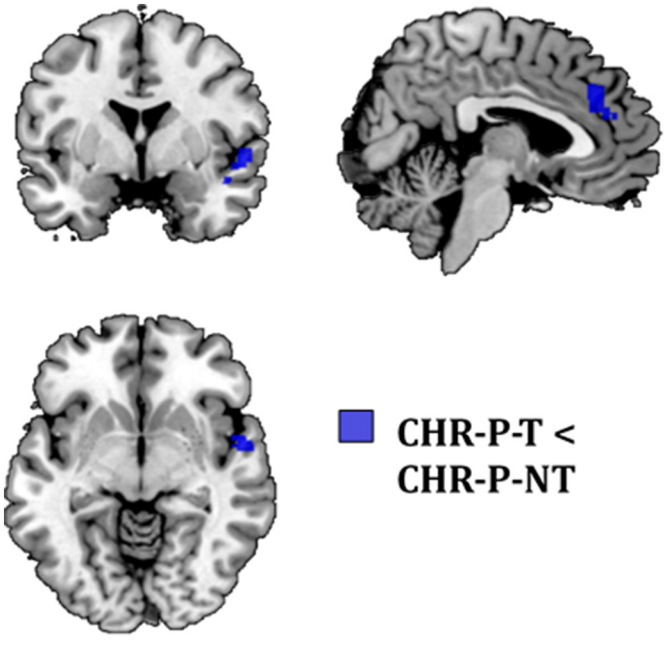

Fig. 2. Meta-analysis of structural abnormalities in CHR-P individuals according to transition to psychosis. Cluster showing between group differences depicted in blue, overlapped on ch2bet template from MRIcron (http://www.bic.mni.mcgill.ca/ServicesAtlases/Colin27). Abbreviations: CHR-P, Clinical High-Risk for Psychosis; HC, healthy controls; CHR-P-T, Clinical High-Risk for Psychosis with transition to psychosis; CHR-P-NT, Clinical High-Risk for Psychosis without transition to psychosis.

4. Discussion

This is, to our knowledge, the first structural neuroimaging meta-analysis which combines cortical information obtained using both VBM and surface-based morphometry techniques in CHR-P individuals to predict the onset of psychosis. The main findings of the present study were that CHR-P-T showed decreased cortical gray matter at baseline in the right temporal pole and superior temporal gyrus, and in the anterior cingulate and right paracingulate gyrus, compared to CHR-P-NT individuals, while CHR-P did not show any areas of decreased or increased cortical gray matter when compared to HC. Tests assessing the robustness of the findings confirmed that results were consistent.

In comparison with previous structural imaging meta-analyses in CHR-P individuals (Ding et al., 2019; Fusar-Poli et al., 2011a), the current study reported a substantially larger number of studies ($N = 31$ in relation to $N = 10$ (Fusar-Poli et al., 2011a) and $N = 14$ (Ding et al., 2019) for the CHR-P versus HC contrast, and $N = 8$ compared to N = 3 for the CHR-P-T versus CHR-P-NT contrast (Fusar-Poli et al., 2011a), and included three statistical maps, in addition to peak coordinates, provided by authors of original articles. Methodological improvements brought by SDM-PSI software (http://www.sdmproject.com) provide more statistically reliable and robust results, including greater accuracy and control of false positives, as well as enabling inclusion of negative results (Albajes-Eizagirre et al., 2019b,c; Radua et al., 2012b). It also benefits from the use of effect sizes, multiple imputation, random-effects models, Freedman-Lane-based permutation, and threshold-free cluster enhancement statistics, among other features (Albajes-Eizagirre et al., 2019c). The methodological improvements bought by the meta-analytic procedures, together with the inclusion of a larger number of samples, may explain the loss of significance of some of the regions reported in previous meta-analyses, although reduced cortical gray matter of the superior temporal gyrus, specifically in the right hemisphere, in individuals with CHR-P-T is consistent with one of the previous reports (Fusar-Poli et al., 2011a). In addition, we provide new evidence of gray matter reduction in the right anterior cingulate cortex as predictor of transition, which may not have been detected previously due to the small number of studies examining this contrast. Thus, our findings suggest that gray matter abnormalities reported so far are not characteristic of the risk group compared to the HC. Individuals with CHR-P constitute a heterogeneous group (Fusar-Poli et al., 2016a), with a differential accumulation of risk factors for psychosis (Oliver et al., 2020). In contrast, our findings are more robust in identifying specific cortical gray matter abnormalities at baseline that characterize CHR-P-T individuals.

