Spatial and chronic differences in neural activity in medicated and unmedicated schizophrenia patients

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A B S T R A C T

A major caveat with investigations on schizophrenic patients is the difficulty to control for medication usage across samples as disease-related neural differences may be confounded by medication usage. Following a thorough literature search (632 records identified), we included 37 studies with a total of 740 medicated schizophrenia patients and 367 unmedicated schizophrenia patients. Here, we perform several *meta*-analyses to assess the neurofunctional differences between medicated and unmedicated schizophrenic patients across fMRI studies to determine systematic regions associated with medication usage. Several clusters identified by the *meta*-analysis on the medicated group include three right lateralized frontal clusters and a left lateralized parietal cluster, whereas the unmedicated group yielded concordant activity among right lateralized frontal-parietal regions. We further explored the prevalence of activity within these regions across illness duration and task type. These findings suggest a neural compensatory mechanism across these regions both spatially and chronically, offering new insight into the spatial and temporal dynamic neural differences among medicated and unmedicated schizophrenia patients.

1. Introduction

Schizophrenia is a chronic psychiatric disorder that affects 1.1 % of the population. It is comprised of multiple cognitive and psychotic symptoms such as hallucinations and delusions (Bersani et al., 2014; Van der Gaag et al., 2014; Ventura et al., 2010; Zimmermann et al., 2005), as well as detrimental negative symptoms such as apathy and withdrawal from social encounters (Dong et al., 2018; Gur et al., 2007; Li et al., 2016; Strauss et al., 2013; Sugranyes et al., 2011). Detrimental symptoms of schizophrenic patients have been attributed to altered anatomical and functional brain indices (Lawrie et al., 2001; Mathew et al., 2014; McDonald et al., 2005; Strasser et al., 2005; Tarcijonas and Sarpal, 2019). With regards to the differences in functionality, patients with schizophrenia have been shown to exhibit deficits in executive control and learning processes, coupled with increased and decreased activity in the prefrontal and anterior cingulate regions (e.g., (Glahn et al., 2005; Minzenberg et al., 2009)). Several caveats arise when investigating the brain correlates of medicated schizophrenic patients in

an empirical setting. Firstly, episode and chronic developmental stages of schizophrenia have been shown to contribute to volumetric decreases within the cingulate, insular, prefrontal and temporal cortices, and the cerebellum. While untreated first-episode psychosis patients display thinning of prefrontal and temporal cortices in a functional connectivity study (Zhang et al., 2015), more extensive changes are displayed in schizophrenic patients who are exposed to long-term usage of antipsychotics (Ho et al., 2011; Van Haren et al., 2011), supposedly by facilitating neuroplastic changes that develop new neural connections (Angelucci et al., 2000). In summary, the chronological stage of schizophrenia at which the brain is assessed may have a significant influence on the obtained results. A second caveat is medication usage, which may significantly contribute to brain activity in schizophrenic patients (Arsalidou et al., 2020). In a review article, it was suggested that while some brain regions become normalized from chronic medication usage, other regions may become denormalized (Abbott et al., 2013). In addition, two independent *meta*-analyses revealed overlapping regions when comparing neural volume before and after medication use (Leung

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et al., 2011) and regions associated with antipsychotic treatment (Bergé et al., 2014). However, as indicated by the former study, changes in grey matter across studies may be caused by a variety of reasons such as neuroleptic treatment, chronicity, and duration of illness (Leung et al., 2011).

To the best of our knowledge, a functional *meta*-analysis on medicated versus unmedicated schizophrenia patients has not been conducted. While multiple empirical studies have attempted to establish regions afflicted by unmedicated schizophrenia patients (Bergé et al., 2014; de la Fuente-Sandoval et al., 2010; Harrison et al., 2006; Torres et al., 2013), few have compared medicated with unmedicated groups directly (Van Snellenberg et al., 2016) or compared groups prescribed with typical versus atypical antipsychotic medication (Abbott et al., 2011; Kumari et al., 2015; 2007; Tran et al., 1997). Due to the lack of articles directly comparing brain activity between medication and unmedicated individuals, it is challenging to assert functional activity to task-related processes, especially when medication has been shown to influence brain activation (C. Abbott et al., 2013; Van Snellenberg et al., 2016). Therefore, the *meta*-analysis approach may be beneficial to examine regions most likely to be affected by antipsychotic medication by comparing medicated and unmedicated schizophrenia patients across studies irrespective of task type. Our main goal is to perform separate *meta*-analyses on medicated and unmedicated schizophrenia patient groups to determine whether medication alters functional activity across studies. We further aim to isolate studies that examined specific types of medication taken by patients in the medication group (i.e. typical, atypical, anti-depressant), irrespective of studies that recruited patients prescribed with multiple medications (Dichter et al., 2010; Kumari et al., 2009; Song et al., 2017; Zedkova et al., 2006). As a supplementary analysis, we may also categorize studies into first-episode psychosis and chronic schizophrenia to determine regions associated with the stage of illness. Finally, we aim to explore illness duration and task type from each of the patient samples reporting relevant clusters from the main *meta*-analyses (medicated vs. unmedicated). By determining whether the clusters provided by medicated and unmedicated are specific to illness duration and task type we may shed light on any systematic patterns of activity across time from illness onset as well as systematic patterns of activity yielded any one task type. By adopting the perspective that drug-naïve schizophrenic patients serve as a baseline, brain activity map revealed by compiling and comparing medicated and unmedicated groups will demonstrate regions most likely to be affected by medication.

The approach to use *meta*-analysis across task-types may inevitably invite the study heterogeneity problem, which is central to understanding *meta*-analytic results. Contributors to this heterogeneity may include task paradigms, type of medication, and patient profiles, which may not be discernible from published results. Heterogeneity observed across studies could not be investigated by subgroup analyses or meta-regression due to the limited number of available studies. In the end, precise answers to broad *meta*-analytic questions about medication effects may be difficult to achieve. However, *meta*-analyses addressing broadly framed questions may yield heterogeneous studies across task-types (Chein and Schneider, 2005; Li et al., 2015; Han and Ma, 2014; Wang et al., 2017). For example, to study age-related changes of fMRI-derived activation, a recent *meta*-analysis compiled 114 fMRI studies on healthy aging across different types of tasks, including memory encoding, memory retrieval, and executive control (Li et al., 2015). For this overall healthy aging *meta*-analysis, the researchers found that older adults showed decreased activation in the visual network and increased activation mainly in the frontoparietal and default-mode network. These findings provide novel evidence to support the view that declining sensory processing may underline cognitive aging which is associated with the frontoparietal compensation process and reduced suppression of the default-mode network. This study suggests that across task-types approach can be used to delineate age-related changes in activation across cognitive domains. A similar approach has successfully been used

to study the overall effects of culture and oxytocin manipulation (Han and Ma, 2014) (Wang et al., 2017). Even for the same cognitive domain, there could be profound differences in experimental paradigms (Schurz et al., 2014) (Molenberghs et al., 2016). Even for the very specific task paradigms, e.g. strategic games, the task structures are also highly diverse, ranging from stag-hunt game, beauty contest game, to patent race game. Nevertheless, a consistent pattern emerges and the ALE results revealed consistent activation in the medial prefrontal cortex and bilateral temporoparietal junction across all theory of mind tasks and broader task parameters (Molenberghs et al., 2016; Schurz et al., 2014).

Here, we examined schizophrenia and medication related brain differences across different task domains. By compiling and performing these analyses we aim to determine: 1) neural activity most sensitive to schizophrenia if left untreated; 2) neural activity most likely influenced by medication usage; 3) neural activity most likely affected by atypical antipsychotic medication; 4) activity that may succumb to alterations as a result of chronic medication usage versus first-episode patients (refer to Supplementary Materials); 5) whether these clusters systematically derive from patients with high and low illness duration; and 6) whether these clusters systematically derive from any given task type. Since antipsychotic medication typically treats psychotic (positive) symptoms (Kane and Correll, 2010; Millan et al., 2012; Remington et al., 2016), which derive from parietal regions of the cerebral cortex (Konopaske et al., 2007), we hypothesize greater concordant activation across studies in the parietal cortex for the unmedicated group compared to the medicated group.

2. Materials and methods

2.1. Literature search

Eligible articles were identified by searching in the Web of Science database (http://www.webofknowledge.com) on 18th June 2019. This was performed by combining a total of 14 searches continuously using the key terms: "fMRI" AND "schizophrenia", and varying key terms corresponding to each search: "unmedicated", "treatment-resistant", "anti-psychotic", "antipsychotic", "never medicated", "neuroleptic", "olanzapine", "risperidone", "Clozapine", "Aripiprazole", "Brexpiprazole", "Quetiapine", "Chlorpromazine", and "Haloperidol". These specific key terms were selected based on reiterations of searches that yielded the maximum number of articles with a minimum number of duplicates. After removing duplicates, a total of 448 articles were screened.

