**Best matches for the following key words were searched:** ((Schizophrenia OR First episode psychosis OR First episode schizophrenia OR clinical high risk psychosis OR ultra high risk psychosis) AND (H-MRS OR Magnetic resonance spectroscopy OR MRS)) AND (GABA OR Gamma amino butyric acid) AND (Frontal cortex OR Prefrontal cortex OR Medial prefrontal cortex OR anterior cingulate cortex OR dorsolateral pre frontal cortex)).

Date: 20/02/19 Time: 5.00 PM

Table 1. Sociodemographic and clinical variables of the study subjects

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Sample Size** | | **Mean age** | | **% Males** | | **DOI** | **DS** | **AAO** | **M** | **UM** | **CPZE** | **BPRS** | **BZD Y/N** |
|  | **C** | **SCZ** | **C** | **SCZ** | **C** | **SCZ** |  |  |  |  |  |  |  |  |
| **ACC** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Ongur., 2010 | 19 | 21 | 36.3 | 39.0 | 63.1 | 66.6 | 21.1 | CS | 17.9 | 20 | 1 | 555 | 29 | Y |
| Tayoshi., 2010 | 29 | 38 | 34.0 | 34.0 | 58.6 | 52.6 | 11.1 | CS | 22.9 | 38 | 0 | 423.7 | 30 | Y |
| Rowland., 2013 (Yg) | 10 | 11 | 33.4 | 30.2 | 50 | 81.8 | 7.7 | CS | 22.5 | 11 | 0 | N.R | 35.5 | N |
| Rowland., 2013 (O) | 10 | 10 | 49.4 | 51.1 | 70 | 70 | 25.5 | CS | 25.6 | 10 | 0 | N.R | 32.2 | N |
| Marenco.,  2015(UM) | 184 | 25 | 30.6 | 28.4 | 84 | 72 | 6.8 | N.R | 21.6 | 0 | 25 | N.A | N.R | N |
| Marenco.,  2015(M) | - | 70 | - | 31.2 | - | 71 | 9.5 | N.R | 21.7 | 70 | 0 | 597 | N.R | Y |
| Brandt.,  2016 | 24 | 24 | 36.6 | 37.5 | 83.3 | 79.1 | N.R | S | - | 24 | 0 | N.R | N.R | Y |
| Chiu., 2018 | 14 | 19 | 27.71 | 29.1 | 64.2 | 57.8 | 1.46 | FES | 27.7 | 19 | 0 | 389.4 | 27 | N.R |
| Reid., 2018 | 21 | 21 | 23.3 | 23.2 | 76.1 | 76.1 | 1.7 | FES | 21.5 | 20 | 1 | N.R | 32.3 | N.R |
| Wang., 2019 | 89 | 74 | 23.3 | 22.3 | 46.1 | 70.3 | N.R | FES | - | N.R | N.R | 188 | N.R | N |
| **Study** | **Sample Size** | | **Mean age** | | **% Males** | | **DOI** | **DS** | **AAO** | **M** | **UM** | **CPZE** | **BPRS** | **BZD Y/N** |
|  | **C** | **SCZ** | **C** | **SCZ** | **C** | **SCZ** |  |  |  |  |  |  |  |  |
| **MPFC** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Goto., 2010 | 18 | 18 | 30 | 29 | 50 | 50 | 0.5 | N.R | 28.5 | 18 | 0 | 521.1 | 38 | N.R |
| Kegeles., 2012 (UM) | 22 | 16 | 33 | 32 | 63.6 | 68.7 | 7 | N.R | 25 | 0 | 16 | N.A | 39 | Y |
| Kegeles., 2012 (M) | - | 16 | - | 32 | - | 68.7 | 9 | N.R | 23 | 16 | 0 | N.R | 32 | N |
| Marsman., 2014 | 19 | 13 | 27.7 | 27.6 | 69.5 | 76.4 | 6.4 | CS | 21.1 | 13 | 0 | N.R | 30 | Y |
| Rowland., 2015 (Yg) | 40 | 29 | 25.3 | 25.7 | 50 | 69 | 5.6 | N.R | 20.1 | 27 | 2 | 562.0 | 39.2 | N |