From a methodological perspective, while there are currently fewer whole-brain surface-based morphometry than VBM studies in CHR-P samples, their inclusion in the present meta-analysis has allowed us to incorporate measures of cortical thickness, which represents a sensitive measure for detecting anatomic changes (Fornito et al., 2008). Cortical thickness is considered to reflect acute processes occurring proximally

to psychosis onset, as the first symptoms emerge (Morrison and Hof, 1997), whereas gray matter volume may also reflect changes in surface area, potentially influenced by processes taking place earlier during neurodevelopment (Sugranyes et al., 2017). There is evidence of high regional correlation between gray matter volume and cortical thickness obtained using VBM and surface-based morphometry, suggesting that the combination of both methods can provide accurate information (Winkler et al., 2010). Nevertheless, the results from the present study are likely to be mainly driven by gray matter volume, since the number of surface-based morphometry studies was low, especially for the transition contrast. Thus, it is not possible to extract conclusions on the specific contribution of baseline changes in cortical thickness to transition to psychosis from the current meta-analysis.

From an etiopathological perspective, the identified brain regions have been implicated in the pathogenesis of psychotic disorders at different levels. The anterior cingulate cortex is a limbic structure which has connections with other limbic areas like the amygdala or orbitofrontal cortex and plays an important role in cognitive control, fear conditioning and socio-emotional processing (Morawetz et al., 2017; Rolls, 2019), which underpin some of the characteristic symptoms of CHR-P (Van Donkersgoed et al., 2015). The anterior cingulate cortex is also implicated in other functions which are not specifically related with psychosis, such us physical pain processing (Bliss et al., 2016). Structural and functional abnormalities of the anterior cingulate have also been found in transdiagnostic mental health studies, and are considered to index general psychopathology and symptom severity (Etkin et al., 2011; Mcteague et al., 2020). Therefore, gray matter reductions in the anterior cingulate cortex may reflect general clinical impairment, which may be more accentuated in CHR-P-T individuals. On the other hand, the superior temporal gyrus is a heteromodal association site, which receives input from multiple sensory or multimodal areas, involved in processing of audiovisual stimuli, including facial recognition (Mesulam, 1998),and cognitive functions, such as language. Impairments in this area have been associated with positive symptoms, including auditory hallucinations, and have been identified to play an important role in the pathophysiology of psychosis (Kim et al., 2021; Reichenberg et al., 2010; Walton et al., 2017). In fact, cognitive impairments in visual knowledge and visual-spatial problem-solving ability have been reported in children and adolescents who later developed adult schizophrenia (Reichenberg et al., 2010). Similarly, emotion recognition deficits, which have been associated with dysfunction of the superior temporal gyrus, have been shown to predict transition to psychosis in CHR-P individuals (Corcoran et al., 2015). Emotion recognition deficits are thought to be associated with impaired motion processing in both CHR-P individuals and patients with schizophrenia, emphasizing the importance of sensory-level visual dysfunction in the etiology of schizophrenia (Martínez et al., 2018). A multimodal meta-analysis performed by our group revealed gray matter volume reductions in the bilateral superior temporal gyrus, as well as in the insula, medial frontal gyrus and anterior cingulate gyrus in patients with a first episode of psychosis, which was associated to functional abnormalities in the same regions during cognitive tasks (Radua et al., 2012a). These findings, in line with cortical structural changes detected in the present meta-analysis, suggest an association between neuroanatomical and functional abnormalities (Fusar-Poli et al., 2011a). It is noteworthy that in the present study, reductions in the anterior cingulate cortex and superior temporal gyrus were limited to the right hemisphere. This is in line with previous meta-analytical evidence by Fusar-Poli et al. (2011a) and also coincides with reports from the largest longitudinal CHR-P sample to date, in which steeper rates of longitudinal cortical thickness reductions were found predominantly in the right hemisphere in CHR-P-T, and included the right superior temporal gyrus (Cannon et al., 2015). The authors hypothesized that the right hemisphere may play a more important role in the initial stages of the disease, and that these deficits progress to the left hemisphere as psychosis develops. Indeed, predominantly right hemisphere dysfunction (Jacobson et al., 2010) and volumetric decrease (Satterthwaite et al., 2016) have been described in young adolescents with psychotic spectrum symptoms, considered to represent an earlier phase of the disease. Furthermore, a recent study has also suggested that the abnormal cerebral asymmetry exhibited by patients with schizophrenia increases over time in CHR individuals (Damme et al., 2020), in whom the left-lateralized abnormalities may become more accentuated as they progress towards the disease. Although limited, this study holds potential implications towards the improvement of individualized models for predicting the onset of psychosis (Fusar-Poli et al., 2018). Over the past years a number of prognostic models have been developed in psychiatry employing methods such as clinical-learning or machine-based learning (Fusar-Poli et al., 2019a; Poldrack et al., 2019). Several risk calculators designed to predict transition to psychosis in CHR-P samples are available, some already externally validated (Cannon et al., 2016; Carrión et al., 2016; Fusar-Poli et al., 2017, 2019b). While predictors in such models so far have mostly focused on clinical and demographic features, more recent machine-learning studies have suggested that adding neuroimaging predictors to clinical predictors can increase prognostic accuracy when assessing CHR-P individuals (Koutsouleris et al., 2018). Current guidelines recommend that predictors are to be pre-specified, and selected on the basis of a priori knowledge (Fusar-Poli et al., 2018), in order to avoid potential bias. Thus, the current meta-analytic findings may help provide a-priori knowledge of regions that may be incorporated in future prognostic models that are being developed as part of ongoing international CHR-P consortia, such as Psyscan (http://psyscan.eu), Accelerated Medicines Partnership in Schizophrenia (https://fnih.org/our-programs/AMP/schizophrenia) or Pronia (http://www.pronia.eu).

