Abstract

Recent years have witnessed increasingly intense research activity concerning early life somatic trauma and dysmorphogenesis which are associated with the later development of schizophrenia. The two somatic factors that have received the most extensive scientific attention as antecedents of schizophrenia are obstetric complications (OCs) and the congenital malformations termed ‘minor physical anomalies’ (MPAs). Head circumference (HC) at birth has also been studied as a measure of prenatal cerebral development. A great number of studies indicate clearly that schizophrenia patients have a significantly increased history of OCs, representing many different OCs from pregnancy, labor-delivery and the neonatal period. The probable common denominator of these OCs is oxygen deprivation. Especially labor-delivery OCs relate strongly to brain structure abnormality in ill twins from monozygotic pairs discordant for schizophrenia. Schizophrenia patients very consistently have evidenced an increased frequency of MPAs in the global head, eyes, mouth, ears, hands, feet and limbs. Specific MPAs occur with considerable frequency even among normal comparison subjects, but combination models for specific MPAs efficiently discriminate most patients from comparison subjects. Schizophrenia patients also have significantly reduced HC at birth, independently of gestational age, suggesting a disturbance in prenatal cerebral development, and most frequently observed in female patients. Evidence has thus accumulated, increasingly, for the role of various forms of early trauma and dysmorphogenesis in subsequent schizophrenia, and efforts continue to determine the manner in which these early trauma influence both the early developing brain and the brain of the adult patient with manifest schizophrenia. Published by Elsevier Science B.V.

Keywords: Pregnancy; Birth; Malformation; Schizophrenia; Hippocampus
1. Introduction

The past two decades have witnessed a burgeoning of scientifically qualified studies on very early somatic trauma and dysmorphogenesis which are associated with the later development of schizophrenia. The often confirmed finding that schizophrenia birth rates are increased in December–January, with a corresponding sharp decrease in September and October, has undoubtedly stimulated this concentration on schizophrenia-related factors during the gestational and early life periods. An increasingly broad range of early life somatic factors are being found to be related to the later development of schizophrenia, including inferred fetal influence resulting from maternal exposure to extreme stress (e.g., death of the offspring’s father during pregnancy [36], unwanted pregnancy [71], maternal depression during mid-pregnancy [41], wartime conditions [41], famine [94], influenza existing in the general population and reflected in both time-delimited epidemics [1] and yearly fluctuations in death rates [90], and urban birth [70]. The particular mechanism(s) by which many of these factors increase the risk for schizophrenia later in life remains unknown, but probably represents some form of resultant maldevelopment or damage to the fetus.

The two early life somatic factors that have received the most extensive scientific attention as antecedents of schizophrenia are obstetric complications (OCs) [59] and minor congenital malformations termed ‘minor physical anomalies’ (MPAs) [83,114]. Both OCs and MPAs represent well-established indices of early maldevelopment and trauma, with a long history of research in relationship to various forms of subsequent psychopathology in the offspring [57,82]. In this paper, we review our own and others’ scientific work on OCs, MPAs and head circumference at birth in schizophrenia, evaluating the basic findings and the scientific effects of using different methodological approaches. We also explore the possible origins and subsequent consequences or correlates of OCs and MPAs in relation to schizophrenia.

2. Obstetric complications (OCs)

We have defined OCs as the broad class of deviations from an expected, normal course of events and offspring development during pregnancy, labor-delivery and the early neonatal period [58]. OCs are typically divided chronologically into ‘pregnancy complications’ (PCs), covering the period from conception until onset of labor, ‘labor-delivery complications’ (LDCs), from the onset of labor until delivery of the child and severance of the umbilical cord, and ‘neonatal complications’ (NCs), optimally from the moment of delivery through the first month of life, but, operationally, usually from delivery until hospital discharge [69].

Our own studies of these phenomena have thus far included five sets of adult patients, plus a prospective investigation of genetic high-risk and normal-risk offspring: Studies I and II included 70 [14,66] and 60 [9] representative Swedish patients with schizophrenia (vs. demographically similar comparison cases), respectively, with OCs investigated through prospectively recorded medical records. Study III consisted of 23 North American monozygotic twin pairs discordant and 10 pairs concordant for schizophrenia, plus normal control twins, blindly assessed through very detailed parental reports [62]. Study IV investigated 45 Swedish schizophrenia patients and 34 normal controls for whom OC information was collected by retrospective maternal recall vs. medical record information [13]. Study V investigated 30 Swedish patients with other psychosis diagnoses (schizo-affective and unspecified functional psychosis) vs. comparison cases, using hospital record information [64]. And study VI investigated 88 offspring of women with psychosis (33 with schizophrenia-related psychoses) and 104 normal-risk offspring of control women, studied prospectively from pregnancy until young adulthood, with personal observation of the labor-deliveries in 83% of the total sample, by the first author (TFM).

