Gray matter volume differences between affective and non-affective first episode psychosis: A review of Magnetic Resonance Imaging studies

A. Calvo , G. Delvecchio , A.C. Altamura , J.C. Soares , P. Brambilla

PII: S0165-0327(17)32317-0
DOI: 10.1016/j.jad.2018.03.008
Reference: JAD 9649

To appear in: *Journal of Affective Disorders*

Received date: 8 November 2017
Revised date: 22 January 2018
Accepted date: 14 March 2018

Please cite this article as: A. Calvo , G. Delvecchio , A.C. Altamura , J.C. Soares , P. Brambilla , Gray matter volume differences between affective and non-affective first episode psychosis: A review of Magnetic Resonance Imaging studies, *Journal of Affective Disorders* (2018), doi: 10.1016/j.jad.2018.03.008

Highlights

- *This review summarizes MRI studies exploring brain deficits in both NA-FEP and A-FEP patients.*
- *The evidence suggested that the two diagnostic groups showed common and distinct pattern of GM deficits.*
- *This review highlights the importance of identifying neural biomarkers of FEP, which may ultimately be useful for more targeted treatments.*

Gray matter volume differences between affective and non-affective first episode psychosis: A review of Magnetic Resonance Imaging studies.

A. Calvo[a*#], G. Delvecchio[b,e#], A.C. Altamura[b], J.C. Soares[d], P. Brambilla[c e*]

[a] *Faculty of Health Sciences. Universidad Internacional de la Rioja (UNIR), Spain.*
[b] *Department of Neurosciences and Mental Health, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy.*
[c] *Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy.*
[d] *Department of Psychiatry and Behavioral Sciences, University of Texas Health Science Center at Houston, TX, USA*
[e] *IRCCS "E. Medea" Scientific Institute, Bosisio Parini (LC), Italy*

* Address for correspondence:

Paolo Brambilla Department of Neurosciences and Mental Health, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, via F. Sforza 35, 20122 Milan, Italy (Email: paolo.brambilla1@unimi.it); Ana Calvo: Faculty of Health Sciences. Universidad Internacional de La Rioja,(UNIR). Almansa street. 101. 28040. Madrid. Spain. (Email: anabelen.calvo@unir.net)

# These authors contributed equally to this article.

Key words: Magnetic Resonance Imaging, gray matter, first episode psychosis, affective, non-affective.

No. of Words (Abstract): 168

No. of Words (Text): 1313

No. of Tables: 1

References: 48

ABSTRACT

Background: Non-affective and affective psychoses are very common mental disorders. However, their neurobiological underpinnings are still poorly understood. Therefore, the goal of the present review was to evaluate structural Magnetic Resonance Imaging (MRI) studies exploring brain deficits in both non-affective (NA-FEP) and affective first episode psychosis (A-FEP). **Methods:** A bibliographic search on PUBMED of all MRI studies exploring differences in gray matter (GM) volume between NA-FEP and A-FEP was conducted. **Results:** Overall, the results from the available evidence showed that the two diagnostic groups share common GM alterations in fronto-temporal regions and anterior cingulate cortex. In contrast, unique GM deficits have also been observed, with reductions in amygdala for A-FEP and in hippocampus and insula for NA-FEP. **Limitations**: Few small MRI studies with heterogeneous methodology. **Conclusions:** Although the evidences are far to be conclusive, they suggest the presence of common and distinct pattern of GM alterations in NA-FEP and A-FEP. Future larger longitudinal studies are needed to further characterize specific neural biomarkers in homogenous NA-FEP and A-FEP samples.

Introduction

Affective and non-affective psychoses are two common psychiatric illnesses characterized by both overlapping and unique brain abnormalities (Hibar et al., 2017; van Erp et al., 2016). Specifically, affective psychoses, and in particular bipolar disorder (BD), have been associated with gray matter (GM) reductions in prefrontal and paralimbic regions, including anterior cingulate cortex and insula, compared to healthy controls (Ellison-Wright and Bullmore, 2010). In contrast, ventricular enlargement and diffuse fronto-temporal GM reductions seem to characterize non-affective psychoses, especially schizophrenia (SCZ) (Berger et al., 2017; Chung et al., 2017; Wright et al., 2000). However, recent evidence also revealed the presence of a substantial overlap in GM volume alterations in BD and SCZ (Ellison-Wright and Bullmore, 2010).

Interestingly, it has also been consistently reported that GM deficits already occur in the early phases of psychosis, as reported by several neuroimaging studies investigating common and distinct pattern of GM alterations in first episode psychosis (FEP) patients with both affective and non-affective psychosis(de Castro-Manglano et al., 2011). Indeed, GM reductions in anterior cingulate cortex and insula seem to characterize both A-FEP and NA-FEP (Birur et al., 2017). In contrast, while NA-FEP patients showed a significant ventricular enlargement as well as a reduction of whole brain and hippocampal volumes in both cerebral hemispheres compared to healthy controls (Vita et al., 2006), A-FEP patients reported significant reductions in total intracranial and white matter volumes (Vita et al., 2009). Nonetheless, Magnetic Resonance Imaging (MRI) studies directly comparing A-FEP and NA-FEP are still scarce.

Methods

This review aimed at summarizing the results of MRI studies investigating GM deficits in both A-FEP and NA-FEP in order to provide a focused overview of the presence of common or distinct GM deficits associated with these two disorders. A bibliographic search on PUBMED of all MRI studies exploring volumes differences in A-FEP and NA-FEP from 2005 up to August 2017 was performed. The search terms used to identify the articles of interest were “Magnetic Resonance Imaging ” in combination with “first episode psychosis", "first episode affective psychosis", "first episode non-affective psychosis", "first episode bipolar disorder", "first episode schizophrenia". We excluded articles if they: a) investigated only white matter alterations, b) explored GM alterations in chronic patients with either BD or SCZ, c) provided results only on longitudinal data, d) employed only a sample of children\adolescents, and e) did not include results from a direct comparison between A-FEP and NA-FEP in the analyses.

