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The relationship between brain structure and neurocognition in schizophrenia: a selective review

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Abstract

Both Kraepelin [1919. Dementia Praecox and Paraphrenia, Livingston, Edinburgh.] and Bleuler [1911. Dementia Praecox or the Group of Schizophrenias. Reprinted 1950 (trans. and ed. J. Zinkin). New York: International Univ. Press.] proposed that cognitive disturbances in schizophrenia are manifestations of brain abnormality. With the advent of magnetic resonance imaging (MRI) methodology, a number of studies have attempted to determine the relationship between brain structure and neurocognition in schizophrenia. We performed a review (1991–to date) of such studies with the aim of identifying the most consistent and compelling findings. The review revealed that whole brain volume tends to correlate with the measures of general intelligence as well as with a range of specific cognitive functions in normal controls and female schizophrenia patients, but this relationship is disrupted in male patients. The enlargement of the third ventricle, relative to the whole brain volume, is associated with deficient abstraction/flexibility, language, and attention/concentration in patients, whereas disproportionally larger lateral ventricles are associated with poorer psychomotor speed and attention/concentration in women, but not in men, with schizophrenia. Archicortical, but not paleocortical, prefrontal cortex tends to associate with the measures of executive function in both sexes regardless of diagnosis. Temporal lobe, hippocampus and parahippocampal gyrus correlate with cognitive abilities such as performance speed and accuracy, memory and executive function, verbal endowment and abstraction/categorization, respectively. Some of these medial temporal lobe/neurocognition relationships appear to be specific to schizophrenia (i.e. not seen in controls). Striatal size is positively associated with goal-directed behavior, but not perseveration, in schizophrenia. Larger cerebellum is associated with higher IQ in normal controls and affected women, but this association is disrupted in affected men. Increased white matter of the vermis is associated with poorer language and immediate verbal memory in schizophrenia. Finally, the methodological limitations of the reviewed studies are discussed and suggestions for future research are offered.

Keywords: Schizophrenia; Magnetic resonance imaging (MRI); Structural abnormalities; Neuropsychology; Cognitive deficits

1. Introduction

Kraepelin (1919) and Bleuler (1911) were the first to propose that schizophrenia is a brain disease, with

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cognitive disturbances as a core feature. Despite this early proposal, the study of brain pathology, cognitive deficits, and their possible inter-relationship took almost a century to become established as one of the primary inquiry lines in schizophrenia research.

Since the seminal Computer Topography (CT) study by Johnstone et al. (1976), which linked lateral ventricular enlargement and cognitive deficits in schizophrenia, a number of magnetic resonance imaging (MRI) studies have examined structure/neurocognition relationship in this disorder. However, there has not been a review of these studies since the publication by Gur (1992). The aim of this paper is to provide such a review, to aid our understanding of structure/function relationship in schizophrenia and to assist in developing new testable hypotheses for future research.

1.1. Structural abnormalities

Almost every cortical and sub-cortical brain structure has been found to be abnormal in schizophrenia. Structural alterations, as identified by MRI studies, include (in the order of replicability): cavum septi pellucidi (92% of the studies); lateral ventricles (80%); amygdaloid/hippocampal complex (74%); third ventricles (73%); basal ganglia (68%) superior temporal gyrus (67%, but 100% for gray matter); corpus callosum (63%); temporal lobe (61%); planum temporale (60%); frontal lobe (60%); parietal lobe (60%); occipital lobe (44%); thalamus (42%); cerebellum (31%); and whole brain volume (22%) (review, Shenton et al., 2001). Inconsistent replicability might exist due to the heterogeneity, gender dimorphic manifestation, as well as the possible non-static nature of schizophrenia (see Shenton et al., 2001 for more detail). Although structural alterations are widespread, the volumetric changes are mostly subtle, with the lateral ventricles and adjacent medial temporal lobe structures (amygdaloid/hippocampal complex and hippocampus), as well as the superior temporal gyrus being altered the most (meta-analysis, Wright et al., 2000). Alterations of gray matter are found more consistently than that of white matter (review, Lawrie and Abukmeil, 1998).

Deviations from normal hemispheric asymmetries have also been observed, with some evidence for the reversal of normal left–right asymmetry of the planum temporale (Shenton et al., 2001), as well as for the attenuation of normal hemispherical asymmetries in patients (Bilder et al., 1994; Sharma et al., 1999) and their obligate carrier relatives (Sharma et al., 1999). The evidence is, however, inconsistent for the reversal of frontal and occipital asymmetries (review, DeLisi et al., 1997).

1.2. Cognitive deficits

Patients with schizophrenia show a broad spectrum of neurocognitive deficits (reviews, Elvevag and Goldberg, 2000; Kuperberg and Heckers, 2000; Sharma and Antonova, 2003). Overall performance deficit can be between 1.5 and 2 standard deviations below healthy controls mean (Bilder et al., 1995), with a possible differential impairment of verbal learning and memory, up to three standard deviations lower (Saykin et al., 1991, 1994). In general, deficits are observed on the tests of higher cognitive functions requiring controlled and active information processing, such as sustained attention (vigilance), executive function, verbal and visuo-spatial working memory, language skills, explicit learning and memory, and perceptual/motor processing (Bilder et al., 1992; Riley et al., 2000).

The cognitive deficits have been shown: (i) to precipitate the psychotic symptoms (Weickert and Goldberg, 2000); (ii) to be relatively stable over time with progressive deterioration after the age of 65 in some patients (Friedman et al., 2001); (iii) to persist upon the remission of psychotic symptoms (Heaton et al., 2001); and (iv) to relate to, but to be separate from, negative symptoms (Harvey et al., 1996; Hughes et al., 2003).

1.3. Theories relating brain pathology and cognitive dysfunction

Kraepelin proposed that frontal lobe abnormality might underlie the disturbances of emotion, volition, and judgment in schizophrenia (Kraepelin, 1919). Goldman-Rakic's work (Goldman-Rakic, 1995, 1999; Goldman-Rakic and Selemon, 1997) on the PFC and working memory lead to the proposal that the prefrontal cortex might be the primary site of schizophrenia pathology, affecting working memory in particular and leading to avolition, behavioral disorganization, and cognitive deficits of executive function, conceptual thinking, and memory formation.

Since the PFC does not function in isolation, other models emphasize the role of cortical and sub-cortical connections that PFC forms with other brain regions. Pearlson et al. (1996) proposed that schizophrenia involves disrupted inter-relationships between the areas of heteromodal association cortex with one another and with the limbic system, basal ganglia and thalamus, resulting in faulty information processing and manifesting as disturbances of higher cognitive functions. Several models have concentrated on prefronto-temprolimbic structural and functional connectivity (Weinberger and Lipska, 1995) and prefronto-temprolimbic interactions with ventral striatum (Buchsbaum, 1990; Carlsson and Carlsson, 1990; Grace, 1991; Gray, 1995, 1998; Csernansky and Bardgett, 1998; O'Donnell and Grace, 1998) to account for schizophrenia symptomatology and cognitive disturbances. Andreasen et al. (1996, 1998, 1999) argued that the fundamental feature of schizophrenia is 'cognitive dysmetria', i.e. deficient processing, prioritizing, retrieval, coordination, and responding to information, underlined by the disruption of cortico-cerebellar-thalamo-cortical circuitry (CCTCC), which has a role in the coordination of both motor and cognitive processes (Schmahmann, 1991, 1996, 1997; Middleton and Strick, 1994, 2000).

Other investigators emphasized that the prefrontal cortex does not have to be structurally altered in order to exhibit functional disruption. Graybiel (1997) proposed a model that focuses on basal ganglia and parallel neuronal circuits that connect them with the neocortex, including efferents from prefrontal cortex to caudate nucleus, motor cortex to putamen, and limbic cortex to nucleus accumbens. The proposed role of the basal ganglia in behavior is the generation of cognitive patterns or templates for actions that involve thought, movement and emotion within these three cortical-basal circuits, respectively, the dysfunction of which would lead to the disturbance of these processes, resulting in cognitive, negative and psychotic features of schizophrenia. Jones (1997) discussed how thalamic cell loss, either as a primary pathology or as secondary to cortical or other sub-cortical pathology, could lead to the disintegration of thought processes in schizophrenia due to the failure of the thalamus to induce oscillation of large ensembles of cortical and thalamic neurons necessary for the binding of the brain states in a functionally integrated manner.

Finally, Crow (1989, 1990, 1993, 1995) has stressed the importance of language disturbances to the understanding of schizophrenic phenomena, and proposed that the failure, due to a genetic predisposition, to form normal language-related brain asymmetries underlies these disturbances.

1.4. The aim and the scope of the review

This article reviews MRI studies examining neuropsychological correlates of brain structures in schizophrenia, with the aim of identifying the most compelling and consistent findings. It focuses on studies that used the Region of Interest (ROI) approach, utilizing methods of image processing and analyses that became available in the early 1990s, thus making the results of the reviewed studies more comparable with one another.

A literature search, using the PubMed electronic journal engine, and manual library search for the relevant publications since 1990, as well as searching the reference lists of the retrieved articles, revealed 35 MRI studies examining structure/neurocognition relationships in first-episode and chronic schizophrenia patients. The majority had a control group (see Table 1). All studies adopted a correlational design, with the exception of two early studies (Raine et al., 1992; Colombo et al., 1993), which investigated whether the volumes of certain structures were reduced in the group of patients with specific cognitive deficits, but did not correlate structural and neurocognitive variables (see Table 1 for the summary of the main findings).

One way to structure a review of this kind is by cognitive function. However, as different studies have used different neuropsychological tests to measure the same cognitive domain, and, conversely, the same tests were used to measure different domains, this approach seemed cumbersome, requiring arbitrary decisions about attributing neuropsychological measures to cognitive domains. We therefore organized the review by brain structures, with the view of a particular structure in terms of the 'node' within the distributed functional neuronal network(s). In order to address two distinct but related issues, namely (i) which structural abnormalities are associated with cognitive deficits in schizophrenia; and (ii) whether structure/function relationships seen in normal individuals are altered in schizophrenia patients, we

Abbreviations: ANT = Animal Naming Test; BNT = Boston Naming Test; BG = basal ganglia; BSRT = Buschke Selective Reminding Test; C = controls; CF = cognitive flexibility; COWA = Controlled Oral Word Association; CVLT = California Verbal Learning Task; DLPFC = dorso-lateral prefrontal cortex; DMPFC = dorsomedial prefrontal cortex; DST = Digit Symbol Test; EF = executive function; F = female; FEP = first-episode patients; FT = finger taping task; GMV = gray matter volume; GP = globus pallidus; GPB = grooved peg board; Hippo = hippocampus; L = left; LM = logical memory (I and II = immediate and delayed); LV = lateral ventricle; M = male; Mem = memory; MF = motor function; M-WCST = Modified version of Wisconsin Card Sort (unambiguous card sorting); NART = National Adult Reading Test; NC = normal controls; NP = neuropsychological; OFC = orbitofrontal cortex; P = patients; PHG = parahippocampal gyrus; PFC = prefrontal cortex; PLS = Partial Least Square; R = right; SAD = Schizoaffective Disorder; SCWT = Stroop colour-word task; SES = socio-economic status; SFG = superior frontal gyrus; SP = schizophrenia patients; STG = superior temporal gyrus; TL = temporal lobe; VF = verbal fluency; VR = Visual Reproduction; YOE = years of education; WAIS = Wechsler Adult Intelligence Scale; WBV = whole brain volume; WCST = Wisconsin Card Sorting Task; WM = working memory; WMS = Wechsler Memory Scale; WMV = white matter volume.