2.1. Total rates and timing of ocs in patients vs. comparison subjects

2.1.1. Our studies

Studies I–III of schizophrenia patients all found significantly increased rates of OCs for the total reproduction in the schizophrenia cases (study I \( p = 0.020 \); II \( p = 0.002 \); III discordant vs. concordant vs. control \( p = 0.008 \). All three studies also showed significantly increased total OCs for the patients at the time of labor-delivery (I \( p = 0.035 \); II: \( p = 0.005 \); III \( p = 0.008 \)) and, to a lesser extent, neonatally (I \( p = 0.032 \); II: \( p = 0.07 \); III \( p = 0.04 \)). None of these three studies showed significant increases in total PCs among patients, in spite of frequently reported PCs for both patient and control subjects. Study IV found a significant increase in OCs in schizophrenia patients when using prospectively recorded medical record information but not retrospective maternal reports (see Section 2.3.1 regarding Methods). The fifth study found no significant increase in OC rates in patients with schizo-affective or unspecified functional psychoses vs. control cases [64], which is notable given the consistency of significant increases among the schizophrenia patients investigated in an identical manner. Our findings of significant increases in OCs in schizophrenia are congruent with the many studies which have been published to date [58,59].

2.1.2. Others’ OC studies

Schizophrenia OC studies which have employed comparison groups and standardized methods for scoring OCs
span the past 40 years. A basic summary of this literature, compiled by us five years ago [59], showed that seven of eight investigations using blind assessments of prospectively recorded medical information and comparison groups (including our study I above [14]) had found significant OC increases in schizophrenia patients, and a similar significant increase in OC rates in patients was found in 9 of 13 studies using retrospective parental reports. Sample sizes in the studies prior to 1995 were generally limited, and to our knowledge, the largest sample of schizophrenia patients that had been studied up to 1995 using prospectively recorded OC information was our sample of 70 Swedish patients [14]. Four other studies [18,19,53,104] using retrospective maternal reports of OCs had sample sizes of 100–207 patients.

During the past five years, studies typically using population register information have investigated increasingly larger samples of schizophrenia patients (i.e., n = 76 patients [41], n = 82 [34], n = 115 [42]; n = 117 [48], n = 167 [35], n = 210 [92], n = 238 [16], n = 312 [37], n = 524 [17]), with additional meta analyses of large sample aggregations across studies (n = 700 [23] and n = 854 [100]; see also [22]). All of the recent studies, with prospectively recorded information and large sample sizes, show significant increases in OCs in patients and/or significant relationships between OCs and other characteristics of the patients.

In contrast, two prospective cohort studies failed, at least initially, to substantiate a relationship between OCs and the later development of schizophrenia. In the first of these studies, which was based on the 1958 British perinatal mortality survey sample, Done et al. [20] used a combination of OC variables that predicted perinatal death in the population to investigate OC history for schizophrenia patients within the cohort, and found nonsignificantly increased odds ratios of 1.4 for 35 patients with a narrow definition of schizophrenia and 1.5 for 57 individuals with more broadly defined schizophrenia. These results are difficult to compare with results from other studies, given the unique scoring system. The other cohort study was that of Buka et al. [7] who used prospectively recorded data from the National Collaborative Perinatal Project in the USA, following up 192 offspring with ‘chronic fetal hypoxia’ to an average of 23 years (range 18–27), i.e., only partially through the subjects’ risk age for schizophrenia. Their first results showed a nonsignificant doubling (odds ratio (OR)1.9, p > 0.05) of rates of schizophrenia and schizophreniform psychosis in asphyxia cases (2.1%) as compared with controls (1.2%). A subsequent replication study of 35 individuals with psychosis by the same authors [8] showed a significant relationship to maternal pre-eclampsia (OR 2.4), hypertension (OR 2.6) and a composite variable representing chronic fetal hypoxia (OR 1.8). Further follow-up of the same sample [105] showed a significant relationship between ‘fetal/neonatal hypoxic ischemic encephalopathy’ and risk for both schizophrenia (relative risk 2.1, p = 0.002) and other nonaffective psychoses (relative risk 4.6, p = 0.0004).