We retrieved 14 MRI studies that met the inclusion criteria. All of these studies employed a 1.5T scanner, except for one which used a 3T scanner (Qiu et al., 2013) for exploring cortical and subcortical regions in A-FEP and NA-FEP patients. Details of the characteristics of the individual studies are shown in Table 1.

Results

With regard to cortical regions, four MRI studies investigated the presence of cortical thickness differences between A-FEP and NA-FEP (Pina-Camacho et al., 2016; Qiu et al., 2013; Ansell et al., 2015;(Nakamura et al., 2007). However, only two MRI studies reported significant results (Pina-Camacho et al., 2016; Qiu et al., 2013). Specifically, greater cortical thinning in the left inferior frontal gyrus, left cuneus, right middle temporal gyrus and right superior temporal sulcus was observed in NA-FEP compared to A-FEP (Qiu et al., 2013). Moreover, Pina-Camacho et al. (2016) found that earlier age at NA-FEP patients had significantly smaller frontal volumes and thinner frontal, temporal, parietal, medial orbitofrontal, insular cortices as well as smaller middle frontal gyrus volumes and thinner precuneus than A-FEP .

Furthermore, it has been shown that NA-FEP patients have significantly less GM volumes in superior temporal gyri, posterior temporal lobe, and lateral and medial frontal regions in respect to A-FEP (Farrow et al., 2005; Takahashi et al., 2009a). Overall, these evidences are in line with previous MRI findings reporting widespread GM abnormalities in SCZ, particularly in fronto-temporal regions (Chan et al., 2009; Kim et al., 2017; Squarcina et al., 2017a; Squarcina et al., 2015), which are crucial to coordinate executive functions, and language processes (Sumich et al., 2005). Additionally, two studies observed smaller GM volumes in cingulate gyrus in NA-FEP (Koo et al., 2008) and A-FEP (Morgan et al., 2007) compared to healthy controls, whereas no significant differences were found between the two patient groups. The cingulate gyrus is a cortical area often found to be implicated in BD and SCZ (Baiano et al., 2007; Crow et al., 2013; Maggioni et al., 2016; Squarcina et al., 2017b) due to its involvement in a range of functions, including emotional, cognitive, attentional, nociceptive, and motor functions (Mesulam et al., 2001).

Interestingly, three studies found unique GM volume reductions in insula in NA-FEP patients compared to healthy controls (de Castro-Manglano et al., 2011; Lee et al., 2016; Takahashi et al., 2009b), similarly to what have been previously reported in individuals at the early phases of SCZ (Ellison-Wright et al., 2008) and in high-risk subjects (Takahashi et al., 2009c). These findings are not surprising especially because the insula plays a crucial role in emotional and cognitive modulation as part of the “limbic integration cortex” (Gasquoine, 2014) and its structural and functional abnormalities in SCZ (Corradi-Dell'Acqua et al., 2012) may play a crucial role in sustaining negative symptoms and cognitive impairments (Crespo-Facorro et al., 2001a; Crespo-Facorro et al., 2001b).

With regard to subcortical regions, two studies reported greater GM volumes (Velakoulis et al., 2006; Watson et al., 2012) and deformed shape in amygdala in A-FEP (Qiu et al., 2013) in comparison to NA-FEP (Velakoulis et al., 2006) or healthy control (Watson et al., 2012). Overall, these evidence are not surprising especially because amygdala enlargement has been implicated in the pathophysiology of BD (Brambilla et al., 2003; Strakowski et al., 1999), even at an early stage of the illness (Singh et al., 2015). Furthermore, amygdala is part of emotional processing network together with hippocampus, ventrolateral and dorsolateral prefrontal cortex, striatum, and portions of the anterior cingulate cortex (Phillips and Swartz,

2014), regions consistently found to be impaired in BD (Brambilla et al., 2008; Green et al., 2007; Houenou et al., 2015; Singh et al., 2015).

With regards to hippocampus, four studies found GM volume reductions in NA-FEP compared with healthy controls (Morgan et al., 2007; Qiu et al., 2013; Velakoulis et al., 2006; Watson et al., 2012), in accordance to previous evidence in SCZ (van Erp et al., 2016). The hippocampus is a complex brain structure that forms part of the Delay-Brion circuit, which specifically encodes information regarding spatial organization and encoding explicit long-term memory, both episodic and semantic, abilities often found to be dysfunctional in patients with psychotic disorders (Boyer et al., 2007). Therefore,abnormalities of the hippocampus seem to be widely implicated in the pathophysiology of SCZ and may in turn represent a candidate biological markers of psychosis (Brambilla et al., 2011; Brambilla et al., 2013). Finally, one study found significant association between increased caudate volume bilaterally and insight impairment only in NA-FEP patients (McFarland et al., 2013).

Discussion

In conclusion, although the biological signatures aiming at differentiating the neural correlates associated with NA-FEP and A-FEP have not been yet fully identified, the above-mentioned evidence reported the presence of common and distinct pattern of GM alterations between these disorders. Specifically, while GM volume deficits in fronto-temporal areas and anterior cingulate cortex seem to characterize both disorders, amygdala abnormalities have been reported mainly in A-FEP while hippocampal and insular shrinkage seems to be the neurobiological signature of NA-FEP.

However, this evidence should be considered in light of few important limitations, which may have limited the generalizability of the findings, including the relatively small sample sizes, the different acquisition and post-processing methodologies and the employment of psychotic patients with different pharmacological treatments.