2.2. Data inclusion/exclusion criteria

The identified articles were deemed eligible if they: (i) included adult patients (no children or adolescents) were diagnosed using DSM or ICD criteria, as well as patient groups reported as schizophrenia, schizoaffective disorder, schizophreniform disorder, or or first episode psychosis; (ii) employed functional magnetic resonance imaging (fMRI) as the imaging modality; (iii) reported a within-subject contrast between an experimental task condition and a control condition, i.e. excluding resting-state fMRI contrast; (iv) applied whole-brain analyses (no region of interest [ROI] analyses were included); (v) reported neural activations in a standardized stereotaxic space (Talairach or Montreal Neurological Institute, MNI); and (vi) reported in English. Talairach coordinates were converted to the MNI coordinates using Brett's algorithm as implemented on the GingerALE software (http://brainmap.org/ale/). Fig. 1 displays a flowchart of how the screening procedure was conducted.

The final dataset included 20 articles for the unmedicated group and 37 articles for the medicated group. Further *meta*-analyses included 17 articles involving first-episode psychosis patients and 46 articles examining chronic schizophrenia patients (see Supplementary Materials). Within the medicated group, a total of 27 articles were deemed eligible
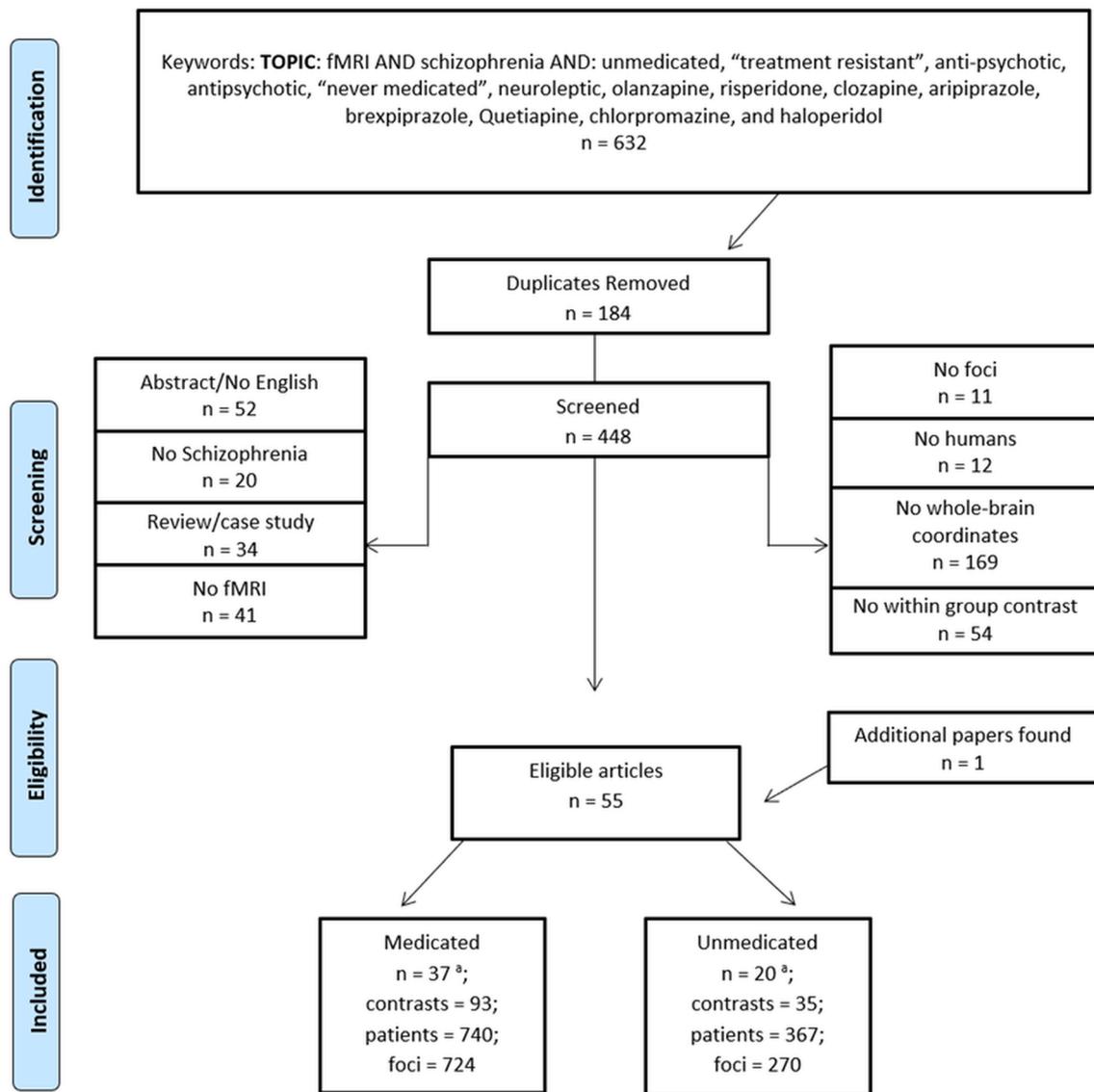
Fig. 1. PRISMA flowchart for eligibility of articles for *meta*-analyses; [a] = one study investigated both medicated and unmedicated groups (van Snellenberg et al., 2016).

that included schizophrenia patients prescribed with atypical antipsychotic medication only, and a corresponding *meta*-analysis was performed (see Supplementary Materials). In addition, five studies examining patients using typical antipsychotics only (Kumari et al., 2007; Payoux et al., 2004; Phillips et al., 1999; Singh et al., 2014; Takahashi et al., 2010), seven articles included patients using both typical and atypical antipsychotic medication (Borofsky et al., 2010; Kumari et al., 2009; 2006; Liddle et al., 2006; Van Snellenberg et al., 2016; Vogel et al., 2016; Zedkova et al., 2006), and two studies included patients with a combination of antidepressant and atypical antipsychotic medication (Dichter et al., 2010; Song et al., 2017), thus analyses for these subsets of medication usage were not performed. Three articles reported data from two schizophrenia groups (Kumari et al., 2015; Modinos et al., 2015; Van Snellenberg et al., 2016), the latter of which included data from both medicated and unmedicated schizophrenia patients.

2.3. Software tools

GingerALE is a freely available, quantitative *meta*-analysis method developed by Turkeltaub and colleagues (Eickhoff et al., 2017, 2009;

Turkeltaub et al., 2012). GingerALE, version 3.0.2 was used (http://brainmap.org/ale/), which relies on activation likelihood estimation (ALE) which compares coordinates compiled from multiple articles and estimates the magnitude of overlap, yielding clusters most likely to become active across studies. The algorithm minimizes within-group effects and provides increased power by allowing for the inclusion of all possible relevant experiments (Eickhoff et al., 2017; Turkeltaub et al., 2012). All coordinates were transformed into a common atlas space: Talairach coordinates were converted to MNI using the Lancaster transformation algorithm (Lancaster et al., 2007). Resulting statistical maps were thresholded at $p < 0.05$ using a cluster-level correction for multiple comparisons and a cluster forming threshold at $p < 0.001$ (Eickhoff et al., 2017) rather than false discovery rate that is not appropriate for inference on topological features (Eickhoff et al., 2016). Analyses contrasting between groups were calculated. Tests for differences and conjunction analysis were used to examine results for ALE maps between groups. The threshold for group-contrasts was set to $p < 0.05$ uncorrected for multiple comparisons (5000 permutations, 50 mm^3 minimum cluster-size) because group-contrast analyses use cluster-level thresholded ALE maps for each group, which have already been controlled for multiple comparisons.

In total, using the *meta*-analysis tools, we conducted the following contrasts in ALE: main activation effect for medicated; main activation effect for unmedicated; contrast analysis between medicated and unmedicated; and conjunction analysis between medicated and unmedicated (see Table 3). In addition, we performed a main activation effect for chronic schizophrenia; main activation effect for first episode schizophrenia; contrast analysis and conjunction analysis between chronic and first episode psychosis (see Supplemental Table 1 for results).