To our knowledge, only one of these recent studies [34] has directly studied the question of which particular reproductive period (i.e., pregnancy vs. labor-delivery vs. the neonatal period) has significantly elevated total OC scores for the schizophrenia patients. That study found a significant increase for total PCs, a nonsignificant tendency for LDCs and no difference at all for NCs (‘post-partum’ conditions). Researchers’ general lack of focus on timing of the trauma seems surprising, given the highly varied neurodevelopment that occurs in the offspring during the time span from conception and early pregnancy to neonatal life. This lack of focus on reproductive period may be a function of having used OC scales or scoring systems that are not conducive to delineating meaningful OC summary scores for each of these natural temporal epochs [66,69].

2.2. Specific OCs in patients vs. comparison subjects

If researchers have generally neglected the question of reproductive periods, they have instead focused on determining exactly which particular OC significantly characterizes schizophrenia patients. This hunt for the ‘silver OC-bullet’ to solve the riddle of the OC-schizophrenia association and explain the mechanism by which OCs lead to schizophrenia seems rather incongruous, given decades of findings showing that quite a number of different OCs tend to characterize schizophrenia groups. As described in detail earlier, e.g., [42,58], various schizophrenia samples have shown increases in deviant gestational age and perinatal development (e.g., preterm, post-term and small-for-gestational-age status, low birthweight), pre-eclampsia, bleeding during pregnancy, premature rupture of the membranes, prolonged labor, inertia of labor, abnormal fetal presentation at delivery, umbilical cord complications, instrumental delivery, and signs of oxygen deprivation expressed in the varying terminology of fetal distress, hypoxia, asphyxia, anoxia, cyanosis, low Apgar Scores, etc. Prolonged labor was the specific OC that appeared in excess across many different earlier samples of patients [58], and this particular OC bears a striking relationship to brain structural deviations in the ill twins in discordant twin pairs (our study III) (see Section 2.6 below). Our conclusion based on earlier work was that the most likely common denominator of these various OCs is oxygen deprivation [58,59], and this concept continues to be a central focus in subsequent OC research in schizophrenia, e.g., [7,8,16,17,42].

In our studies during the past five years, strong trends (p < .10) were found in study I [66] for increased frequencies of preterm and small-for-gestational-age status, breech delivery, prolonged/precipitous labor, and neonatal asphyxia/cyanosis among the patients. In study II [9], significant increases or strong trends were found for small for gestational age, abnormal delivery presentation, umbili-
cal cord complications and prolonged labor among the patients. In study III [62], the discordant twin pairs were significantly characterized by nonterm (primarily preterm) gestation and prolonged/precipitous labor.

While ours and others' samples were relatively small [59], researchers, e.g., [17] have expressed hope that the recent larger population-based studies would yield greater insight into a more limited range of OCs with specific relevance for schizophrenia. Unfortunately, these studies' findings regarding specific OCs show little congruence, as will be illustrated by the following selected results. Kendall et al. [42] found a significant increase in pre-eclampsia, nons spontaneous delivery, and prolonged hospitalization after birth, with nonsignificant trends toward longer duration of labor and lower birthweight. (These authors commented that "if a composite ‘obstetric complication’ score had been calculated for each mother a substantial case/control difference would have been obtained" (p. 557) [42].) One Swedish study by Dalman et al. [16] found significant increases in pre-eclampsia, vacuum extraction and malformations, while another study by Dalman and colleagues [17] found only asphyxia at birth to be significantly related to schizophrenia in a very large sample (n = 524). Another Swedish study, Hultman et al. [35], found schizophrenia to be associated with maternal bleeding in pregnancy and with two ‘demographic’ characteristics (multiparity and birth in late winter), and additionally among males, small-for-gestational-age status at birth. In Hultman et al.'s other study [34], a significantly elevated risk for schizophrenia was related to toxemia signs, early rupture of membranes, instrumental delivery and dis proportionate (both light and heavy) birthweight per body length and small head circumference at birth, as well as to both young and old maternal age. Logistic regression controlling for the effects of other variables showed independent contributions by early rupture of membranes, older maternal age, disproportionately high birthweight (per body length) and small head circumference. In a Northern Finland study, Jones et al. [41] found significant results showing that schizophrenia patients were born early (with age-appropriate birthweight and placental size), had placental complications, and had signs of perinatal brain damage (measured in postnatal signs). The patients’ mothers had also reported being depressed in gestational trimester 2. Furthermore, in a meta analysis of data from 12 different studies using the Lewis-Murray OC scale (which limits the range of potential OCs [66]), Geddes et al. [23] found a significant association between schizophrenia and both specific LDCs (i.e., premature rupture of membranes and forces delivery) and specific NCs (i.e., short gestational age, low birth weight and use of resuscitation or incubator). The multiplicity of specific OCs found to be related to schizophrenia is especially well illustrated by differences across major studies performed by the same research group in the same location ([16] vs. [17], [34] vs. [35]).