Therefore, future larger longitudinal studies are warranted to further assess brain developmental trajectories in homogenous NA-FEP and A-FEP samples in order to better characterize the neural biomarkers of first episode psychosis, which may ultimately be useful for more targeted treatments.

Conflict of Interest

None.

Contributors

AC and GD wrote the first draft of the manuscript along with PB. ACA and JCS contributed to revise the manuscript. All authors agreed with the final content of the manuscript.

Role of the funding source

PB and GD were partially supported by grants from the Ministry of Health (RF-2011-02352308). AC was supported through Alicia Koplowitz grant for Short-Term Placements from the Alicia Koplowitz Foundation.

Acknowledgments

PB and GD were partially supported by grants from the Ministry of Health (RF-2011-02352308). AC was supported through Alicia Koplowitz grant for Short-Term Placements from the Alicia Koplowitz Foundation.

References

Baiano, M., David, A., Versace, A., Churchill, R., Balestrieri, M., Brambilla, P., 2007. Anterior cingulate volumes in schizophrenia: a systematic review and a meta-analysis of MRI studies. Schizophr Res 93, 1-12.

Berger, G.E., Bartholomeusz, C.F., Wood, S.J., Ang, A., Phillips, L.J., Proffitt, T., Brewer, W.J., Smith, D.J., Nelson, B., Lin, A., Borgwardt, S., Velakoulis, D., Yung, A.R., McGorry, P.D., Pantelis, C., 2017. Ventricular volumes across stages of schizophrenia and other psychoses. Aust N Z J Psychiatry 51, 1041-1051.

Birur, B., Kraguljac, N.V., Shelton, R.C., Lahti, A.C., 2017. Brain structure, function, and neurochemistry in schizophrenia and bipolar disorder-a systematic review of the magnetic resonance neuroimaging literature. NPJ Schizophr 3, 15.

Boyer, P., Phillips, J.L., Rousseau, F.L., Ilivitsky, S., 2007. Hippocampal abnormalities and memory deficits: new evidence of a strong pathophysiological link in schizophrenia. Brain Res Rev 54, 92-112.

Brambilla, P., Cerruti, S., Bellani, M., Perlini, C., Ferro, A., Marinelli, V., Giusto, D., Tomelleri, L., Rambaldelli, G., Tansella, M., Diwadkar, V.A., 2011. Shared impairment in associative learning in schizophrenia and bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry 35, 1093-1099.

Brambilla, P., Harenski, K., Nicoletti, M., Sassi, R.B., Mallinger, A.G., Frank, E., Kupfer, D.J., Keshavan, M.S., Soares, J.C., 2003. MRI investigation of temporal lobe structures in bipolar patients. J Psychiatr Res 37, 287-295.

Brambilla, P., Hatch, J.P., Soares, J.C., 2008. Limbic changes identified by imaging in bipolar patients. Curr Psychiatry Rep 10, 505-509.

Brambilla, P., Perlini, C., Rajagopalan, P., Saharan, P., Rambaldelli, G., Bellani, M., Dusi, N., Cerini, R., Pozzi Mucelli, R., Tansella, M., Thompson, P.M., 2013. Schizophrenia severity, social functioning and hippocampal neuroanatomy: three-dimensional mapping study. Br J Psychiatry 202, 50-55.

Corradi-Dell'Acqua, C., Tomelleri, L., Bellani, M., Rambaldelli, G., Cerini, R., Pozzi-Mucelli, R., Balestrieri, M., Tansella, M., Brambilla, P., 2012. Thalamic-insular dysconnectivity in schizophrenia: evidence from structural equation modeling. Hum Brain Mapp 33, 740-752.

Crespo-Facorro, B., Paradiso, S., Andreasen, N.C., O'Leary, D.S., Watkins, G.L., Ponto, L.L., Hichwa, R.D., 2001a. Neural mechanisms of anhedonia in schizophrenia: a PET study of response to unpleasant and pleasant odors. JAMA 286, 427-435.

Crespo-Facorro, B., Wiser, A.K., Andreasen, N.C., O'Leary, D.S., Watkins, G.L., Boles Ponto, L.L., Hichwa, R.D., 2001b. Neural basis of novel and well-learned recognition memory in schizophrenia: a positron emission tomography study. Hum Brain Mapp 12, 219-231.

Crow, T.J., Chance, S.A., Priddle, T.H., Radua, J., James, A.C., 2013. Laterality interacts with sex across the schizophrenia/bipolarity continuum: an interpretation of meta-analyses of structural MRI. Psychiatry Res 210, 1232-1244.

Chan, D., Anderson, V., Pijnenburg, Y., Whitwell, J., Barnes, J., Scahill, R., Stevens, J.M., Barkhof, F., Scheltens, P., Rossor, M.N., Fox, N.C., 2009. The clinical profile of right temporal lobe atrophy. Brain 132, 1287-1298.

Chung, Y., Haut, K.M., He, G., van Erp, T.G., McEwen, S., Addington, J., Bearden, C.E., Cadenhead, K., Cornblatt, B., Mathalon, D.H., McGlashan, T., Perkins, D., Seidman, L.J., Tsuang, M., Walker, E., Woods, S.W., Cannon, T.D., North American Prodrome Longitudinal Study, C., 2017. Ventricular enlargement and progressive reduction of cortical gray matter are linked in prodromal youth who develop psychosis. Schizophr Res.

de Castro-Manglano, P., Mechelli, A., Soutullo, C., Landecho, I., Gimenez-Amaya, J.M., Ortuno, F., McGuire, P., 2011. Structural brain abnormalities in first-episode psychosis: differences between affective psychoses and schizophrenia and relationship to clinical outcome. Bipolar Disord 13, 545-555.