2.4. Post-hoc analysis: SDM software and Meta-regression on illness duration

To further explore our dataset on illness duration and to specifically examine the activation/deactivation directionality, we reiterated the analyses of medicated, unmedicated, first episode and chronic schizophrenia using a software called effect-size seed based differential mapping (ES-SDM; https://www.sdmproject.com). Based on activation likelihood estimation, this analysis combines statistical parametric t-maps and peak coordinates of clusters from multiple studies to increase statistical power (Radua et al., 2012). By including studies that reported either a positive or a negative t-score, we may examine directionality for each group. Contrast and conjunction analysis was also performed using ES-SDM. Effect-size brain maps and variances were derived from reported t-statistics. The full width at half maximum (FWHM) in SDM was set at the default (20 mm) to control for false positives (see Radua et al. 2012). To optimally balance sensitivity and specificity resulting statistical maps were thresholded at p = 0.005 to control for family-wise error rate (Radua et al., 2012). To assess which brain areas were affected by illness duration, a linear model (*meta*-regression) was performed on the illness duration of each study that included this information. Linear models were used for comparing two or more groups, controlling for potential confound variables, or assessing the heterogeneity of the findings by means of *meta*-regressions. For our purposes we used the map that reflects the differences between high illness and low illness duration (i.e. the " 1 m0 z" map). We report the statistical difference between studies with illness duration at maximum compared to minimum thresholded at p = 0.005. Note: all ES-SDM test results are listed in the Supplementary Materials section.

2.5. Post-hoc analysis: Fisher's exact test

Fisher's Exact tests were performed on the group level by performing tests on illness duration and task type on each grouping (e.g., medicated versus unmedicated groups; first-episode schizophrenia versus chronic schizophrenia) to assess whether there were systematic differences in illness duration and task type. In addition, we performed Fisher's Exact tests on the cluster level by examining the frontal and parietal clusters from the main *meta*-analyses (*meta*-analyses on medicated and unmedicated groups) and testing these against the frequency of foci reported with four bins associated with illness duration: 0–4.9 years of illness duration, 5–9.9 years, 10–14.9 years, and 15 + years. This was explored by extracting foci from the raw data which fell within a $10 \, mm^3$ radius of the peak cluster from the main *meta*-analysis and ran a Fisher's exact test due to having<5 counts in at least 20% of conditions. The same approach was performed for task type by extracting foci from each article that fell within a $10 \, mm^3$ radius of the peak cluster from the main *meta*-analysis. Since a majority of these cases employed a cognitive task (~80) we grouped these cases into 'cognitive' and 'other'.

3. Results

3.1. Demographics

Five *meta*-analyses were performed using GingerALE: unmedicated (35 contrasts; 367 patients, 270 foci), medicated (93 contrasts; 740

patients, 724 foci), atypical medications only (47 contrasts; 445 patients, 323 foci), and first-episode schizophrenia (29 contrasts; 285 patients, 224 foci), chronic schizophrenia (95 contrasts; 697 patients, 743 foci (see Supplementary Materials on Results of the latter two *meta*-analyses) all of which satisfy current ALE power recommendations of including a minimum of 17 contrasts (Eickhoff et al., 2017).

The average duration of illness for the unmedicated and medicated group was 4.7 and 9.89 years, respectively, which was tested for differences in frequency among frontal and parietal clusters (see section *3.2.4. Illness duration* for details). For first-episode psychosis and chronic schizophrenia, the mean duration of illness was 3.38 and 10.47 years, respectively. For the patients prescribed with atypical medications only, the average duration of illness was 11.12 years. Mean age (and male percentage) was 26.42 ± 3.40 (59.4%), 33.25 ± 6.31 (70.13%), 24.74 ± 4.04 (68.77%), 34.26 ± 4.90 (68.43%), and 33.36 ± 6.35 (93.49%) for unmedicated, medicated, first-episode schizophrenia, chronic schizophrenia and medicated receiving atypical medications, respectively.

Out of the medicated group, six studies limited their patient group to those prescribed with one atypical antipsychotic medication (e.g. Risperidone (Kumari et al., 2015, 2007; Surguladze et al., 2011); Olanzapine (Kumari et al., 2015, 2007; Stip et al., 2012; Walter et al., 2009); and Quetiapine (Stip et al., 2005). Of the studies that examined patients prescribed with typical antipsychotic medication, three included patient groups taking Chlorpromazine only (Phillips et al., 1999; Singh et al., 2014; Takahashi et al., 2010). Tables 1 and 2 includes the demographic details for each study, corresponding to the unmedicated (n = 20) and medicated (n = 37) groups. Details of first-episode psychosis/ chronic schizophrenia and medication type are also displayed.

3.2. ALE maps

Table 3 displays a complete list of concordant activity for the *meta*-analyses on unmedicated/medicated. For results of the *meta*-analyses on first-episode psychosis, chronic schizophrenia and atypical antipsychotics only see Supplementary Materials. Data from each cluster are listed in order of cluster size in MNI space. Higher ALE values are indicative of a greater likelihood of activation.

Although prior *meta*-analyses have examined first-episode psychosis and chronic schizophrenia (Del Casale et al., 2018; 2016), we emphasize the necessity to reiterate these supplementary analyses to assess areas unique to medication usage and stage of illness using the same statistical thresholds. These additional analyses determined areas that conjunct with medication usage to disentangle regions confounded by nuisance variables. In order to compare concordant activity between these comparisons, we performed a visual inspection to identify overlapping clusters (see Supplementary Materials). Fig. 2 displays regions most likely to become active across eligible studies in medicated and unmedicated groups. Purple circles surrounding specific regions highlight clusters that were unique to each *meta*-analysis when compared to First episode and chronic schizophrenia groups. Fig. 2 and Table 3 denote this information with an asterisk.

3.3. Unmedicated vs. Medicated patients

We first establish baseline activation, identified as regions yielded by the unmedicated group. Clusters within this group may determine areas most sensitive to schizophrenia when left untreated. Significant regions associated with the unmedicated group include a relatively small cluster within the right inferior frontal gyrus (Brodmann area (BA 9), and the right superior parietal gyrus (BA 7). Within the medicated group *meta*-analysis, four large clusters were found to be concordant across studies. The largest cluster was within the left inferior parietal gyrus (BA 40), followed by the right medial frontal gyrus (BA 8), right middle frontal gyrus (BA 6), and right orbitofrontal gyrus (BA 47). The region with the highest likelihood of activation (i.e. highest ALE value) was the right

Table 1
Information on source datasets included in the *meta*-analysis for unmedicated group (n = 20).

Article	n	Mean Age (SD)	Contrasts	Group type	Foci	Stimuli type	Illness duration (years)
Anilkumar et al., 2008	13	26.08 (9.47)	5	FEP	46	Face	NA
Bergé et al., 2014	18	24.83 (4.7)	1	FEP	4	Face	NA
Bertolino et al., 2004	28	26.1 (8.3)	1	SCZ	8	Motor	3.53
Blasi et al., 2009	12	28.2 (6.3)	1	SCZ	1	Emotion	6.75
Bliksted et al., 2019	17	23.94	2	FEP	7	Theory of Mind	13.35
Boksman et al., 2005	10	22 (5)	1	FEP	9	Lexical	1.41
Braus et al., 2002	12	25.1 (4.8)	1	FEP	6	Audio-visual	NA
de la Fuente-Sandoval et al., 2010	12	23.6 (3.5)	1	SCZ	9	Thermal	1.41
de la Fuente-Sandoval et al., 2012	12	23.6 (3.5)	1	SCZ	9	Thermal	1.41
Harrison et al., 2006	8	21.2 (3)	1	FEP	17	Cognitive	0.5
Keedy et al., 2015	21	23.9 (7.9)	3	FEP	7	Motor	NA
Knolle et al., 2018	13	23.85 (6.3)	2	FEP	19	Visual	NA
Lancaster et al., 2016	83	23.95 (3.64)	1	HRP	1	Face/place	NA
Scheuerecker et al., 2008	23	31.6 (11.1)	2	SCZ	18	Cognitive	3.2
Schlagenhauf *et al.*, 2008	10	30.5 (10.6)	1	FEP	1	Reward	2.2
Schlagenhauf et al., 2009	15	30.1 (8.1)	4	SCZ	4	Reward	2.4
Schlagenhauf et al., 2014	24	27.5 (5.2)	2	FEP	18	Cognitive	15.1
van Snellenberg et al., 2016	21	33.2 (10.6)	3	SCZ	61	Lexical	NA
Weiss et al., 2006	7	29.71 (5.02)	1	SCZ	8	Cognitive	4.75
Weiss et al., 2007	8	29.5 (4.99)	1	FEP	17	Reward	5.2

Note: n = sample size; SD = Standard deviation; FEP = First-episode psychosis; SCZ = diagnosed as schizophrenia; HRP = high risk for psychosis; references available in Supplementary materials.

middle frontal gyrus. We found no overlap when compared between groups. In addition, our findings revealed a cluster within the right medial frontal gyrus (2, 30, 38, BA 8), an area that overlapped in concordance among first episode psychosis and chronic schizophrenia (see Supplementary Table 1).