The great contribution of the recent larger studies has been in providing more mathematically certain answers to the question of whether OCs are related to the subsequent development of schizophrenia, and the answer is clearly ‘yes’. Nevertheless, a word of caution seems appropriate concerning the true importance of some of the factors found to be ‘statistically significant’. With the recent powerful scientific designs and major samples, many of the OCs found to significantly characterize schizophrenia (vs. comparison) groups actually represent very few of the patients. For example, Jones et al.'s [41] major findings of low birthweight (p = 0.03) characterized only 7.9% (n = 6) of the patients, the combination of low birthweight and short gestation (p = 0.02) characterized only 5.3% (n = 4), and the placental complications (p = 0.02) were found in only 2.9% (n = 2). Similarly, Hultman et al.'s [35] major finding of maternal bleeding during pregnancy described only 3.6% of the schizophrenia sample, and the small for gestational age status found for males described 7.2% of the total (male plus female) schizophrenia cases. Further, few patients were described by Dalman et al.'s [16] major findings regarding pre-eclampsia (4.6%), vacuum extraction (8.8%) and malformations (6.3%). These rates of specific, highly statistically significant OCs are interesting to compare, for example, with the 52% prolonged labors found in our study of discordant twin pairs (vs. 14% comparison cases) in a much smaller sample [62] (see also Section 2.6 below regarding the relevance of prolonged labor for adult brain structure).

In summary, the findings from the past 40 years clearly suggest that many different specific OCs from all periods of reproduction characterize schizophrenia patients. In the words of Hultman et al. [34] (p. 132), "many different, unspecific OCs, rather than any particular OC, appear to contribute to the increased rate among schizophrenics". It seems increasingly unlikely that a single ‘silver-bullet OC’ will appear, given the plethora and variation of significant specific findings in schizophrenia. A reasonable conclusion would be that different OCs have communality regarding mechanism (e.g., hypoxia) and effect(s) on the developing brain, and that researchers should thus continue their efforts to find such communality across the different specific OCs which characterize patients in the various gestational periods.

2.3. Effects of methodology on study results

Some of the inconsistencies in results found across the various OC studies may be a result of methodological differences, as methodology has clearly been found to influence both the difference between OC rates for patients vs. comparison cases and the manner in which OCs relate to other characteristics of the patients.

2.3.1. Source of OC information

As mentioned above, studies using prospectively recorded OC information (prospective studies, standard-
ized medical records, population registers) have almost unanimously found a significant increase in OCs in schizophrenia patients (vs. controls), while a number of the studies using retrospective parental recall did not find a significant difference [59]. Our recent study IV [13] of OC information obtained through retrospective maternal recall vs. obstetric records showed a considerable discrepancy between the record information and the retrospective reports given (35 years after the deliveries) both by mothers of schizophrenia patients and by mothers of normal control offspring. In both groups, errors of omission (forgetting OCs) were more frequent that errors of commission (augmenting OC histories). Mothers of patients tended (p = 0.06, 2-tailed) to make more retrospective errors than did control mothers, and family history negative cases made significantly more errors of commission (possibly looking for an explanation for the development of schizophrenia in the absence of a family history). Interestingly, this sample of schizophrenia patients had a significant increase in OCs (vs. controls) when OC data were based on medical records, but not when based on retrospective maternal reports.

While these results speak disparagingly for the value of retrospective maternal reports, O’Callaghan et al.’s [76] study supported the veridicality of maternal data, and indeed the results of the twin study III [62] support the conclusion that parents can report OCs of great relevance for the offspring’s future health, when special conditions (such as those attending a known twin reproduction) make the reproduction especially interesting. In the twin study, we found that retrospectively reported OC data related significantly to MPA rates in the twin pairs in adulthood [10], to degree of neurological abnormality in the well co-twins in adulthood [15] and to relative brain structure size differences in the ill vs. well twin in adulthood [67] (see Section 2.6 below). As the parents were not aware of the two twins’ MPA rates, neurological abnormality scores and brain structure characteristics, these findings provide evidence for both the validity of the parental OC reports and the relevance of these OCs for the subsequent somatic characteristics of the twins.

2.3.2. Comparison groups

Most of the published studies which did not find a significant increase in OCs in schizophrenia patients compared the patients with their own siblings [59]. Siblings may tend to be exposed to the same reproductive dystocia (e.g., narrow pelvis, tendency to spontaneous abortion) or life style factors (smoking, poor nutrition), through sharing the same mother as the patient. Further, the patients’ siblings, while not developing schizophrenia, may possibly be negatively influenced in other ways by exposure to OCs. In two separate studies, we found that the increased neurological abnormality found to exist in mentally normal siblings of patients was significantly related to the OC history of the siblings [9,15]. These results might suggest the use of non-relative comparison subjects. On the other hand, the use of extremely large population comparison samples (e.g., Jones et al.’s [41] 10,498 individuals) may lead to identifying ‘significantly increased’ OCs which characterize ‘insignificantly small’ (e.g., only 2%) proportions of the schizophrenia group, as mentioned above.