Ellison-Wright, I., Bullmore, E., 2010. Anatomy of bipolar disorder and schizophrenia: a meta-analysis. Schizophr Res 117, 1-12.

Ellison-Wright, I., Glahn, D.C., Laird, A.R., Thelen, S.M., Bullmore, E., 2008. The anatomy of first-episode and chronic schizophrenia: an anatomical likelihood estimation meta-analysis. Am J Psychiatry 165, 1015-1023.

Farrow, T.F., Whitford, T.J., Williams, L.M., Gomes, L., Harris, A.W., 2005. Diagnosis-related regional gray matter loss over two years in first episode schizophrenia and bipolar disorder. Biol Psychiatry 58, 713-723.

Gasquoine, P.G., 2014. Contributions of the insula to cognition and emotion. Neuropsychol Rev 24, 77-87.

Green, M.J., Cahill, C.M., Malhi, G.S., 2007. The cognitive and neurophysiological basis of emotion dysregulation in bipolar disorder. J Affect Disord 103, 29-42.

Hibar, D.P., Westlye, L.T., Doan, N.T., Jahanshad, N., Cheung, J.W., Ching, C.R.K., Versace, A., Bilderbeck, A.C., Uhlmann, A., Mwangi, B., Kramer, B., Overs, B., Hartberg, C.B., Abe, C., Dima, D., Grotegerd, D., Sprooten, E., Boen, E., Jimenez, E., Howells, F.M., Delvecchio, G., Temmingh, H., Starke, J., Almeida, J.R.C., Goikolea, J.M., Houenou, J., Beard, L.M., Rauer, L., Abramovic, L., Bonnin, M., Ponteduro, M.F., Keil, M., Rive, M.M., Yao, N., Yalin, N., Najt, P., Rosa, P.G., Redlich, R., Trost, S., Hagenaars, S., Fears, S.C., Alonso-Lana, S., van Erp, T.G.M., Nickson, T., Chaim-Avancini, T.M., Meier, T.B., Elvsashagen, T., Haukvik, U.K., Lee, W.H., Schene, A.H., Lloyd, A.J., Young, A.H., Nugent, A., Dale, A.M., Pfennig, A., McIntosh, A.M., Lafer, B., Baune, B.T., Ekman, C.J., Zarate, C.A., Bearden, C.E., Henry, C., Simhandl, C., McDonald, C., Bourne, C., Stein, D.J., Wolf, D.H., Cannon, D.M., Glahn, D.C., Veltman, D.J., Pomarol-Clotet, E., Vieta, E., Canales-Rodriguez, E.J., Nery, F.G., Duran, F.L.S., Busatto, G.F., Roberts, G., Pearlson, G.D., Goodwin, G.M., Kugel, H., Whalley, H.C., Ruhe, H.G., Soares, J.C., Fullerton, J.M., Rybakowski, J.K., Savitz, J., Chaim, K.T., Fatjo-Vilas, M., Soeiro-de-Souza, M.G., Boks, M.P., Zanetti, M.V., Otaduy, M.C.G., Schaufelberger, M.S., Alda, M., Ingvar, M., Phillips, M.L., Kempton, M.J., Bauer, M., Landen, M., Lawrence, N.S., van Haren, N.E.M., Horn, N.R., Freimer, N.B., Gruber, O., Schofield, P.R., Mitchell, P.B., Kahn, R.S., Lenroot, R., Machado-Vieira, R., Ophoff, R.A., Sarro, S., Frangou, S., Satterthwaite, T.D., Hajek, T., Dannlowski, U., Malt, U.F., Arolt, V., Gattaz, W.F., Drevets, W.C., Caseras, X., Agartz, I., Thompson, P.M., Andreassen, O.A., 2017. Cortical abnormalities in bipolar disorder: an MRI analysis of 6503 individuals from the ENIGMA Bipolar Disorder Working Group. Mol Psychiatry.

Houenou, J., Perlini, C., Brambilla, P., 2015. Epidemiological and clinical aspects will guide the neuroimaging research in bipolar disorder. Epidemiol Psychiatr Sci 24, 117-120.

Kim, G.W., Kim, Y.H., Jeong, G.W., 2017. Whole brain volume changes and its correlation with clinical symptom severity in patients with schizophrenia: A DARTEL-based VBM study. PLoS One 12, e0177251.

Koo, M.S., Levitt, J.J., Salisbury, D.F., Nakamura, M., Shenton, M.E., McCarley, R.W., 2008. A cross-sectional and longitudinal magnetic resonance imaging study of cingulate gyrus gray matter volume abnormalities in first-episode schizophrenia and first-episode affective psychosis. Arch Gen Psychiatry 65, 746-760.

Lee, S.H., Niznikiewicz, M., Asami, T., Otsuka, T., Salisbury, D.F., Shenton, M.E., McCarley, R.W., 2016. Initial and Progressive Gray Matter Abnormalities in Insular Gyrus and Temporal Pole in First-Episode Schizophrenia Contrasted With First-Episode Affective Psychosis. Schizophr Bull 42, 790-801.

Maggioni, E., Bellani, M., Altamura, A.C., Brambilla, P., 2016. Neuroanatomical voxel-based profile of schizophrenia and bipolar disorder. Epidemiol Psychiatr Sci 25, 312-316.

McFarland, J., Cannon, D.M., Schmidt, H., Ahmed, M., Hehir, S., Emsell, L., Barker, G., McCarthy, P., Elliott, M.A., McDonald, C., 2013. Association of grey matter volume deviation with insight impairment in first-episode affective and non-affective psychosis. Eur Arch Psychiatry Clin Neurosci 263, 133-141.

Mesulam, M.M., Nobre, A.C., Kim, Y.H., Parrish, T.B., Gitelman, D.R., 2001. Heterogeneity of cingulate contributions to spatial attention. Neuroimage 13, 1065-1072.