Table 1
Reviewed studies of MRI/Neuropsychological relationships

Publication	Total subjects (M/F)	Cognitive measures	Structural areas	Findings		
				MRI deficits ↓ Reduction ↑ Increase	NP deficits	MRI/NP correlations MRI/NP = positive MRI/ − NP = negative
Szeszko et al., 2003	81 (48/33) FEP 23 (14/9) NC	Executive, Motor, Language, Visuo-spatial, Mem, Attention, and Global scales	Cerebellum	Not reported	Not reported	NC: Cerebellum/Global, Visuo-spatial, Executive, Mem scales FEP: none
Sanfilipo et al., 2002	62 (62/0) SP 27 (27/0) NC	Five factors: Verbal IQ/ endowment (*WAIS-R: Similarities, Vocabulary, DST, Information subtests; WMS:* LM I and II); CF (M-WCST); Word Mem (BSRT); Visual Mem (*WMS:* VR, I and II); VF (Category Retrieval, COWA, ANT) + DST correlated with all factors	GMV and WMV: PFC TL STG Hippo PHG	↓ GMV: PFC TL STG	All factors, except CF Strongest effect for VF	NC: R Hippo/VF, − Word Mem L&R PFC GMV/DST SP: L&R Hippo/Word Mem L&R PFC WMV/CF R PHG (trend STG WMV)/ − Verbal IQ
Nestor et al., 2002	15 (15/0) SP	WM: Hebb's recurring digits, Trail Making A and B, Alternating Semantic Categories. Verbal Mem: Verbal paired associates, LM, I and II. Categorisation: WAIS − R Similarities, WCST categories completed	GMV: PFC, STG, posterior TL, PHG WMV: PFC	For MRI and NP deficits see Nestor et al., 1993		*First pair of latent variables*: L&R posterior STG, L&R PHG/WCST, Similarities, Trail A, B and LM II. *Second pair of latent variables:* L&R FL gray matter, L FL white matter/ Alternating Semantic Category, Hebb's RD, Trail B.
Szeszko et al., 2002	75 (43/32) FES Schizophrenia and SAD = 56	41 tests measuring six domains: Memory, EF, Language, Attention, Visuo-spatial, MF	Hippo: anterior and posterior	–	–	Men SP: Anterior Hippo/EF and MF, → stronger than Mem and Language Female SP: none

Zuffante et al., 2001	23 (23/0) SP typical and atypical medication 23 (23/0) NC	Full scale IQ: WAIS-R WM: Spatial Delayed Response Task (SDRT); Self-Ordered Pointing, verbal and non-verbal	GMV and WMV: BA 46	No	Yes	NC: L BA 46/ – SDRT SP: none
Nopoulos et al., 2001	50 (50/0) SP (11 FEP) 50 (50/0) NC	Full scale IQ: WAIS-R	Midbrain and cerebellar vermis Pons and medulla as control regions	↓ Midbrain Vermis/midbrain correlation in SP but not in NC	Not reported	NC: none SP: none
Szeszko et al., 2000	35 (20/15) SP	Full scale IQ: WAIS-R Language, Mem, EF, MF, and Visuo-Spatial processing scales	GMV and WMV: SFG, Anterior Cingulate (AC), OFC	–	–	Male SP: AC/EF, → stronger than with other NP variables Female SP: none
Manschreck et al., 2000	16 (11/5) SP	Motor synchrony: a synchronized tapping response to rhythmic acoustic clicks *Two IVs*: interbeat interval score (IIS), synchrony accuracy (SA)	GMV and WMV: WBV, DLPFC, DMPFC, OFC, corpus striatum, ventral pallidum, LV (temporal horns)	–	–	FL and OFC/ – synchrony accuracy
Krabbendam et al., 2000	27 (13/14) SP 19 (9/10) NC MRI sub-sample: 25 SP, 17 NC	SCWT, Concept Shifting Test (CST); Groningen Intelligence Test (GIT), three subtests	TL, Amygdala/ Anterior Hippo complex, PHG	No	CST SCWT colour-word part	NC: none SP: L PHG/ – SCWT colour-word part
Gur et al., 2000a	70 (40/30) SP 29 neuroleptic naïve 41 previously treated 81 (34/47) NC	Abstraction/Flexibility Attention Verbal Mem Spatial Mem Verbal Abilities Spatial Abilities	GMV and WMV: DLPFC DMPFC OFC lateral and medial	↓ GMV: DLPFC in male bilaterally and in female on the right DMPFC in bothgenders OFC lateral and medial in women	Not reported	NC men: DLPFC/ Abstraction and Attention DMPFC/Attention NC women: DLPFC, DMPFC/Abstraction OFC lateral and medial/Spatial Mem OFC lateral/Spatial ability SP men: DMPFC/Attention SP women: DLPFC/Attention OFC medial/Verbal Mem
Gur et al., 2000b	100 (58/42) SP 39 neuroleptic naïve 61 previously treated 110 (51/59) NC	Abstraction-Flexibility Attention Verbal Mem Spatial Mem Verbal Abilities Spatial Abilities	Hippo Amygdala GMV and WMV: STG Temporal pole (TP)	↓ GMV: Hippo and TP in both genders STG in men ↓ Amygdala in men ↑ Amygdala in women	Not reported	NC men: Hippo/Verbal and Spatial Mem, STG/attention NC women: Hippo and STG/ Spatial Mem, TP/Verbal and Spatial Mem, Abstraction and Spatial Abilities SP men: Hippo/Verbal Mem SP women: Hippo/Verbal and Spatial Mem

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Table 1 (*continued*)

Publication	Total subjects (M/F)	Cognitive measures	Structural areas	Findings		
				MRI deficits ↓Reduction ↑ Increase	NP deficits	MRI/NP correlations MRI/NP = positive MRI/ – NP = negative
Nopoulos et al., 1999	65 (65/0) SP 65 (65/0) NC	WAIS-R Full scale, Verbal and Performance IQ	Total cerebellum, cerebellar lobes, vermis: anterior, superior posterior and inferior posterior	↓ Anterior vermis	Not reported	NC: none SP: Anterior vermis/Full scale and Verbal IQ
Gur et al., 1999	130 (75/55) SP 51 neuroleptic naïve 130 (75/55) NC	Abstraction/Flexibility Attention Verbal Mem Spatial Mem Verbal Abilities Spatial Abilities	GMV, WMV (L&R hemisphere) and CSF	↓ GMV bilaterally with smaller volumes in female SP ↑ Ventricular CSF	All domains, with specific deficits in Attention and Verbal Mem No sex differences	NC men: GMV/ Abstraction, Attention, Verbal and Spatial Abilities NC women: GMV/Verbal and Spatial Mem, Verbal Abilities SP men: GMV/Verbal and Spatial Mem and Abilities SP women: GMV/Attention, Verbal Mem, Verbal and Spatial Abilities
Levitt et al., 1999	15 (15/0) SP 15 (15/0) NC	Not specified	Vermis: lobules I–X. Cerebellum: total and L&R GMV and WMV	↑ WMV of Vermis ↑ L > R cerebellar asymmetry for GMV + WMV and GMV	–	NC: none SP: Vermis WMV/ – LM immediate
Baare et al., 1999	13 (13/0) SP 14 (14/0) NC	Verbal and Visual Mem: CVLT; VR of WMS Subjective Ordering Tests: digit span, missing item scan, randomization, sequential pointing General verbal ability: WAIS Comprehension and Vocabulary; VF	GMV and WMV: PFC DLPFC DMPFC OFC	No, but trend for smaller volumes	Verbal and Visual Mem VF Sequential Pointing Comprehension	NC: PFC/Verbal and Visual Mem, delayed SP: PFC/Verbal and Visual Mem, immediate
Zipursky et al., 1998	77 (43/34) FEP (*S* = 46) 61 (34/27) NC	NART Quick test	Total GMV and WMV (excluding brainstem and cerebellum), CSF	↓ Total GMV Total CSF, ventricular CSF and trend for sulcal CSF	Not reported	NC: none FEP: Total GMV/ Quick test, trend for NART
Torres et al., 1997	20 SP: 10 (7/3) low and 10 (7/3) high on memory score 19 NC: 10(5/5) low and 9(4/5) high on memory score	Rey-Auditory Verbal Learning Test (RAVLT), LM I and II, Rey-osterreith Complex Figures Test (R-O), I and II	WBV and TL (semi -automated method) Hippo (manual tracing)	Not compared Significant R > L Hippo asymmetry in both low and high SP	–	NC: none SP: none

Stratta et al., 1997	35 (26/9) SP 24 (17/7) NC	WCST	Total BG CN Putamen (Pu) Nucleus Accumbens (NA)	*Poor SP performers*: ↓ L CN, Pu than controls ↓ R total striatum than controls ↓ L Pu, L&R Pu + Na than good SP performers *Good SP performers*: ↑ Pu, Pu + Na than controls (a trend)	Median split on WCST (4 categories completed): 12 good and 23 poor SP performers	NC: not reported SP: L striatum and Pu + Na complex/ WCST categories completed L Pu, Na, Pu + Na/ – WCST unique responses Separate correlations for good and poor performers were not reported
DeLisi et al., 1997	41 FEP 26 NC NB: the sub-sample with NP assessment, gender not specified	Receptive Language: Goldman Fristoe Woodcock Test (GFWT), noise distraction and quiet conditions Expressive Language: BNT, COAT, Woodcock Reading Mastery Test, Oral soliloquy Mixed: Wide Range Achievement, WAIS-R; WMS Nonverbal Ability: Symbol Digit Modality Test (SDMT), Raven's Colored Progressive Matrices (RCPM), Vigilance Task Hand Skill: FT	L/R relative width of anterior and posterior frontal, temporal and occipital areas (axial slices) Sylvian fissure (SF), anterior, horizontal and vertical segments (sagittal slices)	↓ Temporal and occipital L > R asymmetry ↓ L horizontal segment of SF at a trend level ↓ L > R asymmetry of the horizontal segment of SF (trend) ↓ Normal male>female asymmetry of the anterior frontal area	RCPM, SDMT, COAT,GFWT (noise distraction and quiet conditions), LM I, VR I and II, Vigilance Task, Oral Soliloquy (more morphological errors and less clausal embedding)	NC: L>R horizontal SF asymmetry/GFWT noise distraction, – GFWT quiet condition, Nonverbal Ability R > L posterior frontal and anterior SF asymmetry/ – COAT R > L anterior frontal, L > R temporal asymmetry/Verbal Mem R > L anterior frontal asymmetry/Nonverbal Ability SP: L > R occipital asymmetry/ – Sentence complexity R>L anterior SF, L>R horizontal SF asymmetry/Vigilance → Non-significant with Bonferroni correction
Sullivan et al., 1996	34 (34/0) SP 47 (47/0) NC	IQ: NART, Vocabulary WAIS-R EF: verbal and non-verbal self-ordered pointing, nonverbal temporal order discrimination, verbal and nonverbal visual search, WCST Short-Term Mem and Production: verbal and nonverbal Brown – Peterson distracter tasks, letter and design fluency Motor Ability: grip strength and fine finger movements Declarative Memory: WMS	Total GMV, WMV and CSF, prefrontal, frontal, frontal-temporal, temporal-parietal, parietal and parietal-occipital regions (semi-automated segmentation)	↓ Total cortical GMV	NART and Vocabulary IQ All four cognitive domains	NC: none SP: GMV/all four cognitive domains, but not NART or Vocabulary Age Scaled Scores
Bilder et al., 1995	29 (18/11): SP = 24 SAD = 5	Full scale IQ: WAIS-R Language, Mem, Attention, EF, MF, Visuo-Spatial Abilities	Amygdaloid complex Hippo anterior and posterior	–	–	Anterior Hippo/EF, stronger than FSIQ Anterior Hippo/MF