2.3.3. OC scoring system

Almost all studies of small- to moderate-sized samples have used one or more OC scoring scales to combine and weight the specific OCs. Four different OC scales have been used by schizophrenia researchers [54,69,81,83]. By applying three of these scales (McNeil–Sjöström [69], Lewis–Murray [54] and Parnas et al. [81]) to the very same data set, we demonstrated that the particular OC scale used strongly influenced both the difference in OCs between patients vs. controls [66], and the relationship OCs have to other potential etiological factors such as family history of psychosis and season of birth [65]. The McNeil–Sjöström scale [69] most consistently discriminated schizophrenia patients from controls, while the Parnas et al. scale [81] showed little discriminatory power, and the Lewis–Murray scale [54] actually registered somewhat more OCs in control cases when applied to twin study data [66]. Furthermore, when family history and season of birth for patients were studied in relation to OCs scored by these three scales, the findings ranged from no relationships at all to completely opposite relationships between these variables and OCs, depending on which OC scale was used to score the data. While it would be difficult to say that one particular set of findings is more ‘correct’ than the other, use of our scale found OCs to be increased in schizophrenia patients born in January–April (but not May–December) and in patients with negative (but not positive) family history of psychosis [65]. These findings would thus be theoretically congruent with OCs as one explanation for the season of birth phenomenon (some OCs do have similar seasonal patterns in Scandinavia [14,65]), and with OCs as an alternative to genetic influence in the etiology of schizophrenia. In contrast, the Lewis–Murray scale found OCs to be increased in patients born in May–December (a period during which both OCs and schizophrenia births should be decreased in frequency) and found no relationship between OCs and family history.

The findings of less discriminatory power for the Lewis–Murray scale may be due to its using a yes/no score for ‘1 or more OCs’ among approximately 25 specific conditions [66].

The apparent lesser discriminatory power of this yes/no scoring approach may also have relevance in a broader manner for estimates of the strength of OCs’ contribution to schizophrenia. Geddes and Lawrie [22] conducted an often cited meta-analysis based on data for 20 case-control, one prospective cohort and two historical cohort studies. The authors concluded that the results suggested that “subjects exposed to OCs are twice as likely to develop schizophrenia” (p 786) but that this estimate may be
inflated due to selection and publication biases. Another possibility is that the OR of 2.0 found in this meta analysis is instead deflated, due to the fact that OCs were only classified as present or absent, i.e., the same approach as that used in the Lewis and Murray scale. Our own studies certainly demonstrate that it is the amount of OCs, and not their presence vs. absence, that differentiates schizophrenia patients from demographically similar comparison subjects. An OR based on only a none/some classification of OCs very likely misses much of their importance for the later development of schizophrenia.

2.4. OCs’ relationship to other etiological and background factors

As described above, the particular methodology used to investigate OCs in schizophrenia has strong effects on the results that are obtained. This fact may lie behind the highly varied results that have been obtained when researchers have studied schizophrenia patients’ OCs in relation to other putative etiological factors such as family history of psychosis and season of birth, and in relation to other background factors. For example, OCs were found to have a significantly negative relationship to family history of psychosis in some studies [14,53,77,88], to be unrelated in other studies [56,73,78,84] and positively related in another study [33]. Similarly, OCs have variously been found to be related to birth in January–April [14], May–December [44] or no particular season [78]. With respect to maternal background characteristics, higher parity and maternal age > 34 years were found to be associated with offspring schizophrenia in one study [87], with generally similar findings for offspring bipolar disorder [43]. On the other hand, younger (rather than older) maternal age, lower social class and single parent status were associated with OCs in reproducing women with psychiatric diagnoses [26]. Independent of psychosis, OCs such as pre-eclampsia, lower birthweight, prolonged labor and increased use of anaesthesia are found in nulliparous women, while multiparous women have more uterine inertia, fetal malpresentation, and umbilical cord prolapse [3,86]. Higher maternal age is associated with bleeding in pregnancy, placental abnormality and some forms of chromosomal abnormalities, and in some societal contexts, low social class is associated with generally increased rates of OCs [11].