Morgan, K.D., Dazzan, P., Orr, K.G., Hutchinson, G., Chitnis, X., Suckling, J., Lythgoe, D., Pollock, S.J., Rossell, S., Shapleske, J., Fearon, P., Morgan, C., David, A., McGuire, P.K., Jones, P.B., Leff, J., Murray, R.M., 2007. Grey matter abnormalities in first-episode schizophrenia and affective psychosis. Br J Psychiatry Suppl 51, s111-116.

Nakamura, M., Salisbury, D.F., Hirayasu, Y., Bouix, S., Pohl, K.M., Yoshida, T., Koo, M.S., Shenton, M.E., McCarley, R.W., 2007. Neocortical gray matter volume in first-episode schizophrenia and first-episode affective psychosis: a cross-sectional and longitudinal MRI study. Biol Psychiatry 62, 773-783.

Phillips, M.L., Swartz, H.A., 2014. A critical appraisal of neuroimaging studies of bipolar disorder: toward a new conceptualization of underlying neural circuitry and a road map for future research. Am J Psychiatry 171, 829-843.

Pina-Camacho, L., Del Rey-Mejias, A., Janssen, J., Bioque, M., Gonzalez-Pinto, A., Arango, C., Lobo, A., Sarro, S., Desco, M., Sanjuan, J., Lacalle-Aurioles, M., Cuesta, M.J., Saiz-Ruiz, J., Bernardo, M., Parellada, M., Group, P.E., 2016. Age at First Episode Modulates Diagnosis-Related Structural Brain Abnormalities in Psychosis. Schizophr Bull 42, 344-357.

Qiu, A., Gan, S.C., Wang, Y., Sim, K., 2013. Amygdala-hippocampal shape and cortical thickness abnormalities in first-episode schizophrenia and mania. Psychol Med 43, 1353-1363.

Singh, M.K., Kelley, R.G., Chang, K.D., Gotlib, I.H., 2015. Intrinsic Amygdala Functional Connectivity in Youth With Bipolar I Disorder. J Am Acad Child Adolesc Psychiatry 54, 763-770.

Squarcina, L., Castellani, U., Bellani, M., Perlini, C., Lasalvia, A., Dusi, N., Bonetto, C., Cristofalo, D., Tosato, S., Rambaldelli, G., Alessandrini, F., Zoccatelli, G., Pozzi-Mucelli, R., Lamonaca, D., Ceccato, E., Pileggi, F., Mazzi, F., Santonastaso, P., Ruggeri, M., Brambilla, P., Group, G.U., 2017a. Classification of first-episode psychosis in a large cohort of patients using support vector machine and multiple kernel learning techniques. Neuroimage 145, 238-245.

Squarcina, L., Perlini, C., Peruzzo, D., Castellani, U., Marinelli, V., Bellani, M., Rambaldelli, G., Lasalvia, A., Tosato, S., De Santi, K., Spagnolli, F., Cerini, R., Ruggeri, M., Brambilla, P., Group, P.I.-V., 2015. The use of dynamic susceptibility contrast (DSC) MRI to automatically classify patients with first episode psychosis. Schizophr Res 165, 38-44.

Squarcina, L., Stanley, J.A., Bellani, M., Altamura, C.A., Brambilla, P., 2017b. A review of altered biochemistry in the anterior cingulate cortex of first-episode psychosis. Epidemiol Psychiatr Sci 26, 122-128.

Strakowski, S.M., DelBello, M.P., Sax, K.W., Zimmerman, M.E., Shear, P.K., Hawkins, J.M., Larson, E.R., 1999. Brain magnetic resonance imaging of structural abnormalities in bipolar disorder. Arch Gen Psychiatry 56, 254-260.

Sumich, A., Chitnis, X.A., Fannon, D.G., O'Ceallaigh, S., Doku, V.C., Faldrowicz, A., Sharma, T., 2005. Unreality symptoms and volumetric measures of Heschl's gyrus and planum temporal in first-episode psychosis. Biol Psychiatry 57, 947-950.

Takahashi, T., Wood, S.J., Soulsby, B., Kawasaki, Y., McGorry, P.D., Suzuki, M., Velakoulis, D., Pantelis, C., 2009a. An MRI study of the superior temporal subregions in first-episode patients with various psychotic disorders. Schizophr Res 113, 158-166.

Takahashi, T., Wood, S.J., Soulsby, B., Tanino, R., Wong, M.T., McGorry, P.D., Suzuki, M., Velakoulis, D., Pantelis, C., 2009b. Diagnostic specificity of the insular cortex abnormalities in first-episode psychotic disorders. Prog Neuropsychopharmacol Biol Psychiatry 33, 651-657.

Takahashi, T., Wood, S.J., Yung, A.R., Phillips, L.J., Soulsby, B., McGorry, P.D., Tanino, R., Zhou, S.Y., Suzuki, M., Velakoulis, D., Pantelis, C., 2009c. Insular cortex gray matter changes in individuals at ultra-high-risk of developing psychosis. Schizophr Res 111, 94-102.

van Erp, T.G., Hibar, D.P., Rasmussen, J.M., Glahn, D.C., Pearlson, G.D., Andreassen, O.A., Agartz, I., Westlye, L.T., Haukvik, U.K., Dale, A.M., Melle, I., Hartberg, C.B., Gruber, O., Kraemer, B., Zilles, D., Donohoe, G., Kelly, S., McDonald, C., Morris, D.W., Cannon, D.M., Corvin, A., Machielsen, M.W., Koenders, L., de Haan, L., Veltman, D.J., Satterthwaite, T.D., Wolf, D.H., Gur, R.C., Gur, R.E., Potkin, S.G., Mathalon, D.H., Mueller, B.A., Preda, A., Macciardi, F., Ehrlich, S., Walton, E., Hass, J., Calhoun, V.D., Bockholt, H.J., Sponheim, S.R., Shoemaker, J.M., van Haren, N.E., Pol, H.E., Ophoff, R.A., Kahn, R.S., Roiz-Santianez, R., Crespo-Facorro, B., Wang, L., Alpert, K.I., Jonsson, E.G., Dimitrova, R., Bois, C., Whalley, H.C., McIntosh, A.M., Lawrie, S.M., Hashimoto, R., Thompson, P.M., Turner, J.A., 2016. Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. Mol Psychiatry 21, 585.