| Rowland., 2015 (O) | 37 | 31 | 51 | 48.3 | 67.5 | 61 | 24 | N.R | 24.3 | 28 | 3 | 668.9 | 38.3 | N |
| Yang., 2015 | 23 | 22 | 25.5 | 26.1 | 43.5 | 41 | 1.6 | FES | 24.5 | 9\* | 13 | N.A | 38 | N.R |
| Wang., 2016 | 23 | 16 | 22.5 | 22.1 | 47.8 | 50 | 0.58 | FES | 21.6 | 0 | 16 | N.A | 43.56 | N.R |
| Chen., 2017 | 24 | 24 | 26.6 | 28.8 | 41.6 | 41.6 | 2\*\* | N.R | - | 0 | 24 | N.A | 46 | N.R |
| Xia.,  2018 | 19 | 17 | 30.9 | 31 | 47.3 | 47 | 7.7 | N.R | 23.3 | 17 | 0 | 544 | 39 | N |
| Sandoval., 2018 | 48 | 46 | 23 | 23 | 50 | 71.4 | 0.98 | FES | 22 | 0 | 28 | N.A | 29 | N |
| **Study** | **Sample Size** | | **Mean age** | | **% Males** | | **DOI** | **DS** | **AAO** | **M** | **UM** | **CPZE** | **BPRS** | **BZD Y/N** |
|  | **C** | **SCZ** | **C** | **SCZ** | **C** | **SCZ** |  |  |  |  |  |  |  |  |
| **DLPFC** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Kegeles., 2012 (UM) | 22 | 16 | 33 | 32 | 63.6 | 68.7 | 7 | N.R | 25 | 0 | **16** | N.A | 39 | Y |
| Kegeles., 2012 (M) | - | 16 | - | 32 | - | 68.75 | 9 | N.R | 23 | 16 | 0 | N.R | 32 | N.R |
| Chen., 2017 | 24 | 24 | 26.6 | 28.8 | 41.6 | 41.6 | 2\*\* | S | - | 24 | 0 | N.R | 46 | N.R |
| Wang.,  2019# | 79 | 69 | 23.3 | 22.3 | 46.1 | 70.3 | N.R | FES | - | N.R | N.R | 188 | N.R | N |
| **UHR** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Menschikov., 2016  (ACC) | 26 | 21 | @ | @ | 100 | 100 | N.A | N.A | - | N.A | N.A | N.A | N.A | N.A |
| Sandoval.,  2016 (mPFC) | 24 | 23 | 21.4 | 20.7 | 79.17 | 65.22 | 0.88 | Pro | 19.8 | N.A | N.A | N.A | N.A | N.A |
| Wang.,  2016 (mPFC) | 23 | 21 | 22.52 | 21.05 | 47.82 | 57.14 | 0.91 | Pro | 20.1 | N.A | N.A | N.A | N.A | N.A |
| Modinos.,  2018 (mPFC) | 20 | 21 | 23.7 | 22.2 | 100 | 100 | N.A | N.A | - | N.A | N.A | N.A | N.A | N |
| **C**- Control; **SCZ**- Schizophrenia; **DOI**- duration of illness in years; **DS**- disease stage; **CS**- Chronic stable; **AAO**- Age at onset; **M**- Medicated; **UM**- not medicated; **CPZE**- Chlorpromazine equivalents; **BPRS**- Brief psychiatry rating scale; **BZD**- Benzodiazepine; **Y**- Yes; **N**- No;  **N.R**- Not reported; **N.S**- not specified; **N.A**- Not applicable**; S**- Stable; **FES**- first episode Schizophrenia; **Pro**- Prodrome; **MPFC**- Medial prefrontal cortex; **DLPFC**- Dorsolateral prefrontal cortex; **ACC**- Anterior Cingulate cortex; **O**- Old; **Yg**- Young  \*Medicated for less than 2 days prior to the scan  \*\*Median number;  \*\*\* Mean duration of untreated illness is 25.7 weeks and that of treated illness is 55.3 weeks**;**  @Range of the age 16-25 years  #the mean age, male percentage and other variables mentioned are of the total sample size of the study | | | | | | | | | | | | | | |