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Table 1 (*continued*)

Publication	Total subjects (M/F)	Cognitive measures	Structural areas	Findings		
				MRI deficits ↓Reduction ↑ Increase	NP deficits	MRI/NP correlations MRI/NP = positive MRI/ – NP = negative
Maher et al., 1995	18 (13/5) SP	Short-term Mem: 4 lists of words in increasing order of approximation to English sentences: lists 1 and 2 = context-free; lists 3 and 4 = context aided	WBV, FL, DLPFC, DMPFC, OFC, Striatum, ventral pallidum, LV (temporal horns)	–	Context-free worse than context-aided recall	FL/context-aided DLPFC/context-aided Striatum/ – context-aided
Vita et al., 1995	19 (12/7) SP 15 (9/6) NC	NP: VF, Picture Naming test (PNT), Sentence Generation Test (SGT)	GMV and WMV: PFL, TL, STG, LV: frontal, body, temporal, occipital	↑ LV: body segment bilaterally and right occipital horn		STG/VF semantic L TL and STG/ – PNT number of errors LV/ – SGT
Kareken et al., 1995	68 (43/25) SP Deficit sub-type = 22 68 (43/25) NC	Abstraction/Mental Flexibility (AMF): WCST Attention: CPT, SCWT, Trail A and B Verbal Mem: LM, CVLT Visuo-Spatial Mem (VSM): Design Reproduction of WMS Language: COWA, ANT, BNT, Token Test Visuo-Spatial Perception (VSP): Block Design, Benton Line Orientation, Geometric Figure Drawing Sensory: Double Simultaneous Sensory Stimulation, Graphesthesis Motor: FT, Thumb-Finger Sequential Touch	WBV, Ventricular CSF Ventricle to Brain Ration (VBR) (excluding 3rd V due to low inter-rater reliability) Semi-automated tissue segmentation	↑ VBR *Deficit SP*: ↓WBV relative to controls	All domains Greatest impairment on Verbal Mem *Deficit SP*: Greater cognitive impairment overall, but the same pattern as in non-deficit SP	NC: VBR/ – VSP, – AMF Ventricular CSF/ – VSP WBV/Attention, AMF, VSM, Language, VSP SP: WBV/AMF, Verbal Mem, Language Deficit SP: WBV/AMF, VSM, Language Non-deficit SP: WBV/Language
Goldberg et al., 1994	15 (8/7) pairs of monozygotic twins discordant for schizophrenia	Full scale IQ: WAIS-R Memory: WMS: LM, VR, Paired Associates Psychomotor speed: Trail A Automatic lexical access: Stroop color reading EF: WCST Verbal ability: VF phonological Attention: CPT (self-paced version)	Hippo, 3rd ventricle, section of LV (coinciding with the longitudinal axis of the TL)	↓ All three areas as found in the previous analysis	All domains	Volume indexes/ performance ratios (IQ adjusted): L Hippo, PFC/LM L&R Hippo, PFC/ Psychomotor speed L LV/ – WCST perseverative errors

Seidman et al., 1994	17 (14/3) SP 13 right-handed	Frontal function: WCST, categories and perseverative responses; Similarities of WAIS-R, CPT; FT TL tests: WMS-R: LM I and II; VR IQ: WAIS-R, vocabulary and block design	WBV FL DLPFC OFC TL (semi-automated method)	–	–	WBV/Similarities Total DLPFC/IQ, WCST categories, – WCST perseveration, LM II L DLPFC/IQ, WCST categories, -WCST perseveration, LM I and II, Similarities,VRI R DLPFC/ – CPT error → contrasted against TL → DLPFC/WCST, IQ, WAIS-R Similarities at trend level L DLPFC/Similarities—the strongest trend
Flaum et al., 1994	72 (50/22) SP 59 (32/27) NC	Full Scale IQ: WAIS-R	WBV TL LV Hippo CN Pu Cerebellum	Not compared	Yes	NC:FSIQ/L&R WBV, L&R TL, L Hippo and cerebellum → FSIQ/R TL significantly stronger, trends for L TL and L&R cerebrum SP: none SP women: FSIQ/L TL, L&R Hippo, cerebellum, and L Pu, trends for cranium and cerebrum SP men: none
Nestor et al., 1993	15 (15/0) SP	Abstraction and categorization: Similarities WAIS-R, WCST categories completed Learning and Mem: WMS-R: LM I and II, VR, Verbal paired associates learning Control tasks: FT, Block design of WAIS-R	TL STG anterior and posterior PHG Hippo	–	Similarities, LM, Block design → the low end of the normal range ↓ WCST	L&R PHG, L&R posterior STG/WCST, Similarities L posterior STG/ Verbal paired associates Control tasks → no correlations
Colombo et al., 1993	18 (12/6) SP 18 (13/5) NC	Mem: WMS, 7 subtests Three factors: I = immediate learning and recall abilities II = attention and concentration III = orientation and long-term information recall	WBV, Lateral (temporal horns) and 3rd ventricles, L&R TL, L&R Hippo	No	Yes	No correlations performed

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Table 1 (*continued*)

Publication	Total subjects (M/F)	Cognitive measures	Structural areas	Findings		
				MRI deficits ↓Reduction ↑ Increase	NP deficits	MRI/NP correlations MRI/NP = positive MRI/ − NP = negative
Hoff et al., 1992	56 (41/15) FEP left handed = 7 57 (39/18) NC left handed = 9 MRI sample: 37 FEP 21 NC Some FEP were on lithium in addition to haloperidol 17 FEP had NP follow up data	Language: e.g. Pro-rated verbal IQ, BNT EF: WCST, categories completed and perseverative responses, SCWT Verbal Mem: CVLT, LM I and II Spatial Mem: BVRT, VR Concentration/Speed: Trail A and B, Symbol Digit Modalities Test, FT Sensory/Perceptual: Finger Gnosis, Finger Number Writing NB: only the most common tests listed	WBV LV TL limbic complex (Amygdala + Hippo + PHG) Lateral Sulcus (LS) bordering the superior portion of Planum Temporale	SP women: abnormal LS L/R ratio (L LS smaller than in other groups, right LS similar to others) For other regions see DeLisi, 1991	All scales *Follow up*: significant improvement on EF, Conc/Speed, and trend for Sensory/Perceptual	NC: L LV/ − Cons/Speed, − Sensory/Perceptual R LV/ − EF, − VerbMem, − Sensory/Perceptual, − Left Hemisphere scale, − Global scale LS L/R ration/ − Sensory/Perceptual, − R Hemisphere scale SP: R TL/Concentration/Speed R limbic complex/Language R LS/Spatial Mem, Concentration/Speed, Right Hemisphere scale, Global scale LS L/R ration/ − VerbMem *Normal* vs. *abnormal laterality SP sub- groups:* abnormal → better Verbal and Spatial Mem, EF and Global scale than normal (No differences in NC)
Bornstein et al., 1992	72 (49/23) SP 31 (13/18) NC	WAIS-R WMS-R WCST Verbal Concept Formation Test (VCAT) Halstead-Reitan Neuropsychological Battery	Ventricle to brain ratios (VBR): LV, 3rd Ventricle	↑ 3rd V VBR Male SP: None Female SP: LV VBR	Not reported	NC: 3rd V VBR/IQ, VF LV VBR/Verbal IQ SP including SAD: LV VBR/Verbal IQ, − Visual span, − FT 3rd V VBT/ − Verbal IQ, − VCAT, − WCST categories, WCST perseveration, − Seashore Rhythm, -Visual span, -Digit Span, Trail Making A, -Knox cube delayed SP excluding SAD: LV VBR/ − Visual span, FT 3rd V VBR/ − VCAT, − WCST categories, − Seashore rhythm, − Digit Span

Di Michele et al., 1992	25 (13/12) SP 17 (10/7) NC	Luria-Nebraska battery: Motor, Rhythmic, Tactile, Visual, Receptive speech, Expressive speech, Writing, Reading, Arithmetic, Memory, Intelligence SP were divided into *normal* (14) and *abnormal* (10) groups based on the total score	L&R TL	*Overall*: ↓ L&R TL, L < R (NC: no difference between L&R TL) *Abnormal SP*: ↓ L&R TL, L>R	Abnormal more impaired than normal on Motor, Rhythmic, Visual, Receptive speech, Mem, IQ	NC: none SP: none
Raine et al., 1992	17 (10/7) SP 18 Psychiatric controls (PC) (12/6) 19 NC (10/9) MRI data sub-sample not specified	FL measures: WCST categories completed and perseverative errors, Spatial Delayed Response Task (SDRT), Block Design Test Non-frontal measures: verbal dichotic listening, nonverbal dichotic listening, and finger sequence repetition (FSR)	L&R PF areas (coronal, midsaggital, transverse cuts) Posterior area (midsaggital cut) L&R posterior areas (transverse cut) L&R TL areas (coronal cut)	↓ L PF coronal area relative to both control groups ↓ R PF coronal area relative to PC ↓ L&R PF midsaggital areas relative to PC ↓ L&R PF transverse areas relative to both groups	SDRT and WCST perseveration relative to NC Block Design relative to both groups No significant differences for non-frontal tasks	No correlations performed
DeLisi et al., 1991	30 (23/7) FEP 15 (9/6) SP 20 (12/8) neurological controls (NeuroC)	Premorbid IQ: Reading subtest of Wide Range Achievement Test Verbal IQ: information, vocabulary and similarities sub-tests of WAIS-R Cognitive measures: *WMS*: LM I and II, Associate Learning (two short-term verbal memory forms) and VR; CVLT; Benton Visual Retention Test (BVRT); WCST; Booklet Categories Test; BNT; VF; Trail Making B	*Coronal slices*: WBV, FL, TL, Amygdala/Hippo complex, PHG, LV, Temporal and Frontal ventricular horns *Axial slices*: CN, LN (GP + Pu)	FEP: ↑ L LV than NeuroC ↑ R LV than NeuroC at trend level ↑ Bilateral Frontal horn than NC SP: ↑ L LV than FEP	Not reported	NeuroC: not reported FEP + SP: Bilateral Hippo/Associated Learning Bilateral PHG/Verbal IQ FEP: Bilateral Hippo/Associated Learning Bilateral PHG/LM

Studies are entered in descending order by the recency of publication. All subjects were right-handed unless otherwise specified in the table. Only data for MRI and NP variables are presented, excluding data for symptoms, demographics and medical history. All patients were on conventional neuroleptics unless otherwise specified in the table. All studies used 'Region of Interest' approach. The names for the cognitive domains are retained as used in the corresponding publication.

present the findings on the integrity of the structural volumes in patients for each brain region where it was available (the information on cognitive deficits can be found in Table 1) in addition to examining and comparing the structure/function relationships in patients and controls.