Given the strong effects of study methodology on the relationships observed between OCs and other variables (Section 2.3 above), it seems prudent to concentrate on the results obtained when a standardized OC scoring system [69] is used to evaluate these relationships. With this approach, we found that increased OCs in schizophrenia patients were related to a) negative family history of psychosis, b) birth in January–April, c) maternal nulliparity and d) age < 35 years, but not e) lower social class [11,14]. Nulliparous mothers of schizophrenia patients (vs. control women) had especially increased rates of LDCs (specifically prolonged and/or precipitous labor, fetal distress, increased possibly harmful analgetics), hypertension, pre-eclampsia, neonatal asphyxia, and small-for-gestational age or dysmaturity in the offspring [11]. The reduced offspring head circumference observed at birth (see Section 4 below) was also significantly characteristic of offspring of these formerly ‘nulliparous’ women, but not of the other mothers.

These results suggest to us that OCs do represent an alternative to genetic influence among patients in representative samples, that at least part of the seasonality of schizophrenia birth rates may be due to seasonal fluctuations in OC rates, and that increased OCs in the mothers of schizophrenia patients occur in association with risk-increasing factors (primarily nulliparity and to some extent lower age) which are not specific for schizophrenia but rather affect reproducing women in general.

2.5. Cause and effect in the OC-schizophrenia relationship

The strong evidence for a relationship between OCs and the later development of schizophrenia, reviewed in Sections 2.1 and 2.2 above, would seem to speak in favor of OCs contributing in some manner to the later development of schizophrenia. Some authors have suggested the alternative possibility that OCs are etiologically irrelevant epiphenomena, caused either by 1) schizophrenia-related behavioral disturbance in the mother, or 2) by preschizophrenic somatic abnormality in the fetus.

1) The above Section 2.4 findings concerning maternal correlates of OCs in schizophrenia are relevant for the question raised by some authors, e.g., [87] of whether there is something behaviorally ‘different’ about the mothers of schizophrenia patients (possibly determined by genetic influence) that causes them to have increased rates of OCs. The strong indication that significantly increased rates of OCs in schizophrenia occur in the presence of a general risk-increasing factor (nulliparity) speaks in favor of the ‘generality’, rather than ‘schizophrenia-specificity’ of the causes of these OCs. Further, even if it were the case that maternal personality or social situation did lead, for example, to heavy smoking, substance abuse, poor nutrition, prolonged labors, preterm delivery and offspring hypoxia, these factors in and of themselves are known to be potentially deleterious to fetal health and development among the general population, e.g., [6,98], and it would be remarkable if such OCs were totally benign and represented only an epiphenomenon when they occurred with significantly increased frequency in individuals later to develop schizophrenia.

2) The possibility that the OCs, and especially the LDCs, observed in schizophrenia are the result, rather than the cause, of fetal abnormality was first raised by Goodman [24,25]. Some authors subsequently concurred in this as a possible interpretation of the increased OCs [31,78], while others did not [21]. For unknown reasons, re-
searchers have seemed content with discussing this idea as a theoretical possibility, rather than subjecting it to empirical test. The concept is nevertheless so central to the relevance of OCs for schizophrenia, that we have conducted explicit empirical tests of the question, using data available in our studies of singletons (I), twins (III) and genetic high-risk cases (VI). The first of these tests was based on Günther-Genta et al.'s [31] proposition that increased rates of umbilical cord complications and abnormal fetal presentation, observed among schizophrenia patients, were an expression of "in utero clumsiness" of the fetus, reflecting previous neurodevelopmental impairment" (p. 168) [31]. As those authors cited our findings of neonatal neurological abnormality in offspring with schizophrenia [61] as evidence for their hypothesis, we based our test on these data, investigating LDCs in relation to neurological abnormality. Opposite to predictions based on Goodman's and Günther-Genta et al.'s hypotheses, we found somewhat lower rates of LDCs among the neurologically abnormal newborns [61]. In our second study of this question [60], we used data from the singleton, twin and high-risk samples to investigate whether LDCs were systematically associated with PCs and signs of fetal abnormality (reduced head circumference, malformations, large within twin pair birthweight differences). The findings were resolutely contrary to the Goodman position: schizophrenia patients with signs of prenatal abnormality did not have more LDCs than other patients, LDCs were not more frequent in genetic-risk cases with malformations than in other risk cases, and patients with an abnormal length of labor actually had significantly fewer PCs and malformations than other patients [60]. We thus find no empirical support for the position that LDCs in pre-schizophrenia individuals are a simple reflection of preexisting fetal abnormality. LDCs thus appear not to be an epiphenomenon but rather an etiological factor in their own right. Nevertheless, LDCs would need not act entirely alone, but may well interact with other factors occurring at earlier or later stages in development, to contribute to subsequent schizophrenia.