Table 2. Neuroimaging variables of the included studies

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Sequence** | **TR** | **TE** | **Shimming** | **Post processing** | **Scanner strength** | **Voxel size** |
| **ACC** | | | | | | | |
| Ongur., 2010 | MEGAPRESS | NA | 68ms | NA | LC model | 4T | 23\*22\*33mm |
| Tayoshi., 2010 | MEGAPRESS | 1500ms | 68ms | NA | LC model | 3T | 30\*30\*30mm |
| Rowland., 2013 (Yg) | MEGAPRESS | 2000ms | 68ms | NA | Csx3 | 3T | 50\*30\*30mm |
| Rowland., 2013 (O) | MEGAPRESS | 2000ms | 68ms | NA | Csx3 | 3T | 50\*30\*30mm |
| Marenco.,2015(UM) | PRESS based J-editing | 1500ms | 68ms | NA | nonlinear fitting program written in IDL | 3T | 20\*20\*45mm |
| Marenco.,2015(M) | PRESS based J-editing | 1500ms | 68ms | NA | nonlinear fitting program written in IDL | 3T | 20\*20\*45mm |
| Brandt.,2016 | STEAM | 3000ms | 14ms | NA | LC model | 7T | 30\*20\*12mm |
| Chiu., 2018 | MEGAPRESS | 2000ms | 68ms | FASTMAP | Gannet 2.0 | 3T | 30\*30\*30mm |
| Reid., 2018 | STEAM | 10000ms | 5ms | FASTESTMAP | LC model | 7T | 27\*20\*10mm |
| Wang., 2019 | STEAM | 3000ms | 14ms | FASTMAP | LC Model | 7T | 20\*30\*20mm |
| **MPFC** | | | | | | | |
| Goto., 2010 | MEGAPRESS | NA | NA | NA | NA | 3T | NA |
| Kegeles., 2012 (UM) | J-EDITING | NA | NA | NA | Levenberg-Marquardt nonlinear least-squares algorithm written in IDL | 3T | 25\*30\*25mm |
| Kegeles., 2012 (M) | J-EDITING | NA | NA | NA | Levenberg-Marquardt nonlinear least-squares algorithm written in IDL | 3T | 25\*30\*25mm |
| Marsman., 2014 | MEGAPRESS | 4000MS | 74MS | Second order B0  shimming using the FASTERMAP algorithm | Custom code | 7T | 25\*25\*25mm |
| **Study** | **Sequence** | **TR** | **TE** | **Shimming** | **Post processing** | **Scanner strength** | **Voxel size** |
| Rowland., 2015 (Yg) | MEGAPRESS | 2000ms | 68ms | Automated shimming followed by manual shimming | GANNET 2.0 toolkit | 3T | 40 × 30 × 20mm |
| Rowland., 2015 (O) | MEGAPRESS | 2000ms | 68ms | Automated shimming followed by manual shimming | GANNET 2.0 toolkit | 3T | 40 × 30 × 20mm |
| Yang., 2015 | MEGAPRESS | 1500ms | 69ms | Manual shim | LC model | 3T | 30\*30\*30 mm |
| Wang.,2016 | MEGAPRESS | 1500ms | 68ms | Automated shimming followed by manual shimming | LC model | 3T |  |
| Chen., 2017 | MEGAPRESS | 1500ms | 69ms | Manual shimming | LC model | 3T | 20\*40\*30mm |
| Xia., 2018 | Mescher-Garwood point resolved  spectroscopy | 1500ms | 69ms | Automated shimming followed by manual shimming | GANNET 2.0 toolkit | 3T | 30\*30\*30mm |
| Sandoval., 2018 | J-edited spin echo difference method | 1500ms | 68ms | NA | Levenberg–Marquardt nonlinear least squares | 3T | 30\*25\*25mm |
| **DLPFC** | | | | | | | |
| Kegeles., 2012 (UM) | J-EDITING | NA | NA | NA | Levenberg-Marquardt nonlinear least-squares algorithm written in IDL | 3T | 25\*30\*25mm |
| Kegeles., 2012 (M) | J-EDITING | NA | NA | NA | Levenberg-Marquardt nonlinear least-squares algorithm written in IDL | 3T | 25\*30\*25mm |
| Chen., 2017 | MEGAPRESS | 1500ms | 69ms | Manual shimming | LC model | 3T | 20\*40\*30mm |
| **Study** | **Sequence** | **TR** | **TE** | **Shimming** | **Post processing** | **Scanner strength** | **Voxel size** |
| Wang., 2019 | STEAM | 3000ms | 14ms | FASTMAP | LCModel | 7T | 20\*30\*20mm |
| **UHR** | | | | | | | |
| Menschikov.,2016 (ACC) | MEGAPRESS | 2000ms | 68ms | NA | jMRUi software | 3T | 30\*30\*30 mm |
| Sandoval., 2016 (MPFC) | J-edited spin echo difference  Method | 1500ms | 68ms | NA | Levenberg-Marquardt nonlinear least-squares | 3T | 30\*25\*25 mm (mPFC)  45\*25\*20mm (caudate) |
| Wang.,2016 (MPFC) | MEGAPRESS | 1500ms | 68ms | Automated shimming followed by manual shimming | LC model | 3T | 30\*30\*30mm |
| Modinos.,2018 (MPFC) | MEGAPRESS | 2000ms | 68ms | Optimized shimming - auto-prescan  performed twice before each scan | LC model | 3T | 40\*35\*20mm |