The review commences with whole brain volume, followed by ventricular size, frontal lobe, temporal and medial temporal lobes, planum temporale, parietal and occipital lobes, basal ganglia, cerebellum, midbrain, and brain asymmetries. Almost all studies, unless testing a very specific hypothesis, have measured more than one region of interest, and thus appear in more than one section, with cross-references between the sections. Table A1 (Appendix A) presents the reviewed studies clustered by section.

The findings relating symptoms to brain structures and cognitive deficits are not considered, since cognitive deficits have been found to be relatively independent of symptomatology (see Section 1.2). However, whenever a symptomatic state and/or a clinical history were relevant to understanding the relationship between MRI and neuropsychological variables, this will be discussed.

2. Relationships between structural brain regions and cognitive measures

2.1. Whole brain volume

Eight studies have investigated the relationship between the whole brain volume (WBV) and cognitive function, six studies with a control group (Colombo et al., 1993; Flaum et al., 1994; Kareken et al., 1995; Torres et al., 1997; Zipursky et al., 1998; Gur et al., 1999), and two without (Seidman et al., 1994; Maher et al., 1995). Of those six studies with a control group, two studies (Flaum et al., 1994; Torres et al., 1997) did not compare patients and controls on the WBV.

Two studies (Zipursky et al., 1998; Gur et al., 1999) found reduced whole brain gray matter volume (GMV), but not reduced white matter volume (WMV), in the patient group. Colombo et al. (1993) observed no WBV difference between patients and controls, perhaps due to the lack of segmentation. Kareken et al. (1995) has found WBV reduction in deficit, but not in non-deficit, patients.

Almost all measures of cognitive functioning were found to correlate with the WBV, and particularly total gray matter, indicating 'bigger brain–better performance' relationship in controls as well as in patients, with the most reliable associations found for the measures of general intellectual ability and composite cognitive processes such as language, abstraction/flexibility, and verbal and spatial reasoning (Seidman et al., 1994; Kareken et al., 1995; Gur et al., 1999). The relationship between WBV and memory was not as consistent, with Gur et al. (1999) reporting a positive association in both patients and controls, whereas other studies finding no relationship of immediate and delayed memory to WBV either in patients (Colombo et al., 1993; Maher et al., 1995; Torres et al., 1997) or in controls (Torres et al., 1997).

There were findings for both patients and normal controls that did not fit into 'bigger brain–better performance' pattern. Firstly, Flaum et al. (1994) found a normal relationship between WBV/IQ in female, but not in male, patients. Secondly, healthy controls failed to show a WBV/IQ association, when such a relationship existed in first-episode (FE) patients of mixed gender, with a significant difference in the strength of gray matter/IQ correlations between the groups (Zipursky et al., 1998). Finally, there were points of convergence and divergence in the WBV/cognition relationship among the predominantly male controls, deficit and non-deficit patients (Kareken et al., 1995), such that significant positive correlations existed between WBV and (i) language for all groups; (ii) abstraction/mental flexibility for controls and deficit patients; (iii) attention, visuo-spatial memory and visuo-spatial perception for controls only; and (iv) verbal memory for deficit patients only.

Overall, WBV has a nonspecific relationship with cognition, associating with the level of general intelligence as well as with more specific cognitive abilities in both patients and controls. However, some of the findings point towards a more complex, and, perhaps, nonlinear relationship between brain size and cognitive abilities in male patients.

2.2. Ventricular size

Six studies have investigated the relationship between the ventricular size and cognitive deficits, four

with a comparison group (Bornstein et al., 1992; Hoff et al., 1992; Goldberg et al., 1994) or groups (DeLisi et al., 1991), and two without (Maher et al., 1995; Vita et al., 1995).

Two studies did not find any associations between an absolute size of lateral ventricles (LV) and cognitive performance in patients (DeLisi et al., 1991; Hoff et al., 1992), despite the increased LV size in FE and chronic patients relative to neurological controls, with greater prominence on the left side in the DeLisi et al. study. The latter study has also measured the size of the third ventricle, finding no size differences or relationship with cognitive function. In the study by Hoff et al. (1992), almost all cognitive domains inversely correlated with LV size in normal controls, with smaller left LV being associated with better concentration/speed and sensory/perception, and smaller right LV being associated with better executive function, concentration/speed, sensory/perception, a global performance scale, verbal memory and a left hemisphere scale. (The association of right LV size with the left hemisphere scale might be due to the mixed handedness sample.) When a subsample of patients was reassessed on neuropsychological measures 2 years later, there was significant improvement on the domains that were most impaired at the time of the initial assessment, that is, executive function, concentration/speed, global scale, and, at the trend level, sensory/perceptual scale. Noteworthy, these are the scales that were found to correlate with the LV size in normal controls. It is possible that the severity of cognitive impairment was partly related to symptomatic state at the time of the first assessment in this sample of FE patients. However, the relationship between symptoms rating and cognitive function was not reported. The possibility that the pattern of correlations similar to that of controls between cognitive scores and LV size would have been found in these patients at 2-year follow-up is intriguing; however, there are no data available on follow-up relationship between cognitive and LV measures.

A counter-intuitive relationship of enlarged absolute LV size and less perseveration has been found in the study of 15 pairs of monozygotic twins discordant for schizophrenia (Goldberg et al., 1994). Affected twins also showed an enlargement of the LV temporal horn and of the third ventricle, but these did not associate with cognitive deficits. Another study (Vita et al., 1995) measured the segments of LV, including frontal, body, temporal, and occipital, in chronic patients and found a significant enlargement of the LV body, but this was unrelated to language function.

The absence of correlations between the ventricular size and cognitive deficits in schizophrenia patients in the studies reviewed might be due to the use of absolute volume measurements. Since patients with schizophrenia might have smaller as well as larger than average cerebrums (Green et al., 1989), relative measurements of ventricular size might be more appropriate. Indeed, a study (Bornstein et al., 1992) that calculated ventricle to brain ratio (VBR) has found enlarged lateral VBR to associate with worse forward Visual Span (attention/concentration), as well as finger tapping task using the non-dominant hand (psychomotor speed) in female schizophrenia patients. However, these associations were attenuated in affected men. Third VBR was also enlarged in men and women with schizophrenia relative to healthy counterparts, and inversely correlated with the tests of abstraction/categorization (Verbal Concept Formation Test, WCST categories completed) and attention/concentration (Seashore Rhythm, Digit Span). Surprisingly, in normal controls, larger lateral VBR and third VBR were associated with better cognitive performance, including larger lateral VBR with verbal IQ; and third VBR with verbal fluency and verbal concept formation. These positive correlations in controls are difficult to interpret. Fewer correlations between VBR and cognitive measures in controls overall might be due to almost negligible variability in VBR, presumably due to the linear relationship between ventricular and brain sizes. In patients, on the other hand, the mean values for the third VBR were twice the magnitude of those found in controls with substantial variability, indicating disproportionately larger third ventricle in relation to brain size on average. In the final study employing VBR measurements (Maher et al., 1995, see also Section 2.1), which examined neural correlates of short-term memory in schizophrenia, neither absolute nor relative LV size correlated with context-free or context-aided-free recall.

To summarize, four main points emerge regarding the relationship of ventricular size to cognition. (1)

The relationship between ventricular size and cognitive function is complex, with both larger LV (in normal controls and female patients; Hoff et al., 1992) and smaller LV (in controls; Bornstein et al., 1992; and in male patients; Goldberg et al., 1994) being associated with better cognitive functioning; (2) the relationship between LV size and cognitive functioning might be disrupted in affected men (Hoff, 1992), paralleling the findings observed for WBV and IQ; (3) the abnormality of ventricular size and its association with cognitive measures are more reliably found when the measures of relative, as opposed to absolute, size are used; and (4) the size of the third ventricle might be more illuminating as to the nature of the cognitive disturbances in schizophrenia, as third ventricular enlargement might indicate the pathology of the thalamus, which is immediately adjacent to the third ventricle. This putative thalamic abnormality might cause disruption of cortico-striatal-thalamo-cortical as well as cortico-cerebellar-thalamo-cortical circuitry, resulting in deficient abstraction/flexibility and attention/concentration (Bornstein et al., 1992).

2.3. Frontal lobe

The studies that examined the whole frontal lobe (FL) are reviewed first, followed by the studies that parcellated prefrontal lobe into sub-regions.

2.3.1. Whole FL

Seven studies have investigated neuropsychological correlates of total FL volume, six with a control group (DeLisi et al., 1991; Vita et al., 1995; Sullivan et al., 1996; Baare et al., 1999; Sanfilipo et al., 2002) or groups (Raine et al., 1992), and one without (Nestor et al., 2002).

Only two of these studies found reduced FL volume in patients relative to normal (Raine et al., 1992; Sanfilipo et al., 2002) and psychiatric (Raine et al., 1992) controls, which might be limited to gray matter (Sanfilipo et al., 2002). Baare et al. (1999) observed smaller GMV and WMV in patients, but had low power to detect significance.

Two studies with a control group observed differences in structure/function relationships for patients and controls. Sanfilipo et al. (2002) found greater prefrontal GMV to be associated with better performance on Digit Symbol task in controls, but not in patients. On the other hand, a positive relationship existed between prefrontal WMV and cognitive flexibility in patients, but not in normal controls. In the second study (Baare et al., 1999), relative PFC volume was associated with verbal fluency and immediate recall for verbal and visual material in patients, and with delayed recall for visual stimuli in controls. These differences in associations between patients and controls might be due to the relative difficulty of the tasks. As suggested by the authors, delayed visual recall, being a more demanding task, could produce more variability in controls, and thus correlate stronger with PFC volume. By the same token, in patients, this task might produce a ‘floor’ effect and hence low variability, resulting in a weak correlation with PFC volume.