Velakoulis, D., Wood, S.J., Wong, M.T., McGorry, P.D., Yung, A., Phillips, L., Smith, D., Brewer, W., Proffitt, T., Desmond, P., Pantelis, C., 2006. Hippocampal and amygdala volumes according to psychosis stage and diagnosis: a magnetic resonance imaging study of chronic schizophrenia, first-episode psychosis, and ultra-high-risk individuals. Arch Gen Psychiatry 63, 139-149.

Vita, A., De Peri, L., Sacchetti, E., 2009. Gray matter, white matter, brain, and intracranial volumes in first-episode bipolar disorder: a meta-analysis of magnetic resonance imaging studies. Bipolar Disord 11, 807-814.

Vita, A., De Peri, L., Silenzi, C., Dieci, M., 2006. Brain morphology in first-episode schizophrenia: a meta-analysis of quantitative magnetic resonance imaging studies. Schizophr Res 82, 75-88.

Watson, D.R., Bai, F., Barrett, S.L., Turkington, A., Rushe, T.M., Mulholland, C.C., Cooper, S.J., 2012. Structural changes in the hippocampus and amygdala at first episode of psychosis. Brain Imaging Behav 6, 49-60.

Wright, I.C., Rabe-Hesketh, S., Woodruff, P.W., David, A.S., Murray, R.M., Bullmore, E.T., 2000. Meta-analysis of regional brain volumes in schizophrenia. Am J Psychiatry 157, 16-25.

Table 1. Selection of studies investigating gray matter volumes in affective and non-affective psychosis.

Authors	Sample, mean age (Male/Female)	Psychopathological measures	Medication	Design	Structural measures	MRI acquisition	Main results	
							Regions	Contrast
Pina-Camacho et al., 2015*	32 A-FEP Age: 22.34 ± 6.04 (8/24) 92 NA-FEP Age: 23.12 ± 6.01 (22/70) 157 HC Age: 23.71 ± 6.01 (23/134)	WAIS-R / WISC-IV PANSS CGI GAS /C-GAS	NA-FEP Antipsychotic treatment (n=87) Lithium (n=1) Other mood stabilizers (n=4) Antidepressants (n=11) Benzodiazepines (n=34) Anticholinergic agents (n=16) A-FEP Antipsychotic treatment A-FEP (n=26) Lithium (n=13) Other mood stabilizers (n=8) Antidepressants (n=8) Benzodiazepines (n=8) Anticholinergic agents (n=5)	Cross-sectional	Multicentric study *Analysis:* ROI analysis *Parameters:* Cortical thickness in frontal, parietal, temporal and occipitotemporal regions. *Statistical analysis:* ANCOVA (p<0.05, Bonferroni corrected). *Covariates:* Site, sex, SES, estimated IQ, and TBV.	1.5 T	Smaller frontal volumes and thinner frontal, temporal, parietal, medial orbitofrontal, insular cortices and smaller middle frontal gyrus volumes and thinner precuneus cortices.	Earlier age at NA-FEP < A-FEP
							Smaller caudal anterior cingulate; larger caudate, putamen and thicker temporal and occipital lobes patients.	A-FEP < HC
							Smaller frontal lobe, caudal middle frontal gyrus, and temporal lobe volumes.	NA-FEP < HC
Ansell et al., 2015	27 NA-FEP (20/7) 25 A-FEP (15/10)	SCID PANSS	Typical antipsychotic (n=25) chlorpromazine (n=19) trifluoperazine (n=19) flupenthixol (n=3) haloperidol (n=1) Atypical	Cross-sectional	Single study *Analysis:* ROI analysis. *Parameters:* Cortical thickness in frontal, parietal, temporal and occipitotemporal regions.	1.5 T	No significant differences.	NA-FEP = A-FEP
							Reduced thickness in the right inferior parietal lobe r and in a small area of the right cingulate sulcus.	A-FEP < HC

			antipsychotic (n=27) Antipsychotic Risperidone (n=17) Olanzapine (n=6) Clozapine (n=4)		*Statistical analysis:* General linear models ($p < 0.001$, family-wise error corrected with FreeSurfer Monte-Carlo approach).		Decreased thickness in frontal, parietal, temporal and occipito-temporal regions.	NA-FEP < HC
Qiu et al., 2012	28 A-FEP Age: 36.89± 11.85 (13/15) 28 NA-FEP Age: 35.57± 9.19 (13/15) 28 HC Age: 36.04± 10.91 (13/15)	PANSS GAS	NA-FEP Antipsychotics (n=28) Mood stabilizer (n=3) antipsychotics and mood stabilizers (n=3) A-FEP Antipsychotics (n=23) Mood stabilizer (n=25) antipsychotics and mood stabilizers (n=19)	Cross-sectional	Single study *Analysis:* ROI analysis and shape analysis *Parameters:* Cortical thickness in frontal, parietal, Temporal and occipital. Shape in hippocampus and amygdala. *Statistical analysis:* ANCOVA ($p<0.05$, Bonferroni corrected). *Covariates:* Years of education, duration of illness, medication.	3 T	Greater cortical thinning in the left inferior frontal gyrus, left cuneus, right middle temporal gyrus and right superior temporal sulcus and significant inward shape deformation in the left hippocampal tail, right hippocampal body and a small region in the right amygdala.	NA-FEP > A-FEP
							The shape of the amygdala was deformed.	A-FEP and NA-FEP < HC
							Significant inward shape deformation in left hippocampal tail and right amygdala.	NA-FEP vs A-FEP
							Cortical thinning more widespread in temporal regions.	NA-FEP > A-FEP
McFarlane et al., 2013	32 FEP Age: 27.8 ± 7.6 (23/9) 13 A-FEP 19 NA-FEP	PANSS SUMD	Atypical antipsychotics Olanzapine (n= 15) Risperidone (n=3) Quetiapine (n=5)	Cross-sectional	Multicentric study *Analysis:* ROI analysis *Parameters: GM* volumes in caudate.	1.5 T	There was a significant association between increased caudate volume and insight impairment for right and left caudate.	NA-FEP