3.4. Illness duration

In total, 18 studies reported illness duration between 0 and 4.9 years, 14 reported between 5 and 9.9 years, 12 between 10 and 14.9 years and 8 studies reported samples greater than 15 years (see Tables 1 and 2). We extracted foci reported from the *meta*-analysis on medication usage and plotted the frequency of foci reported across all studies across the previously mentioned illness duration bins, irrespective of medication usage or schizophrenia type (i.e. chronic vs. first-episode psychosis). The purpose of this procedure was to assess whether illness duration may have systematically contributed to the likelihood of activity across studies pertaining to medication usage.

The Fisher's Exact test revealed at least one difference among independent samples ($p = 0.022$, Fisher's exact test). With exception to the right medial frontal gyrus (BA 8), all other right frontal clusters from both medicated and unmedicated schizophrenic groups were more prevalent in patients with an illness duration of<5 years (see Fig. 3, light grey bars; $p = 0.0084$), suggesting a systematic pattern of active frontal regions within 5 years of illness onset. All parietal clusters exacted from the main analysis of medicated and unmedicated schizophrenic groups were more prevalent in patients with an illness duration between 10 and 14.9 years (see Fig. 3, dark grey bars; ($p = 0.0134$), suggesting more prevalence of parietal activity within 10 to 15 years of illness duration. This suggests that the location of relevant clusters may be most sensitive at different stages of illness duration. However, given that this finding is dependent on the results of the main analysis we cannot rule out the possibility that clusters reported from either group (medicated and unmedicated) are systematically ascribed to early and late illness duration. Therefore, this may suggest that clusters reported in the main *meta*-analyses of medicated and unmedicated schizophrenia groups may not necessarily be confounded by illness duration and is worth investigating in future empirical studies.

3.5. Task type

The majority of the studies included a cognitive task (n = 24), 12 studies employed a visuospatial task, and eleven studies used a face/emotion based task. Other studies included stimuli related to reward (n = 6), motor (n = 5), lexical processing (n = 4), theory of mind (n = 2), auditory (n = 2), and thermal (n = 2). Two seperate Fisher's Exact tests were used to assess whether there was systematic bias towards a particular task type for each grouping (i.e. medicated versus unmedicated patients and first episode schizophrenia versus chronic schizophrenia). The tests revealed no statistically significant differences between medication status ($p = 0.279$, Fisher's exact test) and illness stage ($p = 0.234$, Fisher's exact test). Graphs for the different groupings can be shown in Fig. 4.

By including only studies that reported foci that fell 10 mm^3 within the range of frontal and parietal clusters from the main *meta*-analysis we were able to explore on the cluster level whether the clusters reported in the analysis were systematically bias towards cognitive tasks since ~ 80% of these studies used cognitive tasks. This Fisher's Exact test revealed a statistically significant result ($p < 0.001$, Fisher's exact test), with all regions expect the right orbital frontal cortex have more 'cognitive' tasks than 'other' tasks (all $p < 0.05$). These results suggests that while no systematic bias can be declared for task type across groups, the majority of clusters reported in the *meta*-analysis are mostly attributed to cognitive tasks. This may indicate that cognitive tasks and thus cognitive processes are mostly affected in schizophrenia patients hence why these clusters and the association with cognitive tasks may contribute a greater amount to the results.

4. Discussion

Investigations on schizophrenic patients with first-degree relatives, unmedicated prodromal, antipsychotic naïve, or first-episode patients succumb to recruitment challenges in experimental settings due to the lack of control of medication prescribed to patients (Arsalidou et al., 2020). Despite this, few examples have surfaced comparing functional MRI recording in unmedicated patients with medicated schizophrenia patients (Abbott et al., 2011; Kumari et al., 2015, 2007; Tran et al., 1997). Due to the difficulties of controlling medication usage, detecting systematic neurological differences between these groups is limited, yet perhaps unbound by the *meta*-analysis approach.

Table 2

Information on source datasets included in the *meta*-analysis for medicated group (n = 37).

Article	n	Mean Age (SD)	Number of contrasts	Group type	Foci	Stimuli type	Illness duration	Medication type
Borofsky et al., 2010	14	13.34 (2.14)	2	FEP	23	Lexical	0.5	Atypical + typical
Bourque et al., 2013	23	30.21 (6.35)	1	SCZ	9	Visuospatial	6.69	Atypical
	20	33.8 (7.04)	1	SCZ	1	Visuospatial	12.21	Atypical
Brüne et al., 2008	9	27.89 (6.66)	1	FEP	14	Theory of Mind	3	Atypical
Dichter et al., 2008	12	29.4 (10.2)	2	SCZ	23	Visual scenes	NA	Atypical + Anti-D
Eack et al., 2017	36	26.25 (6.83)	1	SCZ	4	Visuospatial	NA	Atypical
Francis et al., 2016	35	22.7 (4.7)	2	FEP	13	Cognitive	1.61	Atypical
Gur et al., 2007	16	30.1 (30.1)	1	SCZ	8	Face/emotion	9.6	Mostly atypical
Guse et al., 2013	12	36	2	SCZ	20	Cognitive	>0.5	Atypical
Kim et al., 2010	12	40.2 (10.23)	2	SCZ	11	Cognitive	14.1	Atypical
Kumari and Sharma, 2002	6	34.67 (4.41)	1	SCZ	1	Visuospatial	10.5	Atypical
Kumari et al., 2006a	21	43.75	8	SCZ	57	Cognitive	16.8	Atypical
Kumari et al., 2006b	12	34 (4.86)	2	SCZ	21	Cognitive	11	Atypical + typical
	13	33.85 (7.57)	3	SCZ	35	Cognitive	10.7	Atypical + typical
Kumari et al., 2007	10	39 (8.33)	1	SCZ	3	Cognitive	17.2	Typical
	10	33.2 (11.51)	1	SCZ	9	Cognitive	8.5	Atypical
	9	40.2 (11.96)	1	SCZ	10	Cognitive	15.5	Atypical
Kumari et al., 2009	36	37.72	10	SCZ	92	Cognitive	10.74	Atypical + typical
Kumari et al., 2015	7	35.57 (13.73)	2	SCZ	22	Visuospatial	14.86	Atypical
	8	41.25 (16.97)	2	SCZ	14	Visuospatial	12.25	Atypical
Liddle et al., 2006	28	31.6 (10.1)	2	SCZ	40	Auditory	7	Atypical + typical
Mendrek et al., 2005	12	28.75 (9.13)	1	SCZ	18	Cognitive	NA	Atypical
Minzenberg et al., 2018	27	26.2 (8)	1	SCZ	3	Cognitive	NA	Atypical
Modinos et al., 2015	18	24.4 (4.1)	1	HRP	8	Emotion	NA	Atypical
	18	27.9 (5)	1	FEP	10	Emotion	NA	Atypical
Moran et al., 2018	20	38.5 (10.1)	1	SCZ	9	Addiction	NA	Atypical
Nahas et al., 2003	6	36.8 (11)	1	SCZ	4	Lexical	NA	Atypical
Payoux et al., 2004	6	35.7 (4.3)	1	SCZ	11	Motor	11.7	Typical
Phillips et al., 1999	5	43	3	SCZ	16	Face/emotion	18	Typical
	5	31	3	SCZ	20	Face/emotion	4	Typical
Polli et al., 2008	18	42 (11)	1	SCZ	14	Visuospatial	17	Atypical
Shafritz et al., 2019	33	22.1	2	FES	12	Cognitive	2.2	Atypical
Singh et al., 2014	14	34.06 (9.89)	1	SCZ	7	Motor	9.6	Typical
Song et al., 2017	14	29.1 (7.8)	1	SCZ	4	Cognitive	7.1	Atypical + Anti-D
Stip et al., 2005	12	28.2 (9.4)	1	SCZ	3	Visual	5	Atypical
Stip et al., 2012	15	35.83 (10.12)	1	SCZ	8	Visual	NA	Atypical
Surguladze et al., 2011	16	42.6 (11.7)	6	SCZ	27	Face/emotion	15.3	Atypical
	16	43.7 (9.4)	6	SCZ	20	Face/emotion	18.6	Typical
Takahashi et al., 2010	12	31.8 (7.2)	1	SCZ	3	Visual	9.8	Typical
van Snellenberg et al., 2016	30	36.4 (7.5)	3	SCZ	60	Cognitive	14.2	Atypical + typical
Vogel et al., 2016	20	33.5 (7.2)	1	SCZ	8	Cognitive	8.8	Atypical + typical
	22	28.4 (7.3)	1	FEP	1	Cognitive	2.35	Atypical + typical
Walter et al., 2009	16	38 (9)	2	SCZ	7	Reward	4.6	Atypical
Weiss et al., 2003	16	32.7 (5.9)	1	SCZ	9	Cognitive	6.23	Atypical
Wolf et al., 2007	10	31.1 (9.4)	2	SCZ	6	Cognitive	7.4	Atypical
Zedkova et al., 2006	10	33.5 (7.5)	2	SCZ	6	Cognitive	11.5	Atypical + typical

Note: n = sample size; SD = Standard deviation; FEP = First-episode psychosis; SCZ = diagnosed as schizophrenia; HRP = high risk for psychosis; Anti-D = Antidepressants; references available in Supplementary materials.