This study also controlled the core findings for some important confounders. Results from the CHR-P-T versus CHR-P-NT contrast remained unchanged when analyzing only antipsychotic naïve and quasi-naïve samples, suggesting that the findings were not driven by the effects of antipsychotic treatment. Antipsychotic treatments in CHR-P individuals are not recommended as first line treatment, and only used in low doses for short periods of time (Schmidt et al., 2015), so the effects of medication on brain structure are unlikely to be comparable to the effects observed in established psychosis. Meta-regression also revealed no age-related differences, which could be due to a lack of power to detect small effects, and possibly also to the fact that our design was not sensitive to within sample age differences. A recent meta-analysis found no age impact on the risk of developing psychosis in CHR-P samples (Fusar-Poli et al., 2016a). However, it is noteworthy that while adolescence is thought to be an especially important period in terms of the neurobiological pathways leading to psychosis (Keshavan et al., 2014), few studies so far have focused on adolescents with CHR-P, or have considered structural imaging findings in the context of neurodevelopmental change (de Wit et al., 2016; Ziermans et al., 2012).

This study has several methodological limitations. Effects of other moderators that may potentially influence cortical structure were not explored due to insufficient data provided from the original studies, such as type of CHR-P subgroup, treatment with antidepressant medication, psychological interventions, or comorbid alcohol or drug use. Although this is the largest meta-analysis of structural imaging in CHR-P individuals performed so far, the sample size, especially when assessing transition to psychosis, could have limited the power to detect differences surviving FWER correction. Nevertheless, the empirical validation of this threshold has showed that it may be over-conservative, as the actual false positive rate using FWER $p < 0.05$ was approximately 1% (Albajes-Eizagirre et al., 2019c). In fact, the use of more than one statistical threshold is considered to be a critical factor for grading the strength of the evidence from previous studies (Fusar-Poli and Radua, 2018; Radua et al., 2018). While providing knowledge to researchers developing predictive models, translatability of our results to the individual level will require caution, given the modest effect sizes of single studies. Finally, application of a cortical mask in the analysis excluded potential volumetric differences in subcortical and cerebellar structures

that could play a role in transition to psychosis, although we considered this to be beyond the scope of the present study.

5. Conclusions

Cortical gray matter reduction in the anterior cingulate, paracingulate and right superior temporal cortex are observed in CHR-P individuals who later developed a psychotic disorder. This evidence can refine prognostic and etiopathological research in early psychosis.

Role of the funding source

This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2021.05.008.

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