			Paliperidone (n= 4) Aripiprazole (n=2) SSRI (n=4) SNRI (n=1)		*Statistical analysis:* Spearman's nonparametric bivariate correlations		Insight was not significantly correlated with right or left caudate volume.	A-FEP
Takahashi et al., 2009a^	162 FEP: 34 A-FEP Age: 22 ± 3.1 (18/16) 46 NA-FEP Age: 21.5 ± 3.6 (34/12)	WAIS-R SCID RPMIP	Typical antipsychotic (n=42) Atypical antipsychotic (n=108) Lithium (n=1 7)	Cross-sectional	Single study *Analysis:* ROI analysis *Parameters:* GM volumes in insula. *Statistical analysis:* Repeated-measures MANCOVA (results were considered significant only when the results with both absolute and relative volumes reached significance) *Covariates:* Age and ICV	1.5 T	Bilateral volume reduction in the anterior insula.	NA-FEP < A-FEP and HC
							No differences in the insula.	A-FEP = HC
Takahashi et al., 2009b ^	162 FEP: 46 NA-FEP Age: 21.5 ± 3.6 (34/12) 34 A- FEP Age: 22 ± 3.1 (18/16)	SCID WAIS-R	Typical antipsychotic (n=42) Atypical antipsychotic (n=108)Lithium (n=17)	Cross-sectional	Single study *Analysis:* ROI analysis *Parameters:* GM volumes in superior temporal gyrus (STG) and its subregions [planum polare (PP),	1.5 T	Reduced GM volumes in HG, PT, and caudal STG bilaterally.	NA-FEP < A-FEP and HC

					Heschl gyrus (HG), planum temporale (PT), rostral STG, and caudal STG]. *Statistical analysis:* Repeated-measures ANCOVA. *Covariates:* age and ICV.		No differences between for any STG subregion was observed.	A-FEP = HC
Lee et al., 2016	23 A-FEP Age: 22.7 ± 5.1 (20/3) 22 NA-FEP Age: 25.3 ± 8.3 (19/3) 23 HC Age: 24.2 ± 3.9 (19/4)	WAIS-R GAS MMSE BPRS	NA-FEP Typical antipsychotic (n=7) Atypical antipsychotic (n=17) Overlap antipsychotic (n=3) Lithium (n=1) VPA (n=2) Overlap Mood stabilizer (n=0) A-FEP Typical antipsychotic (n=8) Atypical antipsychotic (n=15) Overlap antipsychotic (n=3) Lithium (n=6) VPA (n=7) Overlap Mood stabilizer (n=0)	Cross-sectional and longitudinal	Single study *Analysis:* ROI analysis *Parameters:* GM volumes in insula and temporal pole. *Statistical analysis:* Repeated-measures ANOVA. *Covariates:* Relative volumes.	1.5 T	Smaller GM volumes in bilateral insula and temporal lobe. No statistically significant differences in volumes.	NA-FEP < A-FEP and HC A-FEP = HC
Morgan et al., 2007	73 FEP Age: 27.1 ± 7.6 29 A-FEP (11/18)	WAIS-R WHO–SCAN	NA-FEP Typical	Cross-sectional	Multicentic Study *Analysis:* ROI analysis	1.5 T	No differences in total GM volumes	NA-FEP = A-FEP

	44 NA-FEP (31/13)		antipsychotics (n=13) Atypical antipsychotics (n=2) A-FEP Typical antipsychotics (n=14) Atypical antipsychotics (n=22)		*Parameters:* GM volumes in cingulate gyrus, insula, fusiform gyrus and hippocampus. *Statistical analysis:* ANCOVA (Permutation testing was used to assess statistical significance). *Covariates:* Age, total grey matter volume.		Regional cortical GM reductions within bilateral anterior cingulate gyrus, left insula and left fusiform gyrus were found.	A-FEP <HC
							Hippocampal reduction.	NA-FEP <HC
Nakamura et al., 2007	34 A-FEP Age: 22.1 ± 3.1 (26/8) 29 NA-FEP Age: 24.3 ± 5.8 (24/5) 36 HC Age: 22.9 ± 3.8 (31/5)	GAS BPRS	No data available	Cross-sectional and longitudinal	Single study *Analysis:* ROI analysis *Parameters:* Neocortical GM volumes. *Statistical analysis:* ANOVA (p-value Bonferroni corrected). *Covariates:* Intracranial contents.	1.5 T	No differences in neocortical GM volumes.	NA-FEP = A-FEP
							Smaller neocortical GM volumes.	NA-FEP and A-FEP <HC
Velakoulis et al., 2006[A]	34 A-FEP Age: 21.7 ± 2.4 (18/16) 103 NA-FEP Age: 21.8 ± 3.9 (76/27) HC 87 Age: 26.9 ± 10 (55/32)	BPRS CASH	FEP: Typical antipsychotic (26%) Atypical antipsychotics (69%) No medications (5%)	Cross-sectional	Single study *Analysis:* ROI analysis. *Parameters:* GMvolumes in hippocampus and amygdala. *Statistical analysis:* ANOVA (Cohen d standardized effect sizes). *Covariates:* ICV, sex, age.	1.5 T	Left hippocampal GM volume reduction.	NA-FEP <HC
							Amygdala GM volume enlargement.	A-FEP > NA-FEP
Watson et al., 2012	24 A-FEP Age: 36.0 ± 10 (8/16) 24 HC matched with A-FEP	PANSS WAIS NART	NA- FEP Typical antispychotic	Cross-sectional	Single study *Analysis:* ROI analysis	1.5 T	Bilateral hippocampus and amygdala volume reductions.	NA-FEP < A-FEP