We attempted to highlight regions most likely affected by medication in schizophrenia patients using a *meta*-analytic approach. For this report, several *meta*-analyses were performed across studies to determine the likelihood of activation for medicated schizophrenia patients. To establish an adequate baseline of activation, the *meta*-analysis of medicated schizophrenia patients was compared with a *meta*-analysis of unmedicated schizophrenia patients. To discount other possible confounds such as the duration of experiencing psychotic symptoms and the type of medication used, additional *meta*-analyses were performed (also see Supplementary Materials section for maps created using ES-SDM). Finally, we examined the frequency of foci overlapping with the main findings (Table 3) to assess whether these clusters may be attributed to illness duration.

Antipsychotic treatment has been shown to target cortical areas such as the parietal cortex (Konopaske et al., 2007) and aims to alleviate positive symptoms such as hallucinations, delusions, and disorganized thought processes, and which does not necessarily alleviate negative symptoms (Kane and Correll, 2010; Millan et al., 2012; Remington et al., 2016). The dorsolateral prefrontal cortex, on the other hand, has been a target for negative symptoms (Cohen et al., 1999; Dlabač-de Lange et al., 2010; Freitas et al., 2009). Based on these premises, we hypothesized

that the unmedicated group should reveal greater parietal activity compared to the medicated group. This hypothesis was supported by the results in that no parietal cortex cluster unique to the *meta*-analysis on the medicated group was found concordant across studies, yet a cluster unique to the *meta*-analysis on the unmedicated group was reported. This was further supported in the atypical medication only, in which no parietal concordant activity was shown. In addition to supporting the hypothesis, we establish several discoveries:

1. Right-lateralized inferior frontal and parietal gyri activity across studies for the unmedicated group and right orbital frontal gyrus specific to the medicated group;
2. Regions unique to the chronicity of schizophrenia disorder include activity within the right-lateralized frontal and parietal gyri, yet also included the posterior cingulate and left middle frontal gyrus across studies;
3. Patients medicated with atypical antipsychotics only yielded a cluster within the medial frontal gyrus, an area concordant in other *meta*-analyses medicated groups such as medicated, first-episode psychosis, and chronic schizophrenia;

Table 3
Concordant brain regions related to medication.

Main analysis							
Unmedicated patients							
Cluster #	Volume mm^3	P value	ALE Value	x	y	z	Brain region
1	600	3.01E-06	0.019	48	10	26	R Inferior Frontal Gyrus BA 9*
2	576	3.01E-06	0.019	18	−68	52	R Superior Parietal Gyrus BA 7*
Medicated patients							
Cluster #	Volume mm^3	P value	ALE Value	x	y	z	Brain region
1	3712	1.56E-08	0.034	−44	−48	50	L Inferior Parietal Gyrus BA 40
2	2352	4.34E-07	0.029	4	30	40	R Medial Frontal Gyrus BA 8
3	1528	2.18E-09	0.037	38	2	54	R Middle Frontal Gyrus BA 6
4	1168	1.03E-07	0.031	34	26	−10	R Orbital Frontal Gyrus BA 47*
Conjunctions							
Medicated-AND-Unmedicated							
Cluster #	Volume mm^3	P value	ALE Value	x	y	z	Brain region
no suprathreshold clusters							
Contrasts							
	Medicated > Unmedicated						
Cluster #	Volume mm^3	P value	ALE Value	x	y	z	Brain region
1	1272	0.0098	2.333	−40	−40	58	L Inferior Parietal Gyrus BA 40
2	832	0.0062	2.500	36	32	−10	R Orbital Frontal Gyrus BA 47*
3	368	0.0266	1.933	40	8	54	R Middle Frontal Gyrus BA 6
4	64	0.0332	1.835	−40	−20	58	L Precentral Gyrus BA 4
	Unmedicated > Medicated						
Cluster #	Volume mm^3	P value	ALE Value	x	y	z	Brain region
1	522	0.0042	2.635	22	−68	50	R Superior Parietal Gyrus* BA 7
2	368	0.0058	2.524	46	10	22	R Inferior Frontal Gyrus BA 9*
3	112	0.0168	2.124	−50	−50	38	L Inferior Parietal Gyrus BA 40

Note: MNI coordinates (x, y, z) of brain regions surviving a cluster-level threshold of p < 0.05 and a cluster forming threshold of p < 0.001 for single studies. Contrast threshold was set to p = 0.05, 5000 permutations, >50 mm^3, ALE = Activation Likelihood Estimate L = Left, R = Right; BA = Brodmann Area;*=areas unique to main *meta*-analyses.

4. Several right-lateralized frontal gyri foci were more prevalently reported in samples with early illness duration, yet unspecific to medicated or unmedicated groups.

4.1. Medicated vs. Unmedicated patients

The *meta*-analyses related to medicated and unmedicated groups revealed clusters within specific brain regions, namely a cluster within the right inferior frontal gyrus (BA 9) and right superior parietal gyrus (BA 7) for the unmedicated group and right orbital frontal gyrus (BA 47) for the medicated group. All other clusters, including inferior parietal gyrus, dorsal medial frontal gyrus, middle frontal gyrus, overlapped with clusters from the first episode/ chronic *meta*-analyses. It is unclear whether differences in these overlapping clusters are due to medication or chronology of illness or both. From the studies included in the *meta*-analysis on unmedicated schizophrenia participants, the inferior frontal cortex cluster was previously interpreted to involve a variety of processes such as facial recognition (Anilkumar et al., 2008), and working memory (Scheuerecker et al., 2008; Van Snellenberg et al., 2016), which may overlap with the dorsolateral prefrontal cortex.

For well over a decade the dorsolateral prefrontal cortex/inferior frontal gyrus has been sought to be a target for the medication in schizophrenia patients (Artigas, 2010; Blasi et al., 2009; Callicott et al., 2003; Fahim et al., 2005; Kumari et al., 2009; Potvin et al., 2015; Snitz et al., 2005; Van Snellenberg et al., 2016), in which drugs modulate prefrontal output to basal ganglia circuits, blocking striatal dopamine receptors (Artigas, 2010). This coincides with claims that cognitive symptoms in schizophrenia have been linked with altered anatomical and functional brain indices, specifically emphasizing the frontal

cortices (Jamadar et al., 2010; Quintana et al., 2003, 2001; Zhou et al., 2014). Furthermore, functional neuroimaging research has examined brain areas of adults with schizophrenia showing increased and decreased implication in prefrontal brain regions when solving cognitive tasks (Barch, 2005; Callicott et al., 2003; Glahn et al., 2005; Minzenberg et al., 2009). Therefore, acknowledgement of this region in the unmedicated group as the most likely to occur across studies deserves emphasis with regards to how medication may alleviate such cognitive impairments and brain functionality.