Two studies without a control group have reported a relationship between FL volumes and the performance on the so-called frontal lobe tasks. Nestor et al. (2002), using partial least square analysis, found an association between greater GMV and WMV and better working memory in patients. Raine et al. (1992) investigated a sub-group of patients with an impaired performance on frontal, but not non-frontal, measures, and found bilateral PFC reductions when compared with normal and psychiatric (predominantly major depressive disorder) controls (Raine et al., 1992).

Other studies did not find any relationship between prefrontal volumes and cognitive abilities in patients, perhaps due to an approximate definition and measurement of the ROIs corresponding to anatomical brain regions and an arbitrary construction of cognitive domains (Sullivan et al., 1996), as well as a lack of gray and white matter segmentation in two early studies (DeLisi et al., 1991; Raine et al., 1992).

To summarize, total FL volume is associated with executive functioning, working memory, verbal fluency, and immediate memory in schizophrenia. There were differences in the pattern of structure/function relationship between patients and controls, which might be due to different degrees of variability in performance depending on the relative difficulty of the task (Baare et al., 1999), as well as the volumes of prefrontal brain tissue, with patients being more variable in prefrontal WMV, and controls being more

variable in prefrontal GMV (Sanfilipo et al., 2002). Additionally, similar volumes of prefrontal gray matter in schizophrenia may not result in similar levels of cognitive performance to that of controls; for example, due to disrupted connectivity between PFC and other regions involved in the cognitive processes engaged by the task, or due to the lack of strategy use, prohibiting an optimal utilization of available prefrontal gray tissue.

2.3.2. Regions of PFC

Seven studies have examined neuropsychological correlates of the PFC sub-regions: four (Maher et al., 1995; Baare et al., 1999; Manschreck et al., 2000; Gur et al., 2000a) studied dorsolateral prefrontal cortex (DLPFC), dorsomedial prefrontal cortex (DMPFC), and orbito-frontal cortex (OFC); one (Seidman et al., 1994) investigated DLPFC and OFC; one (Szeszko et al., 2000) examined the superior frontal gyrus, anterior cingulate and OFC; and one (Zuffante et al., 2001) focused on Brodmann area 46. All, but three studies (Seidman et al., 1994; Maher et al., 1995; Manschreck et al., 2000) had a control group.

Of the two studies with a control group exploring DLPFC, DMPFC, and OFC, one study (Gur et al., 2000a) observed alterations in all three sub-regions. Gur et al. (2000a) reported a reduction in DLPFC volume in both male and female patients, a greater DMPFC volume reduction in males than females, and OFC reduction only in females. These reductions were limited to gray matter. The GMVs of the sub-regions were examined in relation to six cognitive domains (abstraction/flexibility, attention, verbal and spatial memory, and verbal and spatial abilities), predicting correlations with abstraction/flexibility and attention. Correlations with other domains were exploratory and were adjusted for multiple comparisons ($p < 0.01$). In accordance with the prediction, greater GMV of DLPFC correlated with better performance on abstraction/flexibility, and greater GMV of DLPFC and DMPFC correlated with better attention in healthy men. For healthy women, greater GMV of DLPFC and DMPFC correlated with better abstraction/flexibility. For male patients, correlations between the GMV of DLPFC and cognitive domains of interest were attenuated, and the only positive correlation was found between DMPFC and attention. For female patients, greater GMV of DLPFC was associated with better attention; greater GMV of lateral and medial OFC with better spatial memory; greater GMV of lateral OFC with spatial abilities; and greater GMV of medial OFC with better verbal memory. These findings are in line with functional and lesion data, which suggests that dorsal PFC is associated with executive function, while ventral PFC is involved in memory (Miller and Cohen, 2001).

In another study (Maher et al., 1995; see Section 2.2), contextual memory, but not rote memory, correlated positively with the relative frontal volume in schizophrenia patients (mostly male), with the main contribution of DLPFC to this relationship. According to the authors, this finding suggests the DLPFC is associated with redundancy utilization during verbal memory tasks, presumably by facilitating the encoding of information through the use of context.

In a later study from the same laboratory (Manschreck et al., 2000), the authors tested the hypothesis that motor synchrony, a task requiring redundancy utilization for optimal performance, would be associated with PFC volume and with context-aided verbal memory in a group of predominantly male patients with schizophrenia or schizoaffective disorder. Greater volumes of OFC were found to associate with poor motor synchrony. As suggested by the authors, this result might be artifactual in a sense that greater OFC volume might simply reflect smaller volume of DLPFC, which was positively correlated with context-aided memory in the earlier study (see above, Maher et al., 1995). However, this does not explain why neither absolute nor relative DLPFC volumes were found to correlate with motor synchrony in Manschreck's et al. study. Alternatively, the authors further commented, this association might reflect the role that OFC plays in organizing repetitive behavior. This, however, does not explain why larger OFC volume would be associated with poorer motor synchrony. A possible interpretation of this association might be related to the fact that OFC, by the virtue of its connections with limbic and olfactory cortices, plays a role in affective processing. Larger volumes of OFC might result in heightened affective salience of the stimuli in individuals with schizophrenia—a feature of cognitive processing that would be detrimental for utilization of redundancies in the stream of

stimuli. In fact, one of the phenomenological features of schizophrenic experience is that every event is perceived as salient or meaningful (Hemsley, 1994). However, as no normal control group has been used in the study, it is not known whether OFC volumes were in fact enlarged in this patient group.

Seidman et al. (1994) examined the relationship of DLPFC and OFC volumes with verbal and performance IQ, verbal and spatial memory, and executive function in a predominantly male group of chronic schizophrenia inpatients. Greater total DLPFC volume was associated with higher IQ, as well as better performance on WCST and delayed Logical Memory. Hemisphere specific associations were also found, such that greater left DLPFC volume was associated with higher IQ, better WCST, Similarities, immediate and delayed Logical Memory, and immediate Visual Reproduction performance, whereas greater right DLPFC was associated with fewer errors on the Continuous Performance Task (CPT). OFC did not correlate significantly with any neuropsychological measures.

Szeszko et al. (2000) measured gray and white volumes of superior frontal gyrus (SFG), anterior cingulate (AC), and OFC in order to test the hypothesis that the dorsal 'archicortical' (SFG and AC), but not ventral 'paleocortical' (OFC), PFC would be associated specifically with executive and motor function in FEP patients. Tests of language, attention, memory, and visuo-spatial function were used as control variables to examine the specificity of findings. Their hypothesis was confirmed in male, but not in female, patients: larger AC volume correlated with better executive function, and this association was significantly stronger than with other cognitive domains and general IQ. This finding is in agreement with the results of Seidman et al. (1994) study (reviewed above), in which archicortical, but not paleocortical, PFC volume associated with executive function in a cohort of predominantly male patients. However, the part of the archicortex associated with executive function was different in two studies, which might be due to different methodology, with Szeszko et al. (2000) using gyral landmarks for measuring the volume of the sub-region, whereas Seidman et al. (1994) calculated volume from a single slice. The difference might also be due to the tests employed, with Szezsko et al. using the measures of executive and inhibitory motor control, which are associated with AC function (Braver et al., 2001), while Seidman et al. used the measures of abstraction/flexibility, categorization and sustained attention, which are most robustly associated with DLPFC function (Garavan et al., 2002). Nevertheless, both studies have found an involvement of the archicortex in executive cognitive and motor function, but not of the paleocortex, which is associated with guiding emotional aspects of cognition (Fuster, 1985).

The last study (Zuffante et al., 2001) to be reviewed here tested a very specific hypothesis. The authors measured Brodmann area (BA) 46 and working memory in 23 male schizophrenia patients and 23 male healthy controls to investigate whether compromised working memory in schizophrenia is associated with BA 46 volume, an area known to be associated with working memory function in primates (Goldman-Rakic, 1987) and healthy humans (McCarthy et al., 1994). The patients did not show BA 46 volume alterations, but had impaired performance on spatial and non-spatial working memory tasks, which was not independent of lower general intelligence. There was no association between working memory performance and BA 46 volume in patients. These findings might imply that working memory impairment could arise due to several possibilities, including: (i) structural abnormalities in other PFC regions supporting working memory, such as BA 9 and BA 40, or other cortical regions, including anterior cingulate, premotor and supplementary motor areas, and posterior parietal cortex (Smith and Jonides, 1998), (ii) disrupted connectivity (i.e. white matter abnormalities) within the working memory network; (iii) inefficient function of BA 46 in the face of structural integrity. In controls, larger left BA 46 volume was associated with *poorer* spatial working memory, but this association was insignificant with Bonferroni correction.

Overall, it appears that the archicortical PFC correlates most consistently with the tasks of executive function (Seidman et al., 1994; Szeszko et al., 2000), attention (Gur et al., 2000a), and verbal (Seidman et al., 1994; Maher et al., 1995; Gur et al., 2000a) and visual (Seidman et al., 1994) memory in schizophrenia, reflecting a normal pattern of structure/function relationships. However, the pattern of correlations between structural and functional measures

appears to be different for patients and controls (Gur et al., 2002a), for men and women (Szeszko et al., 2000; Gur et al., 2002a), and might be attenuated in affected men (Gur et al., 2002a). There is also an indication of differential hemispheric involvement in the type of function, with left DLPFC being associated with abstraction/flexibility, categorization and non-verbal immediate memory, and right DLPFC being associated with sustained attention (Seidman et al., 1994). The paleocortex (OFC) appears to have a complex relationship with examined cognitive domains, perhaps due to an interaction between the nature of the task and the gender of the subjects (Seidman et al., 1994; Manschreck et al., 2000; Gur et al., 2000a).

Importantly, not all frontal functions seen to be impaired in patients were found to correlate with reduced total and regional PFC volumes in the reviewed studies (Gur et al., 2000a; Baare et al., 1999). Conversely, not all studies have found abnormal PFC volumes, while observing deficits in frontal function (Zuffante et al., 2001; Baare et al., 1999). Abnormalities in other brain regions might be contributing to the impaired performance on so-called frontal measures in schizophrenia, as PFC function depends on the integrity of other cortical and subcortical structures that together constitute distributed functional networks.

2.4. Temporal lobe

The studies that examined the whole temporal lobe (TL) are reviewed first, followed by those studies investigating the superior temporal gyrus (STG) and medial temporal lobe structures.

2.4.1. Whole TL

Thirteen studies measured the volume of the whole TL, ten with a control group or groups (DeLisi et al., 1991; Di Michele et al., 1992; Hoff et al., 1992; Colombo et al., 1993; Flaum et al., 1994; Vita et al., 1995; Torres et al., 1997; Krabbendam et al., 2000; Gur et al., 2000b; Sanfilipo et al., 2002), and three without (Nestor et al., 1993; Seidman et al., 1994; Maher et al., 1995).

Only one study (Sanfilipo et al., 2002) found total TL volume reduction in patients relative to controls, which was limited to gray matter. Other studies did not observe TL reductions, perhaps due to the lack of segmentation into gray and white matter, or the insensitivity of the measurements in the earlier studies (DeLisi et al., 1991; Di Michele et al., 1992; Hoff et al., 1992; Colombo et al., 1993; Vita et al., 1995; Sullivan et al., 1996), which used thick (5–6 mm) slices.