2.6. OCs and brain structure deviation in schizophrenia

The monozygotic twin study III permitted the unusual research opportunity to study the relationship between OCs and adult deviations on hippocampi and brain ventricle size in schizophrenia. Suddath et al. had previously studied [93] the brain structure characteristics in a subset of 15 discordant monozygotic twin pairs from this Torrey et al.-based study [95], and found that reduced hippocampi and increased ventricles consistently characterized the ill twin, compared with the well co-twin in adulthood. The twin study design has the notable advantage of controlling for the influence of genetic factors on brain structures within the twin pairs. Question was raised by Suddath et al. as to the origin and timing of this impressive divergence between the brain structures of the ill vs. well twins. A number of studies of discordant monozygotic twins have suggested the importance of LDCs for such discordance [58], and our previous investigation of the OC histories of the discordant pairs clearly identified LDCs as a strong discriminative characteristic of this subgroup of twins (study III, described above). We thus had the opportunity to study OC data in relation to brain structure deviation evaluated by magnetic resonance imaging (MRI) in 22 twin pairs discordant for schizophrenia.

Independently assessed OCs showed statistically significant relationships to both hippocampi and the brain ventricles, in the following specific manner [67]: Especially small right and left hippocampi in the ill twin were each significantly related to increased rates of LDCs only. Further, both especially large right lateral ventricles and large total ventricle size (sum of right, left and third ventricles) were significantly related to increased rates of LDCs, NCs and total OCs. As a single OC variable, prolonged labor showed very strong relationships to reduced hippocampi and increased right and total ventricle sizes in the ill (vs. well) twin. Prolonged labor occurred frequently (75%) and exclusively among ill twins with especially small left hippocampi (p = 0.0003), a brain area of special interest in relation to positive psychotic symptoms in schizophrenia [5]. In contrast, prenatal influences represented by both PCs and MPAs were, if anything, less frequent among ill twins with especially deviant brain structure characteristics.

The question of possible prenatal influences in schizophrenia is of considerable interest, and we now turn to evaluation of this major area of investigation, considering both MPAs and prenatal cerebral development reflected in head circumference at birth.

3. Minor physical anomalies (MPAs)

MPAs are minor structural deviations which are found in numerous areas of the body (head, eyes, ears, mouth, hands, feet) and which are of little general physiological or cosmetic importance [101,102]. MPAs have nevertheless been extensively studied in relation to various forms of psychopathology, because MPAs are considered to represent "indelible fingerprints" of fetal maldevelopment during early pregnancy. Firstly, MPAs develop during the first and possibly second early trimesters of pregnancy, a period of major development of the brain. Secondly, MPAs are typically found in the ectoderm and thus share their embryonic origin with that of the brain [38]. An increased frequency of MPAs in individuals with a given form of psychopathology would thus represent prima facie evidence for early developmental origins of this psychopathology. Indeed, studies have shown that increased rates of MPAs attend a broad range of mental, behavioral and physical disorders, being found to be associated with
hyperactivity, autism, epilepsy, speech and hearing disabilities, learning impairments, poor motor coordination, mental retardation [55], attention deficit disorder, fetal alcohol syndrome, cerebral palsy and schizophrenia [57].

3.1. Mpas in adult schizophrenia patients and their siblings

At least 12 different studies have found increased rates of MPAs in adults with schizophrenia [38], while one other study failed to find a significant increase in patients [2]. Our study of MPAs in monozygotic twins discordant for schizophrenia showed a nonsignificant trend toward higher MPA rates in the ill than the well co-twin [10], in spite of a very high degree of within-pair similarity ($r = 0.77$, $p < 0.001$) on MPA level [10]. This similarity found within monozygotic twin pairs does not characterize pairs of schizophrenia patients and their own normal siblings ($r_s = 0.12$, ns) [38].

Our recent study (II) of MPAs in schizophrenia patients (vs. normal comparison subjects) found statistically significant increases in the patients on both total MPAs and MPAs in each of five specific body areas (global head, eyes, ears, mouth, hands). Patients’ MPAs were also increased in the remaining body area (feet) when investigated with the new MPA items whose inclusion was unique to our study. Interestingly, the normal siblings of these patients had significantly increased rates of MPAs both in total and in eye and mouth regions, but as mentioned above, no intra-familial correlation was found on amount or even specific type of MPAs. A cut-off score for increased MPAs (six or more MPAs) that described only 5% of 75 normal comparison subjects characterized fully 60% of the schizophrenia patients and 38% of their mentally normal siblings [38]. The evidence obtained thus far indicates overwhelmingly that MPAs represent antecedents of schizophrenia.