Interestingly, while activation of the right dorsolateral prefrontal cortex was found most prevalent among studies with unmedicated groups, activity within the right orbital frontal cortex was most prominent for groups using antipsychotic medication. Studies from the *meta*-analysis on medicated patients that reported this region have attributed its functionality to a variety of cognitive processes under different contexts such as impaired semantic processing in the context of thought disorder (Borofsky et al., 2010), working memory encoding (Francis et al., 2016; Van Snellenberg et al., 2016), oddball target detection (Liddle et al., 2006), selective attention (Weiss et al., 2003), and procedural learning (Zedkova et al., 2006). Most notably, one article reported left only prefrontal cortical activation in healthy controls, while patients with schizophrenia additionally recruited the right prefrontal cortex, suggesting that schizophrenia patients may require further recruitment of prefrontal regions to perform the task with the same accuracy as healthy controls (Weiss et al., 2003). This latter interpretation is suggestive of a compensatory mechanism that recruits distant brain regions, e.g. posterior brain regions to compensate for lack of prefrontal cortex functionality, albeit equal behavioral performance (Glahn et al., 2005; Quintana et al., 2003, 2001; Ragland et al., 2007), as well as local brain regions, e.g. adjacent frontal regions as a result of the
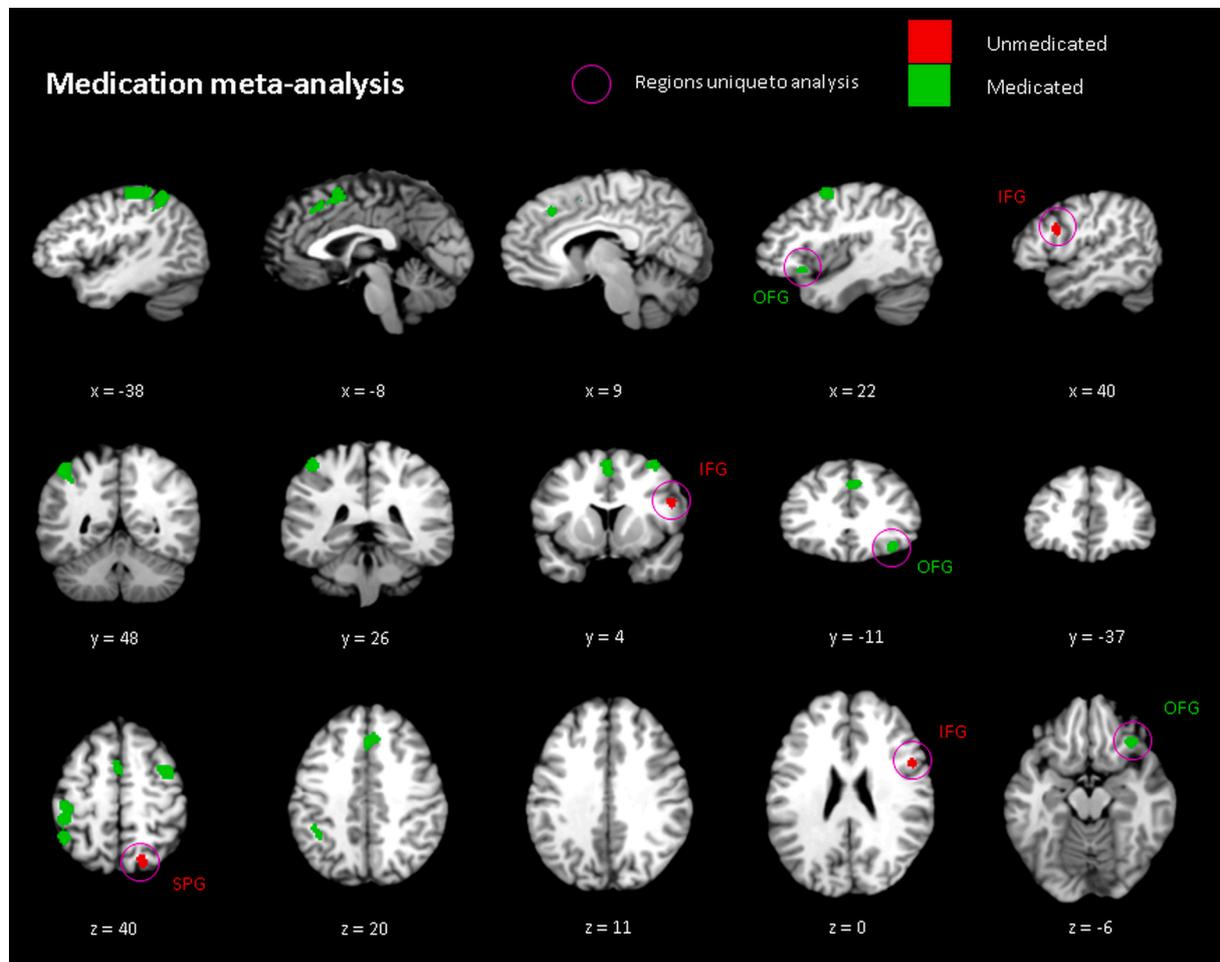
Fig. 2. Concordant activation for unmedicated schizophrenia (in red), and medicated schizophrenia (in green). Purple circle represents regions unique to analysis. Significant clusters were thresholded at p < 0.05 using a cluster-level correction for multiple comparisons and a cluster forming threshold at p < 0.001. IFG = Inferior Frontal Gyrus; OFG = Orbital Frontal Gyrus; SPG = Superior Parietal Gyrus. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

dysfunctional prefrontal hierarchical organization when normalized regions become dysfunctional (Kim et al., 2010; Tan et al., 2006).

Early evidence of a compensatory mechanism to counteract deficient prefrontal activity derived from a study that demonstrated reduced prefrontal cortex activation yet increased posterior parietal cortex activation relative to healthy controls, potentially as a means to adopt alternative cognitive strategies to maintain behavioral performance (Johnson et al., 2006; Quintana et al., 2003). Moreover, other studies have attributed compensatory mechanism to other brain areas (Glahn et al., 2005; Kim et al., 2010; Quintana et al., 2001; Ragland et al., 2007), which may explain the variation of hypo- and hyper-frontality among schizophrenic patients compared to healthy (Barch, 2005; Callicott et al., 2003, 2000; Crossley et al., 2016; Eisenberg and Berman, 2010; Glahn et al., 2005; Minzenberg et al., 2009), rather than medication usage per se (Riehemann et al., 2001). Furthermore, antipsychotic medication has been shown to target cerebral cortical regions within dopaminergic and serotonergic neural pathways (Artigas, 2010; Howes and Kapur, 2009; Kapur and Mamo, 2003; Roth et al., 2003). This latter premise may suggest that compensatory neural adaptation which recruits local and distant neural regions may be restricted to regions within these neural pathways. This interpretation would also concur with diminished behavioral performance associated with reward learning, cognition, and motor processes (Kathmann et al., 2013; 2000; Kelly et al., 2019; Nielsen et al., 2016, 2012; Shafritz et al., 2019; Vaitl et al., 2002; Van Snellenberg et al., 2016; Zimmermann et al., 2006), processes that recruit brain regions within dopaminergic and

serotonergic neural pathways.

Given the observed results in the *meta*-analysis and prior reported conclusions, the trade-off between concordant activation of the right inferior prefrontal cortex and parietal cortex for unmedicated patients and right orbital frontal cortex in medicated patients may involve multiple compensatory mechanisms: 1) a local hierarchical reorganization of functionality *within* the frontal lobe and; 2) distant compensatory mechanisms involving the redistribution of function *between* frontal and parietal cortical areas among medicated schizophrenic patients, perhaps restricted by dopaminergic or serotonergic neural pathways and targeted by antipsychotic medication.