Two studies observed positive associations between TL volume and cognitive functioning that were specific to schizophrenia (i.e. not seen in controls), including picture naming accuracy in chronic patients (Vita et al., 1995; also seen for the STG, see Section 2.4.2) and concentration/speed in FE patients (Hoff et al., 1992). Association with picture naming might be specific to the TL, as it has not been observed for the PFC (Vita et al., 1995).

One study (Flaum et al., 1994; see Section 2.1) reported a disrupted TL/cognition relationship in affected men, with greater bilateral TL volume associating with higher IQ in female patients and controls of both sexes, but not in male patients.

Other studies (DeLisi et al., 1991; Di Michele et al., 1992; Seidman et al., 1994; Maher et al., 1995; Sullivan et al., 1996; Sanfilipo et al., 2002) reported no relationship between TL volume and specific deficits in schizophrenia, such as attention, abstraction/flexibility, verbal and nonverbal memory. In addition, Torres et al. (1997) did not find any difference in TL between patients who scored high or low on verbal and non-verbal memory tasks. There were no volume differences for high and low scoring controls either. Finally, Colombo et al. (1993) did not find TL size to be abnormal in patients with severe short-term memory and attention/concentration impairments. It is possible that deficits in abstraction/flexibility, memory and attention/concentration in schizophrenia are due to the PFC volume alterations, as reviewed earlier (Seidman et al., 1994; Szeszko et al., 2000; Gur et al., 2000a). Alternatively, more specific regions of TL might associate stronger with some of these cognitive processes, including learning and memory, and abstraction/flexibility, as reviewed further.

2.4.2. Superior temporal gyrus

Four studies have measured STG volume, three with a control group (Vita et al., 1995; Gur et al., 2000b; Sanfilipo et al., 2002), and one without (Nes-

tor et al., 1993). Two studies (Gur et al., 2000b; Sanfilipo et al., 2002) have found reduction of STG gray matter in men, but not in women (Gur et al., 2000b). Vita et al. (1995) did not segment the STG into gray and white matter, which might explain their negative finding.

Greater left STG volume was associated with better verbal fluency and picture naming accuracy specifically in patients (Vita et al., 1995). In another study (Nestor et al., 1993), greater GMV of left and right posterior STG correlated with better abstraction/categorization, and greater GMV of left posterior STG with learning of verbal paired associations in male patients. The posterior STG, which includes Wernicke's area, is involved in language comprehension and semantic processing. Therefore, one interpretation of these findings, as suggested by the authors, is a dysfunction of the semantic system, which might underlie deficits in abstraction/categorization, picture naming, and semantic verbal fluency in schizophrenia. Sanfilipo et al. (2002), however, did not find either GMV or WMV of STG to associate with verbal fluency in the face of differential impairment of this function in their cohort of patients.

Other STG/cognition associations seem to be specific to controls. Greater STG volume was associated with greater processing speed (Sanfilipo et al., 2002), and with spatial memory in healthy women and attention in healthy men (Gur et al., 2000b). It is possible that greater integrity/efficiency of semantic system associated with posterior STG volume would have a positive effect on cognition, particularly processing speed.

2.4.3. Medial temporal lobe

Parahippocampal gyrus (PHG) was measured in four studies, three with a control group (Krabbendam et al., 2000; Sanfilipo et al., 2002) or groups (DeLisi et al., 1991), and one without (Nestor et al., 1993). None of the studies reported abnormal PHG volumes in patients. Hoff et al. (1992) measured the total volume of amygdala, hippocampus and PHG as a limbic complex and did not find it to be abnormal in FE patients.

Greater PHG volume was associated with higher verbal intelligence in both FE and chronic patients (DeLisi et al., 1991) and in a separate sample of FE patients of mixed gender (Hoff et al., 1992). However, an inverse relationship between right PHG volume and verbal intelligence was found in male chronic patients (Sanfilipo et al., 2002). The latter finding might reflect a disrupted relationship between structure and neurocognition in affected men, observed for other brain regions. Alternatively, larger right PHG volume might be indicative of the alteration of the normal, language related left-larger-than-right asymmetry of the posterior temporal lobe, manifesting as an inverse association between right PHG and verbal IQ in these male patients. Whatever the direction of this association, it seems to be specific to schizophrenia, as no relationship was found between PHG volume and verbal intelligence in normal controls in any of the studies. Other findings include an association of greater PHG volume with better performance on the color-word part of the Stroop test in chronic patients (Krabbendam et al., 2000); abstraction/categorization in male chronic patients (Nestor et al., 1993); associative learning in a mixed group of FE and chronic patients (DeLisi et al., 1991); and memory for stories in FE patients (DeLisi et al., 1991). None of these relationships were observed in healthy controls. Thus, it appears that, although not volumetrically abnormal, PHG has a number of associations with cognitive functions specific to schizophrenia.

The studies investigating the relationship between the hippocampus and amygdaloid/hippocampal complex and cognitive deficits outnumber the studies of any other specific brain region reviewed in this paper. One of the reasons for this interest is that the anatomic and functional affiliations of the limbic cortex in general, and the hippocampus in particular, can theoretically contribute to clinical, psychophysiological and cognitive abnormalities observed in schizophrenia (Stevens, 1973; Torrey and Peterson, 1974; Weinberger and Lipska, 1995; Bilder and Szeszko, 1996). Moreover, animals with hippocampal lesions mirror the course and manifestation of schizophrenia with remarkable precision (reviews, Schmajuk, 1987; Lipska and Weinberger, 2002).

Ten studies measured hippocampus (DeLisi et al., 1991; Colombo et al., 1993; Flaum et al., 1994; Nestor et al., 1993; Bilder et al., 1995; Torres et al., 1997; Gur et al., 2000b; Krabbendam et al., 2000; Szeszko et al., 2002; Sanfilipo et al., 2002). Out of six studies with a control group (DeLisi et al., 1991;

Colombo et al., 1993; Torres et al., 1997; Krabbendam et al., 2000; Gur et al., 2000b; Sanfilipo et al., 2002), only one has found reduction in the hippocampal GMV in affected men and women (Gur et al., 2000b). However, as hippocampal reduction might be limited to gray matter, other studies might have failed to find hippocampal abnormality due to the lack of segmentation. Also, the evidence for the hippocampal reduction is not as strong in FE patients as it is in chronic patients (DeLisi et al., 1991).

Although not altered in most studies, hippocampal volume associated with different aspects of memory in patients, as well as in controls. In a study of monozygotic twins discordant for schizophrenia (Goldberg et al., 1994), greater left hippocampal intra-pair volume difference was associated with greater intra-pair difference in memory for stories. Gur et al. (2000b) have found greater bilateral hippocampus to be associated with better verbal and spatial memory in both men and women regardless of diagnosis. In contrast, Sanfilipo et al. (2002) have observed dissociation in the direction of correlations between patients and controls, such that left and right hippocampal volumes positively correlated with verbal memory in patients, whereas an inverse relationship between right hippocampal volume and verbal memory existed in controls. This finding is difficult to reconcile, especially considering that greater right hippocampal volume has also associated with better verbal fluency and Digit Symbol task performance in controls. These latter relationships were not present in the patient group, despite differential deficit of verbal fluency. Among negative findings in regards to memory function is the lack of any association between hippocampal volume and either verbal or visual memory in FE and chronic patients studied by DeLisi et al. (1991). Additionally, Torres et al. (1997) did not find hippocampal volume difference between patients differentiated by high and low ability of delayed memory, or between high and low performing controls.

Hippocampal volume has also been found to associate with the functions commonly attributed to the integrity of frontal lobes, supporting the notion that the deficits of higher order cognitive functions in schizophrenia might be due to the disruption of frontal-limbic circuitry (Lipska and Weinberger, 2002). Thus, two studies from the same laboratory (Bilder et al., 1995; Szeszko et al., 2002; the latter study included a sub-sample of patients from the first study) reported positive correlations between anterior hippocampus and executive and motor functions in FE patients. In the earlier study (Bilder et al., 1995), correlations of hippocampal volume with executive, but not motor function, were significantly stronger than with full scale IQ. Also, there was no correlation of these cognitive domains with either posterior hippocampus or amygdala, suggesting the specificity of the observed association. There was no difference in the magnitude of this association between male and female patients. The latter study (Szeszko et al., 2002) had a larger sample, and has observed significant differences in the strength of correlations between men and women with FE psychosis. In affected males, larger anterior hippocampus was associated with better executive and motor function, and significantly stronger than with memory or language. In affected females, no significant correlations were found, although there was a trend for an association between anterior hippocampus and memory.

Nestor et al. (1993) did not find any association between hippocampal volume and executive function in male chronic patients. This study measured abstraction and categorization aspects of executive function, whereas Bilder et al. (1995) and Szeszko et al. (2002) measured perseveration and inhibitory control. Thus, it is possible that only those measures of executive function that are indices of ‘projectional control’ are associated with hippocampal volume.

Finally, the amygdala was measured as a separate structure only by Gur et al. (2000b), who found reduced volume of the amygdala in men and increased volume in women with schizophrenia, but this was not associated with cognitive functioning either in patients or in controls.

To summarize, the total TL volume is associated with picture naming (Vita et al., 1995) and concentration/speed (Hoff et al., 1992). These associations might be specific to the TL and to schizophrenia. The GMV of the posterior STG might be associated with abstraction/categorization and verbal learning (Nestor et al., 1995), but the specificity of this association remains unclear. Hippocampal volume is associated with memory function in both patients

and normal controls of both genders (Gur et al., 2000b, but see DeLisi et al., 1991). Finally, executive function requiring inhibitory control of behavior might be related to anterior hippocampal volume in schizophrenia (Bilder et al., 1995), particularly in affected men (Szeszko et al., 2002), whereas abstraction and categorization might be related to the volume of PHG (Nestor et al., 1993). PHG volume is also associated with a range of cognitive processes that might require access to a semantic system and this association might also be specific to schizophrenia (DeLisi et al., 1991; Nestor et al., 1993; Krabbendam et al., 2000).

2.5. Parietal and occipital lobes

Only one study (Sullivan et al., 1996, see also Sections 2.3 and 2.4) investigated functional correlates of the posterior brain regions. This study measured the volumes of parietal and parieto-occipital regions in 34 men with schizophrenia and 47 healthy men. There were no significant differences either in GMV or WMV of these regions between the groups, and no significant correlations with four cognitive domains, which included executive function, verbal fluency, short-term memory, declarative memory and motor ability. Since the sub-regions of parietal lobe are functionally differentiated, global measurements of the posterior brain regions might have masked any specific associations with examined cognitive domains.

2.6. Basal ganglia

Five studies have measured basal ganglia (BG), three with a control group (DeLisi et al., 1991; Flaum et al., 1994; Stratta et al., 1997), and two without (Maher et al., 1995; Manschreck et al., 2000).