	Age: 35.6± 9.7 (8/16) 25 NA- FEP Age:28.8 ± 9 (19/6) 25 HC matched with NA-FEP Age: 28.2± (8.5) (19/6)		(n=0) Atypical antipsychotic (n=19) Lithium (n=0) A-FEP Typical antispychotic (n=1) Atypical antipsychotic (n=24) Lithium (n=2)		*Parameters:* GM volumes in hippocampus and amygdala *Statistical analysis:* ANOVA. *Covariates:* IQ, sex, age.			
							Larger right amygdala volumes but similar left amygdala volumes.	A-FEP > HC
Koo et al., 2008	41 A-FEP Age: 22.8 ± 4.5 (32/9) 39 NA-FEP Age: 23.9 ± 5.5 (30/9) 40 HC Age:23 ± 3.2 (31/9)	WAIS R GAS BPRS	No data available	Cross-sectional and longitudinal	Single study *Analysis:* ROI analysis. *Parameters:* GM volumes in cingulate gyrus and its subregions. *Statistical analysis:* Repeated-measures ANOVA (Tukey Honestly Significant Difference tests). *Covariates:* Relative volumes.	1.5 T	Smaller cingulate volumes.	NA-FEP < HC
							No differences in cingulate volumes.	A-FEP = HC A-FEP = NA-FEP
de Castro-Manglano et al., 2011	28 FEP Age: 18.6 ± (4.9) (17／11) 18 A-FEP 10 NA-FEP 20 HC Age: 20.5 ± (5.7) (11／9)	HDRS PANSS GAS CGI	Olanzapine (n=11) Risperidone (n=8) Ziprasidone (n=4) Aripiprazole (n=1) Aloperidol plus Clozapine and Olanzapine (n=2) Mood stabilizers (n=9)	Cross-sectional and longitudinal	Single study *Analysis:* ROI analysis. *Parameters:* GM volumes in frontal, insular, parietal, and cerebellar cortices.	1.5 T	Smaller GM volumes in frontal, insular, parietal, and cerebellar cortex.	FEP <HC
							No significant differences	A-FEP = NA-FEP

			Antidepressants (n=15)		*Statistical analysis:* ANOVA ($p < 0.05$ after false discovery rate). *Covariates:* Total GM volume, age, sex.		Decreased GM volumes in left superior frontal gyrus, left thalamus, middle frontal gyri bilaterally, right inferior frontal, postcentral and rectal gyri, right rolandic operculum, superior temporal gyrus and cerebellum.	A-FEP <HC
Farrow et al., 2005	8 A-FEP range age (14-20) (4/4) 25 NA-FEP range age (13-25) (18/7) 22 HC range age (13-25) (13/9)	PANSS	No data available	Cross-sectional and longitudinal	Multicentric study *Analysis:* Whole brain analysis. *Parameters:* GM volumes in frontal, lateral, and posterior regions, cingulate gyrus. *Statistical analysis:* ANOVA ($p<0.001$ uncorrected). *Covariates:* Global brain volumes, age.	1.5 T	GM deficits were observed in lateral and medial frontal regions and in bilateral posterior temporal lobe regions.	NA-FEP < A-FEP
							GM deficit was localized to bilateral inferior temporal gyrus.	A-FEP < NA-FEP

FEP: First Episode Psychosis; A-FEP: affective FEP; NA-FEP: Non-Affective FEP; HC: Healthy controls; BPRS: Brief Psychiatric Rating Scale; GAS: Global Assessment Scale; CGAS: Children's Global Assessment Scale; GM: Gray Matter; MMSE: Mini-Mental Status Examination; WHO–SCAN: WHO Schedules for Clinical Assessment in Schedules for Clinical Assessment in Neuropsychiatry; RPMIP: Royal Park Multidiagnostic Instrument for Psychosis; WAIS-R: Wechsler Adult Intelligence Scale-Revised; CGI: Clinical Global Impression scale; PANSS: Positive and Negative Symptom Scale; SUMD: Scale to Assess Unawareness of Mental Disorder; SCID: Structured Clinical Interview for DSM-IV Axis I Disorders; YMRS: Young Mania Rating Scale, HRSD: Hamilton Rating Scale for Depression; BPRS: Brief Psychiatric Rating Scale; CASH: Comprehensive Assessment of Symptoms and History; NART: The National Adult Reading Test; HG: Heschl Gyrus; PT: Planun Temporale; STG: Superior Temporal Gyri; CGI : Clinical Global Impression scale; SES: parental socioeconomic status: IQ: Intelligent Quotient; TBV: Total brain volume; SSRI: Selective serotonin reuptake inhibitors; SNRI: Selective Serotonin–norepinephrine reuptake inhibitors. * Study also included 72 other psychosis. ^ Study also included 57 schizophreniform disorder and 25 with other psychoses. [Δ] Study also included 89 patients with established schizophrenia, 21 ultra-high risk and 18 other psychoses.