4.2. Atypical antipsychotic medication

Another goal for this report was to address commonly reported brain activity found in patients prescribed with atypical antipsychotic medication only. The purpose of this question relates to the differences in motor symptoms between medicated with typical and atypical antipsychotics. Motor symptoms are frequently observed in both medicated and unmedicated schizophrenia patients (Docx et al., 2012; Peralta and Cuesta, 2010; 2001; Walther, 2015; Walther and Strik, 2012) yet typical antipsychotic medication seems to exacerbate motor symptoms (Bertolino et al., 2004; Müller et al., 2003, 2002; Rogowska et al., 2004). In light of this, some have investigated the neural reaction to typical compared to atypical antipsychotic drugs (Abbott et al., 2011; Kumari et al., 2015, 2007; Tran et al., 1997). For instance, using an auditory
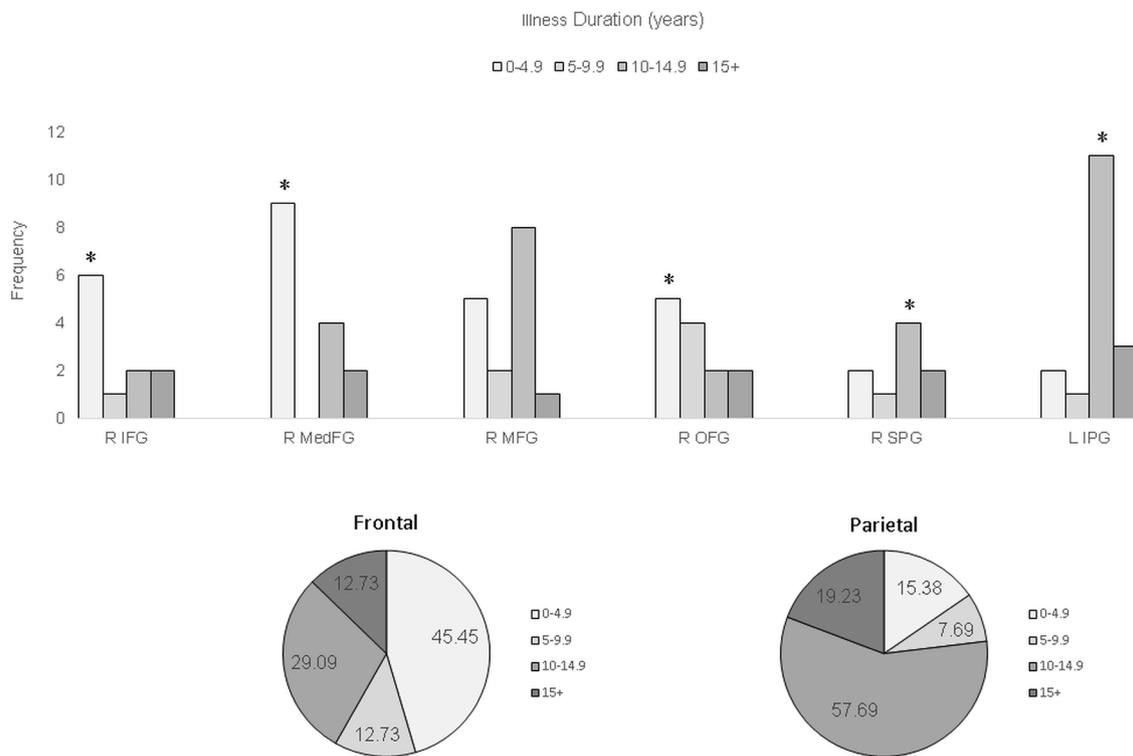
Fig. 3. The frequency of foci reported in each illness duration group, denoted as groups with illness duration between 0 and 4.9, 5–9.9, 10–14.9 or 15+ years. (Below) Frequency across frontal and parietal clusters represented in percentage in the form of pie charts. Asterisk provides statistical difference between task type for each cluster, with exception to the right Middle Frontal Gyrus cluster. R = Right; L = Left; IFG = Inferior Frontal Gyrus; IPG = Inferior Parietal Gyrus; MedFG = Medial Frontal Gyrus; MFG = Middle Frontal Gyrus; OFG = Orbital Frontal Gyrus; SPG = Superior Parietal Gyrus.
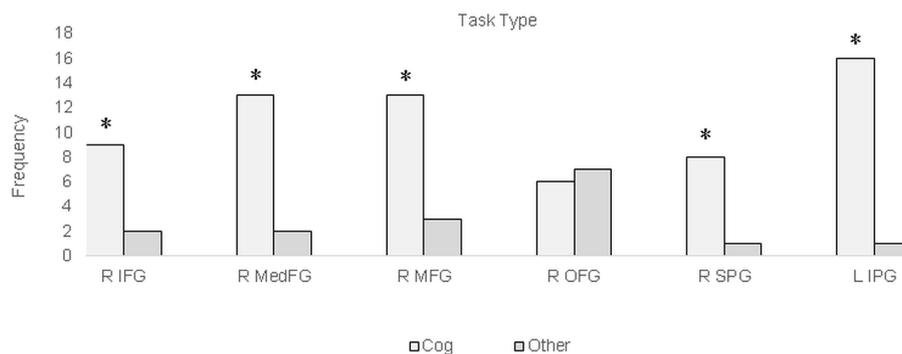
Fig. 4. The frequency of foci reported in each task type, denoted as Cognitive (Cog) or Other. Asterisk provides statistical difference between task type for each cluster, with exception to the right Orbital Frontal Gyrus cluster. R = Right; L = Left; IFG = Inferior Frontal Gyrus; IPG = Inferior Parietal Gyrus; MedFG = Medial Frontal Gyrus; MFG = Middle Frontal Gyrus; OFG = Orbital Frontal Gyrus; SPG = Superior Parietal Gyrus.

motor task antipsychotic medication sufficiently altered motor-related neural networks in schizophrenia patients, which was inversely correlated with dosage (Abbott et al., 2011). Moreover, the type of antipsychotic medication prescribed to patients also affected the activation patterns of these motor networks. A similar finding was reported among patients being treated with typical compared to atypical antipsychotic medication (Risperidone or Olanzapine Kumari et al., 2007). Within this report, prepulse inhibition of the startle response, a measure of sensorimotor gating, was significantly impaired in typical antipsychotic patients compared to atypical antipsychotic prescribed patients.

Our findings revealed a cluster within the right medial frontal cortex (BA 8), an area that overlapped in concordance among first-episode psychosis and chronic schizophrenia (see Supplementary Table 1). In prior *meta*-analyses, this region has been shown to be reduced in subjects with clinical high risk for psychosis compared to healthy controls on the

functional level (Fusar-Poli, 2012) but not on the structural level (Chan et al., 2011; Fusar-Poli et al., 2011). Notably, the medial frontal cortex is an area that has been attributed to the processing of predictions under uncertainty (Volz et al., 2005; 2004; 2003) but more recently has been shown to have common activation within the cingulate motor area and the pre-supplementary motor area during response inhibition and error processing (Evers et al., 2006; Nakata et al., 2009; Schiffer et al., 2014; Song and Hakoda, 2015; Ullsperger and Von Cramon, 2001; Yaple et al., 2021a). Since the medial frontal cortex is associated with motor as well as cognitive functions, perhaps this finding may offer insight into how cognitive and motor symptoms (and the corresponding brain regions) are targeted by atypical antipsychotic medication.

4.3. Chronology: Stage and duration of illness

A large number of studies including drug-naïve schizophrenic were also characterized as having first-episode psychosis, although not exclusively. Performing *meta*-analysis on samples with first-episode psychosis with chronic schizophrenia patients would allow one to identify areas that overlap with medicated and unmedicated patients to discover areas unique to each *meta*-analysis. The analyses on the first-episode psychosis sample revealed a cluster within the right medial frontal gyrus (BA 8), an area that overlapped with both medicated groups and the subsample of those prescribed with atypical medication users only. Noteworthy, is that no clusters overlapped between unmedicated and first-episode psychosis, suggesting that none of the clusters within the unmedicated sample could be exclusively attributed to the first episode psychotic group.

The *meta*-analysis among chronic schizophrenic patients revealed a larger quantity of clusters; the three largest clusters overlapping with the medicated group (Supplementary Table 1). Four clusters were unique to chronic schizophrenia, suggesting these regions were most prevalently active during long-term stages of the illness. These clusters included bilateral frontal cortices, posterior cingulate cortex and right inferior parietal cortex, confirming concordant activity specific to dopaminergic or serotonergic neural pathways during later development of the neurological disorder (Artigas, 2010; Kapur and Mamo, 2003; Roth et al., 2003).

For exploratory purposes, we performed a series of *meta*-analyses including foci denoted with a negative t score (deactivated data) using ES-SDM. This was performed in order to compare our findings with more focalized maps (ALE) that include directionality of activity by utilizing the t-score (as well as the foci) as an additional dimension to the analysis. Clusters with the ES-SDM results were much larger compared to ALE results and varied in locality as well as laterality. Perhaps this was due to the inclusion of additional foci (with negative t-values) and the difference in FWHM between each software. Overall, ALE and SDM results both reveal concordant activation of executive regions (e.g., frontal, parietal and cingulate clusters). This is logical due to the notion that most of the tasks used were within a cognitive domain. The most interesting findings from the SDM analysis were the results obtained from the chronic medicated groups, specifically the map created from negative t-scores. These analyses revealed right middle temporal, left angular gyrus and left median cingulate gyri. Although these findings do not necessarily highlight differences between medicated and unmediated groups, it may shed light on the clusters that become systematically blunted over long durations of the illness. The temporal lobe in particular has been noted to be a region related to schizophrenia (Corlett et al., 2007; Gradin et al., 2011; Lieberman et al., 2018; Sun et al., 2009). In addition, the left angular gyrus becomes concordantly deactivated both in chronic schizophrenia patients as well as the medicated group. The left angular gyrus has been reported to relate to be abnormal in chronic and first-episode schizophrenia (Nierenberg et al., 2005; Niznikiewicz et al., 2000).