In the most recent study, Stratta et al. (1997) investigated the hypothesis that executive dysfunction and disruption of goal-oriented behavior in schizophrenia might be associated with striatal abnormalities. The total BG volume, the volume of the caudate nucleus (CN), and the joint volume of the putamen (Pu) and nucleus accumbens (NA) were measured in chronic patients and healthy controls (separate volumes of Pu and NA were only available for a subsample of patients). Patients were divided into poor and good performers based on their WCST categories completed score. No differences in age, duration of the illness or sex were found between poor and good performers. As hypothesized, poor performers had significantly smaller volumes of the BG structures, with the reduction of the total right striatum and left CN and Pu relative to normal controls, and left Pu and bilateral Pu–NA complex relative to good WCST performers. Good performers did not significantly differ from controls and, in fact, exhibited a trend for larger volumes of Pu and Pu–NA complex bilaterally. Striatal volumes in both good and poor performers were not related to the dosage of neuroleptic medication, which is known to alter the volume of BG structures (Chakos et al., 1994). In patients, volumes of the left BG and Pu–NA complex positively correlated with the number of categories completed. In addition, unique errors on WCST inversely correlated with left Pu, NA, and Pu–NA complex. Perseverative errors did not significantly correlate with striatal volumes. As has been discussed in TL section, perseveration in schizophrenia might be related to the disruption of fronto-limbic circuitry (Bilder et al., 1995; Szeszko et al., 2000). It is unclear whether the found associations are specific to schizophrenia, as no correlations between WCST variables and striatal volumes were performed for the control group. Nevertheless, Stratta et al. (1997) provided support for the notion that the ability to organize goal-directed behavior is positively related to striatal volume in schizophrenia.

Flaum et al. (1994; see also Sections 2.1, 2.3, 2.4)) examined the volumes of CN and Pu in relation to the full scale IQ. The only association between the striatal volumes and IQ was the correlation of larger left Pu with higher full scale IQ in female patients, but not in male patients or normal controls. In fact, this correlation was the only one to significantly differentiate affected women from healthy controls.

DeLisi et al. (1991) measured the volumes of CN and the lenticular nuclei (Pu + globus pallidus) in FE and chronic patients, and neurological controls. Chronic patients had the largest CN volumes, while FE patients had the smallest, but neither group differed significantly from neurological controls. No significant correlations were found between the striatal volumes and cognitive measure, which included WCST and serial word learning, amongst others.

Two studies from the same laboratory (Maher et al., 1995; Manschreck et al., 2000; see also Sections 2.2, 2.3 and 2.4) investigated the relationship between striatal size and the redundancy utilization ability, and observed an inverse correlation between striatal size and context-aided memory (Maher et al., 1995), but not motor-synchrony (Manschreck et al., 2000). It is possible that larger striatal volumes in Maher et al. study were associated with greater neuroleptic exposure, which, in turn, might be related to greater disease severity and hence poorer learning and memory, however no information was available on lifetime neuroleptic exposure.

Finally, Jeste et al. (1998) investigated the relationship of structural and neuropsychological variables to the age of onset of schizophrenia (AOS). Although the structure/function examination was not the primary goal of the study, the findings are interesting and relevant. Earlier AOS was associated with poorer abstraction/categorization, larger volumes of CN and LN, and smaller volumes of the thalamus. Despite the inter-domain correlations of neuropsychological and structural variables, there were no significant cross-domain correlations. When the authors performed a series of stepwise regressions with two-, three-, and four-variable models to predict the AOS in schizophrenia, they found that out of seven significant models, the model that accounted for the most variance (27.5%) included poorer learning, smaller thalamic and larger LN volumes as predictors. However, when the duration of illness, current age and current neuroleptic dosage were controlled for, the only model that remained significant included poorer abstraction/cognitive flexibility, smaller thalamus and larger CN.

To summarize, there is some evidence for an association between striatal size and executive function in schizophrenia (Stratta et al., 1997; but see DeLisi et al., 1991; Jeste et al., 1998). However, there is no evidence for the positive association between striatal size and learning and memory from the studies reviewed, and in fact the inverse relationship might exist (Maher et al., 1995). Moreover, enlarged LN and poor learning might be associated with earlier disease onset (Jeste et al., 1998). More studies are needed to investigate cognitive correlates of BG pathology, taking into account gender differences and exposure to neuroleptics. In particular, there is a lack of studies investigating the output site of BG, the globus pallidus. The function of globus pallidus interna might play an important role in the executive tasks associated with DLPFC function (Owen et al., 1996).

2.7. Cerebellum

Four studies (Flaum et al., 1994; Nopoulos et al., 1999; Levitt et al., 1999; Szeszko et al., 2003) have investigated cerebellar volume and its sub-regions and their relation to cognitive functioning in schizophrenia. All studies had a control group, but two studies (Flaum et al., 1994; Szeszko et al., 2003) did not report on between-group morphological differences.

The total cerebellar volume was found to be unaltered in men with schizophrenia (Nopoulos et al., 1999; Levitt et al., 1999), but there was greater left-than-right cerebellar asymmetry of gray matter (Levitt et al., 1999). Cerebellar vermis, on the other hand, might be abnormal in affected men. Nopoulos et al. (1999) reported reduced volume of the anterior vermis, which was associated with lower full scale IQ and verbal, but not performance, IQ. Levitt et al. (1999) reported increased vermal white matter, which was associated with poorer immediate memory for social stories (Logical Memory). These associations between altered vermal volumes and cognition were specific to schizophrenia.

Other studies (Flaum et al., 1994; Szeszko et al., 2003) have observed a lack of cerebellum/cognition relationships in men with schizophrenia when such were found in normal controls. Flaum et al. (1994; see also Sections 2.1, 2.4 and 2.6)) found greater left and right cerebellar volume to be associated with higher IQ in normal men and women as well as in women with schizophrenia, but not in affected men, with this difference significantly differentiating affected men. Similarly, Szeszko et al. (2003) reported a positive correlation between total cerebellar volume and global neuropsychological functioning, visuo-spatial, and memory scales in healthy, but not affected, men, with the strength of the correlations being significantly different between the groups.

To summarize, men with schizophrenia might have cerebellar abnormalities that are limited to the anterior vermis (Nopoulos et al., 1999) and an increase of white matter (Levitt et al., 1999), which are associated

with lower general and verbal ability and the dysfunction of narrative memory, respectively. Total cerebellar volume does not seem to be altered and does not associate with cognitive ability in affected men. In healthy people (Flaum et al., 1994; Szeszko et al., 2003) and women with schizophrenia (Flaum et al., 1994), on the other hand, total cerebellar volume bares positive association with cognitive ability. Given these findings, a systematic investigation of total and regional cerebellar gray and white matter morphology and their relationship to cognitive dysfunction in schizophrenia, with gender differences taken into account, is warranted.

2.8. Midbrain

Nopoulos et al. (2001) investigated midbrain volume and its relationship with IQ. The midbrain, as well as pons and medulla as control regions, were measured in 50 men with schizophrenia and 50 healthy men. Midbrain volume, but not pons or medulla, was significantly smaller in affected men, but the volume reduction was not associated with lower IQ.

2.9. Brain asymmetry and cognitive function

Two studies (Hoff et al., 1992; DeLisi et al., 1997) have directly investigated the effect of disrupted brain asymmetries on cognition in schizophrenia.

Hoff et al. (1992, also see Sections 2.2 and 2.4) measured the length of the lateral sulcus (LS), which corresponds to the length of the planum temporale (PT) (posterior area associated with language) in a mixed gender sample of FE patients and normal controls. A lack of normal left/right LS asymmetry was found in female, but not male, patients. Surprisingly, a sub-group of patients with the lack of normal asymmetry demonstrated *better* global, executive, verbal and spatial memory functions than the sub-group with normal asymmetry. Language functioning, however, was not related to the degree of LS asymmetry in patients. For the control group, there were no differences in cognitive performance between the abnormal and normal asymmetry sub-groups.

DeLisi et al. (1997) assessed neuropsychological correlates of the frontal, temporal, and occipital asymmetries, as well as the segments of sylvian fissure (anterior, horizontal, and vertical) in FE patients and normal controls. Both male and female patients had reduced left/right asymmetry of the temporal and occipital lobes. Surprisingly, the degree of left/right occipital asymmetry was inversely correlated with the complexity of expressive language. A trend for a reduction of left hemisphere length as well as reduced left/right asymmetry of the horizontal segment of SF (overlying PT) was also observed. However, the degree (reversed, reduced, or normal) of laterality of this region, hypothesized to be crucial for language, did not associate with language disturbances, but related to vigilance (sustained attention). Vigilance was also positively correlated with the degree of left/right asymmetry of the anterior sylvian fissure. Normal subjects exhibited a different and an extensive pattern of correlations between the degree of brain asymmetries and cognition. Left/right asymmetry of the horizontal sylvian fissure segment correlated positively with receptive language performance in a noise distraction condition, but inversely in a quiet condition. In addition, greater asymmetry of this region associated with better nonverbal memory. Greater posterior frontal and anterior sylvian fissure asymmetries associated with better phonological verbal fluency. Greater right/left anterior frontal asymmetry associated with better verbal memory and nonverbal ability. Finally, greater left/right temporal asymmetry associated with better verbal memory. None of these relationships survived a correction for multiple comparisons either in patients or in controls.

In summary, the current evidence points towards reduced asymmetry of the language related areas in FE patients, but does not support its hypothesized association with language disturbances. In healthy individuals, normative asymmetry of language related areas appears to associate with a range of cognitive domains, including language.

3. Discussion and suggestions for future research

3.1. Methodological limitations and suggested solutions

The most important methodological drawback, in our view, is a general lack of a hypothesis-driven

examination of structure/function relationship in schizophrenia, with a few exceptions. Related to this, most studies performed a large number of correlations without prior hypothesis and with no correction for multiple comparisons. Thus, chance findings cannot be ruled out. However, the Bonferroni method of adjusting for multiple comparisons might be overly conservative and, in the face of the structure/function correlations being moderate, might result in a Type II error. Future 'region of interest' studies might make use of multivariate statistical techniques such as the partial least square (PLS) analysis (as applied by Nestor et al., 2002). PLS technique allows for the exploration of the relationship between a large number of variables in a relatively small sample (conditions with which studies of structure/function relationship are typically presented) without the risk of running Type I error. A further related problem is that only a few studies have performed a formal testing of the differences between patients and controls in the structure/function relationships, making it unclear whether the found correlations significantly differentiated affected and unaffected individuals.

Other methodological issues impose limitations on replicability and generalisability of the findings. These issues include: (i) different landmarks and different methods used in outlining and measuring the structures; (ii) different cognitive tests used to assess the same cognitive domain, as well as the same test used to assess different domains in different studies; (iii) the rational for the test grouping into specific domains not always given, and the construct validity of the resulting domains rarely assessed; (iv) no systematic investigation of sex differences; and (v) a lack of control group in some studies.