**T**- Tesla; **V**- Voxel in cc; **TR** –the repetition time; **TE** –echo time; **NA**- Not available; **O**- Old; **Yg**- Young; **Max**-maximum**; M**- Medicated; **UM**- not medicated

Table 3. Screening instruments used in the included studies to diagnose schizophrenia and screen healthy controls

|  |  |  |
| --- | --- | --- |
| **Study** | **Screening Instrument** | |
| **C** | **SCZ** |
| **ACC** |  |  |
| Ongur., 2010 | N.R | SCID |
| Tayoshi., 2010 | CI: DSM IV TR | CI: DSM IV TR |
| Rowland., 2013 (Yg) | SCID-NP | SCID-P |
| Rowland., 2013 (O) | SCID-NP | SCID-NP |
| Marenco., 2015(NM) | SDI | SDI |
| Marenco., 2015(M) | SDI | SDI |
| Brandt., 2016 | MINI | MINI |
| Chiu., 2018 | SCID-I | SCID-I |
| Reid., 2018 | N.R | N.R |
| Wang., 2019 | SCID | SCID |
| **MPFC** |  |  |
| Goto., 2010 | N.R | SCID |
| Kegeles., 2012 (UM) | SCID-I | DIGS |
| Kegeles., 2012 (M) | SCID-I | DIGS |
| Marsman., 2014 | CASH | CASH |
| Rowland., 2015 (Yg) | SCID-NP | SCID-P |
| Rowland., 2015 (O) | SCID-NP | SCID-P |
| Yang., 2015 | MINI-6 | CI: DSM-5 |
| Wang., 2016 | SCID-NP | SCID-P |
| **Study** | **Screening Instrument** | |
| **C** | **SCZ** |
| Chen., 2017 | MINI-6 | MINI-6; CI: DSM IV |
| Xia., 2018 | SSI | CI: DSM IV |
| Sandoval., 2018 | SCID | SCID |
| **DLPFC** | | |
| Kegeles., 2012 (NM) | SCID-I | DIGS |
| Kegeles., 2012 (M) | SCID-I | DIGS |
| Chen., 2017 | MINI-6 | MINI-6; CI: DSM IV |
| Wang., 2019 | SCID | SCID |
| **UHR** | | |
| Menschikov., 2016 (ACC) | N.R | N.R |
| Sandoval., 2016 (mPFC) | SCID | SIPS |
| Wang., 2016 (mPFC) | SCID-NP | SIPS & SOPS |
| Modinos., 2018 (mPFC) | CI: DSM IV | CAARMS |
| **C**: Control; **CAARMS**: Community Assessment of At-Risk Mental States; **CASH**: Comprehensive Assessment of Symptoms and History; **CI:DSM IV**: Clinical Interview and diagnosed as per DSM IV; **CI:DSM IV TR**: Clinical Interview and diagnosed as per DSM IV TR; **CI:DSM-5**: Clinical Interview and diagnosed as per DSM-5;  **DIGS**: Diagnostic Instrument for Genetic Studies; **MINI**: Mini International Neuropsychiatric Interview; **N.R**: Not Reported; **SCID**: Structured Clinical Interview for DSM-IV Disorders; **SCID-I** Structured Clinical Interview for DSM-IV Axis I Disorders; **SCID-NP**: Structured Clinical Interview for DSM-IV-TR, Non-Patient Version **SCID-P**: Structured Clinical Interview for DSM-IV-TR, Patient Version; **SCZ**: Schizophrenia; **SDI**: Structured Diagnostic Interview; **SIPS**: Structured Interview for Prodromal Syndromes; **SOPS**: Scale of Prodromal Syndromes; **SSI**: Semi-Standardized Interview; | | |