Since early and late stages of illness do not necessarily equate to short and long duration of illness (e.g. chronic schizophrenia with an illness duration of <5 years (Bertolino et al., 2004; Scheuerecker et al., 2008; Schlagenhauf et al., 2014; 2009), or first-episode psychosis patients with illness duration greater than 10 years (Bliksted et al., 2019), we also examined the number of foci reported for each relevant cluster and the illness duration corresponding to each report (Fig. 3). These histograms revealed a larger prevalence of right prefrontal cortex foci during early stages of illness (0–4.9 years of illness duration) compared to other illness duration bins, specifically within the right inferior frontal cortex (BA 9), right medial frontal cortex (BA 8), right middle frontal cortex (BA 6) and the orbital frontal cortex (BA 47). The histograms also revealed an increased frequency of foci reporting right superior parietal cortex (BA 7) and left inferior parietal cortex (BA 40), specifically for lengthened illness duration (10–14.9 years). Worth noting is the

observed number of studies reporting samples with a mean illness duration greater than 15 years, which may be relatively uncommon (eight articles; see Tables 1 and 2) and therefore may not necessarily indicate a meaningful increase in frequency for parietal cortex activity during 10–14.9 years of illness duration. Instead, we suggest that the parietal cortex is more prevalently active across studies in samples with greater illness duration. Taken together, our data suggest that while the right prefrontal cortex is most prevalent in samples of short illness duration, bilateral parietal cortex is most prevalent in samples with long illness duration.

Altered prefrontal and parietal cortex activation have been hypothesized to reflect compensatory adaptive mechanisms to maintain behavioral performance on tasks involving working memory (Tan et al., 2006; Zhou et al., 2014; ; Yaple et al., 2021b), task switching (Jamadar et al., 2010), and facial recognition (Quintana et al., 2011, 2003, 2001). Within this framework, we speculate whether the heightened frequency of prefrontal and parietal foci reported across samples with an early and late duration of illness, respectively, may indicate adaptive activation differences not only spatially, but also temporally. Spatial local and distant compensation mechanisms have been previously shown to reflect differences in brain activity in schizophrenia, perhaps for the purpose to adopt alternative cognitive strategies in order to maintain task performance compared to healthy controls (Quintana et al., 2003; Tan et al., 2006). Temporal compensatory adaptation, on the other hand, stems from the duration of illness irrespective of medication usage. Perhaps this may shed light on the difficulty to localize differences in neural activity across samples since the activity of frontal and parietal areas depends on medication usage as well as illness duration.

5. Practical implications

Currently, more than 30% of schizophrenic patients are treatment-resistant to antipsychotic medication (Elkis, 2007), and those who are treated may have positive symptoms relieved, leaving negative symptoms unchanged (Leucht et al., 2009a; b). Therefore, novel non-pharmaceutical remedies have been tested for their efficacy such as cognitive behavioral therapy emphasizing positive symptoms (see Burns et al., 2014 for *meta*-analysis), probiotics (Dickerson et al., 2014; Grover et al., 2019; Severance et al., 2017; 2012; Tomasik et al., 2015), deep-brain stimulation (Bikovsky et al., 2016; Corripio et al., 2016; Klein et al., 2013; Ma and Leung, 2014; Perez et al., 2013) and non-invasive neurostimulation via repetitive transcranial magnetic stimulation (rTMS (Mehta et al., 2019; Miyamoto et al., 2014; Nucifora et al., 2019). Other superficial areas targeted for neurostimulation treatment include the dorsolateral prefrontal cortex which allegedly reduces negative symptoms in non-responders (Cohen et al., 1999; Dlabač-de Lange et al., 2010; Freitas et al., 2009). However, discrepancies in the stimulation methods among studies have been critically reviewed concluding a lack of replicated findings (Dougall et al., 2015). The current *meta*-analyses list regions with the highest likelihood of being active across studies which may improve methods for localizing targeting stimulation zones, as compared to locating areas based on a priori hypotheses from individual studies. Specifically adopting the coordinates within the current *meta*-analysis may improve the replicability across neurostimulation studies, as well as determining the illness duration for each patient prior to selecting specific targeted regions of the brain.

6. Limitations

There are several limitations that are worth mentioning. First, the *meta*-analysis on the medicated group revealed a region within the left parietal cortex. However, it is important to acknowledge that the *meta*-analysis approach is unable to statistically test whether the left parietal cortex observed in the *meta*-analysis of medicated patients is relevant for this sample since the left parietal cortex was also observed in the resampling of the same data, i.e. from the chronic schizophrenia *meta*-

analysis (Supplementary Table 1). Therefore, confirmation of this conclusion should be taken lightly.

Second, the *meta*-analyses attempted to highlight the neural substrates affected by medication in schizophrenia patients and related confounds, and not specific to a particular neuropsychological task or cognitive process. Each of the previous fMRI studies recruited a specific task and was unable to provide a global view of the neural effects of the disease and medication across different task domains. Notably, a similar approach has been used to study practice-related changes, culture effect, aging effect, and effects of oxytocin manipulation (Chein and Schneider, 2005; Li et al., 2015; Han and Ma, 2014; Wang et al., 2017).

Third, the datasets for the medicated groups and the unmedicated group differ in several ways. There are more papers included in the unmedicated group (n = 37) than in the medicated group (n = 20). There are also more non-social cognitive tasks (e.g. lexical, cognitive control, visual tasks) than social-affective tasks (e.g. reward, emotion, theory of mind tasks) in both groups. Because the number of social tasks is fewer than the required number (n = 18) of studies for ALE *meta*-analysis, we did not perform sub-analysis to explore the potential domain-specific effect. Future studies may further control for potential confounding factors such as the number of studies and type of tasks and further resting-state fMRI studies are needed.

Finally, due to the low focality and thus large cluster sizes produced from the SDM results, it is difficult to identify areas that are unique to the unmedicated group and our findings should not be over-interpreted.

Few articles recruit patients prescribed with specific medication (e.g. Chlorpromazine (Phillips et al., 1999; Singh et al., 2014; Takahashi et al., 2010), Olanzapine (Kumari et al., 2015; 2007; Stip et al., 2012; Walter et al., 2009), Risperidone (Kumari et al., 2015; 2007; Surguladze et al., 2011), and thus we find it invalid to make assessments regarding neurological differences associated with specific psychological phenomena or specific antipsychotic or anti-depressant medication. This caveat leaves the open question of whether the current results can be explained by more specific differences between samples such as dosage, age of onset or whether a sample is prescribed with specific antipsychotic medication (e.g. Olanzapine, Risperidone, Quetiapine) or a combination of antipsychotic and antidepressant medication (Dichter et al., 2010; Song et al., 2017). As more empirical testing is reported, these questions may become answerable. In addition, 16 studies included patients with first-episode psychosis (FEP), which is associated with a number of other psychiatric conditions, including other conditions in the schizophrenia spectrum, bipolar disorder, and major depressive disorder with psychotic features. Future studies with a clinical characterization and outcome of FEP becomes are needed.

Other caveats include studies that reported state-related differences (task minus resting state), while other studies reported task-related differences (e.g. Theory of Mind versus non-Theory of Mind contrast; Brune et al., 2008). Unfortunately, task types as well as contrast type are different in studies that cannot be controlled for without excluding these studies altogether. Meta-analytic findings are often driven by the heterogeneity of the included studies. Whilst ALE software does not allow the investigation of heterogeneity of the selected studies, we tried to minimize the heterogeneity potential problem through the relatively strict inclusion criteria definition. Also, notably the recent ALE algorithm uses a random-effects inference and incorporates both within and between study variance, which is more conservative than the fixed-effects model. Future studies may further control for potential confounding factors such as number of studies, type of tasks and illness/ medication severity.

7. Conclusion

In this report, a series of *meta*-analyses were computed to assess the neurofunctional differences between medicated and unmedicated schizophrenia patients. From the *meta*-analyses associated with medication and unmedicated samples, both analyses revealed right frontal

and parietal gyri concordance, yet the only one cluster reported within the medication group shared no overlap with other *meta*-analyses, establishing that only one area was unique to the medicated group, the right orbital frontal gyrus. Longitudinal studies and further *meta*-analytic approaches are needed to further elucidate the involvement of specific neural substrate differences as a result of antipsychotic medications. This finding is coupled with a shift from the frontal activity for short-lived illness duration to more parietal activity during later durations.

CRediT authorship contribution statement

Zachary Adam Yaple: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft. **Serenella Tolomeo:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Rongjun Yu:** Conceptualization, Funding acquisition, Methodology, Writing – original draft, 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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103029.

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