Discrepancies between patients and controls in the pattern of structure/function correlations were present in most studies. These differences might represent statistical artifacts, altered structure/function relationship in schizophrenia, or an interaction of both. For example, relative task difficulty and relative structural volume variability would produce different ranges of scores and volumes in two groups for the same set of structural/functional variables, resulting in correlations of a different strength. In order to account for this possibility and to aid the interpretation of the findings, future studies should report on structural and functional differences between the groups and examine relative variability of performance and volumetry before proceeding towards the examination of structure/function relationship. In other cases, however, differences in structure/function relationship between patient and controls might reflect a genuine finding. However, only few studies have tested whether such between-group correlation differences were significant, with other studies leaving the implications of their findings unclear. Future studies should make a clearer distinction between the findings of a relationship between structural alterations and cognitive deficits from that of an altered structure/function relationship in schizophrenia.

A more general issue regarding the investigation of structure/function relationships using standard neuropsychological tests is that they were developed for the assessment of cognitive disturbances occurring due to brain lesions of either surgical or organic origin. These tests were not designed to map accurately onto a specific brain structure, and generally involve several cognitive processes interacting with each other for the optimal task performance. However, we believe that neuropsychological tests can still be used to investigate structure/function relationship in an informative way, if the structure with which a test is found to correlate is to be viewed as a 'node' within the neuronal network(s); and if all the structures that are thought to be involved in a particular cognitive process measured by the test are examined in relation to this process.

3.2. Main findings and patterns

Despite the methodological shortcomings, there has been some consistency in structure/function relationships in both schizophrenia patients and healthy individuals. In general, total brain volume tends to have a nonspecific relationship with cognition, with bigger brains associating with better performance. Similarly, measures of general cognitive ability, such as IQ, tend to correlate with a number of brain regional volumes, including left and right cerebral hemispheres, hippocampus, and cerebellum in normal

controls and female patients, but these relationships might be disrupted in men with schizophrenia (Flaum et al., 1994). Since the frontal lobe has a unique involvement in higher cognitive processing and behavioral control, the volume of dorsal PFC, particularly its gray matter, is positively correlated with a range of cognitive processes in both patients and controls, including abstraction, attention, verbal memory, and psychomotor speed (Gur et al., 2000a; Sanfilipo et al., 2002).

A number of associations appear to be specific to schizophrenia. Greater cognitive flexibility in patients associated with greater GMV and particularly WMV of the PFC (Nestor et al., 2002; Sanfilipo et al., 2002), as well as smaller 3rd ventricle VBR (Bornstein et al., 1992). These associations indirectly implicate the role of fronto-thalamic circuitry in cognitive flexibility in schizophrenia. Other specific associations suggest that the dysfunction of language, as well as higher cognitive processes that require verbal endowment and abstraction/categorization of verbal information, might be associated with the volumes of STG and PHG (DeLisi et al., 1991; Hoff et al., 1992; Nestor et al., 1993; but see Sanfilipo et al., 2002).

Reviewed findings suggest that executive dysfunction in schizophrenia might be associated with the volumes of several distributed structures apart from the PFC. Executive tasks normally engage a number of distinct processes and abilities: (i) identification and categorization of information relevant to the task, (ii) development of a strategy or acquisition of a rule necessary for the task performance; and (iii) inhibition of pre-potent yet redundant responses. The data from the reviewed studies suggest that the first ability might be related to the volumes of PHG and STG and the function of semantic system associated with these regions (Nestor et al., 1993). Second ability might be related to the integrity of the striatum (Stratta et al., 1997). In fact, recent modeling work suggests that hierarchical updating and the sequencing of actions may involve interactions between the PFC and the basal ganglia (Houk and Wise, 1995). Finally, the third ability might be dependent on the integrity of the anterior hippocampus (Szeszko et al., 2002) and the AC (Szeszko et al., 2000). Abnormality in this fronto-hippocampal circuitry might result in a failure of error detection/inhibition in schizophrenia, leading to perseveration. Possible thalamic abnormality and deficits in 'set shifting' associated with fronto-thalamic interaction might also disrupt the third ability (Bornstein et al., 1992). All these neuronal circuits have been implicated in the models of schizophrenia pathophysiology (see Section 1.3). It must be acknowledged, however, that these functional distinctions mapped onto different neuronal circuits are only heuristics. Nevertheless, heuristics are helpful at least at the initial stages of understanding the complexity of inter-dynamics involved in brain function.

3.3. Suggestions for future research

Taking into consideration the methodological issues noted earlier, studies are needed to investigate brain structures that have mostly been neglected so far. Specifically, the integrity of the thalamus and its specific contribution to cognitive dysfunction in schizophrenia need systematic examination. Since reduced thalamic volume is related to earlier onset of symptoms (Jeste et al., 1998), it is undoubtedly important for understanding the pathogenesis of schizophrenia.

Further studies of the cerebellum and its subregions and their cognitive correlates are warranted, as it appears to be a promising line of inquiry based on the results of the reviewed studies. In particular, vermal-midbrain-thalamo-limbic connections might be related to cognitive and behavioral deficits characteristic of schizophrenia. In fact, the volumes of vermis, midbrain and temporal lobe structures were found to correlate with each other in men with schizophrenia, but not in normal controls (Nopoulos et al., 1999), suggesting that the inter-development of these structures might be related to a common denominator in affected men. Furthermore, cerebellar lesions involving its posterior lobe and vermis were reported to associate with perseveration, visual-spatial disorganization, impairments of working memory, planning, set shifting, verbal fluency, abstract reasoning, visual memory, logical sequencing, as well as blunt or inappropriate affect (Schmahmann and Sherman, 1997). These cognitive and affective disturbances

are inconspicuously characteristic of individuals with schizophrenia.

There is also a need for a more focused investigation of the amygdala and its role in cognitive functioning in schizophrenia. Keshavan et al. (1998) have recently found reduced volumes of amygdala and hippocampus in the offspring of parents diagnosed with schizophrenia. The amygdala might be relevant to the understanding of the hippocampal abnormality. It was recently suggested (Benes and Berretta, 2000) that the function of amygdala might contribute to the induction of abnormalities in the CA3 and CA2 section of the hippocampus. In fact, substantial histopathological alterations in hippocampal CA3 and CA2, but not CA1, have been consistently reported in post-mortem studies of schizophrenia patients (Falkai and Bogerts, 1986; Jeste and Lohr, 1989; Benes et al., 1998).

The anterior cingulate (AC) has also been relatively neglected in the investigation of structure/function relationships in schizophrenia. Tamminga et al. (2000) have recently emphasized the importance of AC to the understanding of emotional and cognitive dysfunction in schizophrenia, as it receives one of the richest dopaminergic innervations of any cortical area (Gaspar et al., 1989).

There is a great need for studies that would examine cognitive correlates of the parietal lobe and its sub-regions, which form distinct inter-connections with neocortical structures concerned with higher cognitive processes such as language, spatial perception and awareness, attention, and working memory (Mesulam, 1990, 1998) in homogeneous groups of schizophrenia patients.

The integrity of the midbrain and its cognitive correlates deserve further investigation. The midbrain is of particular interest in schizophrenia, as it contains the source nuclei of three dopaminergic pathways in the human brain: nigrostriatal (originating in SNr), mesolimbic and mesocortical (both originating in the ventral tegmentum). Interestingly, Minabe et al. (1990) described a case of a 40-year-old woman who had developed a syndrome consistent with schizophrenia diagnosis following midbrain tegmental lesion. As a part of the cortico-cerebellar and limbic-cerebellar circuits, as well as the site of origin of three dopaminergic pathways, midbrain might be associated with deficits of learning and memory, attention and working memory, as well as affective processing.

None of the reviewed studies have investigated neural correlates of motor and somatosensory cortices in schizophrenia. There is evidence from histological research suggesting decreased cell size in the motor cortex of schizophrenia patients (Benes et al., 1986). Studies are needed to pursue this line of inquiry.

4. Conclusion

The present article reviews the findings of structure/neurocognition relationship in schizophrenia to aid hypothesis generating and testing for future research. It is hoped that the review will assist in promoting the research rigor through the identification of the methodological issues, which limit the interpretation and the implication of the past findings. The future challenge lies in extracting a unique contribution of a given structure within a distributed network to a given cognitive process. To this end, future research should define as precisely as possible a cognitive process (or processes) underlying a behavioral measure and to investigate its relationship with all brain structures that might constitute the functional network involved in this cognitive process. New automated data processing techniques, such as the Voxel Based Morphometry (Ashburner and Friston, 2001), provide powerful and objective methods for investigating the neural network/cognitive process relationships by enabling the correlation of a given cognitive measure with the totality of the brain on a voxel-by-voxel basis. Application of such methods will undoubtedly advance our understanding of structure/function relationships in schizophrenia.

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Appendix A

Table A1
Reviewed studies clustered by structure

Whole brain volume	Flaum et al., 1994; Gur et al., 1999; Kareken et al., 1995; Maher et al., 1995; Seidman et al., 1994; Torres et al., 1997; Zipursky et al., 1998
LV and 3rd V	Bornstein et al., 1992; DeLisi et al., 1991; Hoff et al., 1992; Goldberg et al., 1994; Maher et al., 1995; Vita et al., 1995
PFC	Baare et al., 1999; DeLisi et al., 1991; Gur et al., 2000a; Maher et al., 1995; Manschreck et al., 2000; Nestor et al., 2002; Raine et al., 1992; Sanfilipo et al., 2002; Seidman et al., 1994; Sullivan et al., 1996; Vita et al., 1995; Zuffante et al., 2001
TL	DeLisi et al., 1991; Di Michele et al., 1992; Flaum et al., 1994; Gur et al., 2000b; Hoff et al., 1992; Jeste et al., 1998; Krabbendam et al., 2000; Maher et al., 1995; Nestor et al., 1993, 2002; Raine et al., 1992; Sanfilipo et al., 2002; Seidman et al., 1994; Sullivan et al., 1996; Torres et al., 1997; Vita et al., 1995
STG	Gur et al., 2000b; Nestor et al., 1993, 2002; Sanfilipo et al., 2002; Vita et al., 1995
Hippocampus/ Amygdala	Bilder et al., 1995; DeLisi et al., 1991; Di Michele et al., 1992; Flaum et al., 1994; Goldberg et al., 1994; Gur et al., 2000b; Hoff et al., 1992; Krabbendam et al., 2000; Nestor et al., 1993; Sanfilipo et al., 2002; Szeszko et al., 2000, 2002; Torres et al., 1997
PHG	DeLisi et al., 1991; Di Michele et al., 1992; Hoff et al., 1992; Krabbendam et al., 2000; Nestor et al., 1993, 2002; Sanfilipo et al., 2002
Parietal, Parieto/ occipital	Raine et al., 1992; Sullivan et al., 1996
Basal ganglia	DeLisi et al., 1991; Flaum et al., 1994; Jeste et al., 1998; Levitt et al., 1999; Maher et al., 1995; Manschreck et al., 2000; Stratta et al., 1997
Thalamus	Jeste et al., 1998
Midbrain	Nopoulos et al., 2001
Cerebellum	Levitt et al., 1999; Nopoulos et al., 2001
Brain asymmetry	Hoff et al., 1992; DeLisi et al., 1997

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