3.2. Measurement issues and specific mpas

To our knowledge, all but two of the studies investigating MPAs in schizophrenia have exclusively employed the scale developed by Waldrop et al. [101,102] more than 30 years ago. This scale consists of 18 items representing the six body areas mentioned above. Most MPA items are rated as present/absent, while a few items are scored on a graded scale, and the resulting score represents a weighted MPA score. The contents of the Waldrop scale would be expected to be highly relevant for investigations of schizophrenia, since this scale was originally constructed on the basis of Goldfarb and Botstein’s observations of MPAs in childhood schizophrenia patients [50].

Researchers would be hard pressed to find another measure that has yielded such consistent results across studies in schizophrenia research as MPAs measured by the Waldrop scale. Nevertheless, in spite of the great success in characterizing schizophrenia patients, the scale seems to have fallen into partial disrepute among many researchers. The scale has been criticized for being restricted in its scope (many other MPAs also exist) and for being difficult to use, requiring subjective judgments regarding the existence and degree of the MPAs, e.g., [5,97]. (Such criticism is interesting in a research field that lacks a consistent and generally agreed-upon definition of the disease under study, with re-definition with each new DSM-version, and a varying admixture of both specific symptoms and additional criteria across the many systems used to define schizophrenia in the 30 years during which the Waldrop scale has been successfully used.)

Given the criticism of the Waldrop scale, we recently conducted a study of MPAs in schizophrenia, using both the Waldrop scale and 23 additional MPA items in the same body areas. The new items were chosen on the basis of pediatric sources [27,52,91]. Our study [38] showed that both Waldrop scale items and the ‘new scale items’ identified significantly higher rates of MPAs in the patients. The Waldrop scale found significant increases in MPAs in total as well as in head, eyes, ears, mouth and hand areas, while the new scale items found significant increases in total and in all specific areas except the ears. Furthermore, the patients showed an increased frequency (at $p < 0.02$, 2-tailed) on 14/41 specific items; eight of these 14 came from the Waldrop scale, while the remaining six were new items.

Logistic regression analysis was used for the purpose of determining which specific MPA items best discriminated patients from comparison subjects, and we found that five specific items made independent contributions (at $p < 0.05$) [38]: the three strongest items (curved fifth finger, $p = 0.001$; epicanthus, $p = 0.008$; high/steepled palate, $p = 0.01$) all came from the Waldrop scale, while the remaining two items (hyperconvex fingernails, $p = 0.03$; thin upper lip, $p = 0.05$) came from the new scale. New scale MPAs, while significantly more frequent among patients than comparison subjects, thus did not have the same capacity to discriminate patients from normal comparison subjects as did the Waldrop scale items. In addition, greater differences were found between the normal siblings of the patients vs. the comparison subjects on the Waldrop items than on the new scale items. With respect to reliability, we have found quite satisfactory interrater reliability on the Waldrop scale, including on specific quantitative items such as curved fifth finger and head circumference, when the assessors train together and develop agreement as to the operational criteria that are to be used. Our opinion is that the Waldrop scale is much better than the reputation it seems to have received among some researchers, and that careful training of raters prior to the study will increase the value of the MPA data obtained.

The most outstanding work on MPAs in schizophrenia has undoubtedly been done by the Dublin group (Lane, Waddington, O’Callaghan, et al.), who have used not only
the Waldrop scale but also actual anthropometric measurements of distances between, e.g., 40 landmarks in the trunk, limb, head and face, to describe body size and shape in schizophrenia patients vs. controls [50, 51, 85]. While our logistic regression model correctly classified 73% of the patients and 85% of the comparison subjects (overall 80% correct) [38], the Dublin group’s models correctly classified 85% of the patients and 57% of the controls (overall 71%) in one data set [50] and 89% of male patients vs. 58% male controls, and 88% female patients vs 79% female controls using other data [85]. The Dublin studies have demonstrated, among other things, a widespread disproportionality in various body areas such as the trunk, limbs (including lower leg), head and face, witnessing general early developmental disruption in schizophrenia. Those authors have focused on the importance of a particular cranio-facial profile as central to schizophrenia, identifying "an overall narrowing and elongation of the mid-facial and lower facial region with widening of the skull base and extensive abnormalities of the mouth, ears and eyes" (p. 1160) [50]. While our study lacks these sophisticated anthropomorphic measurements, our results certainly concur (along with others) in identifying high/steeped palate and epicanthus as important discriminating characteristics of patients with schizophrenia. These two specific MPAs (among many others) significantly characterized the patients vs. controls in both the Dublin sample (p < 0.001, p < 0.001, respectively) and our sample (p < 0.0001, p = 0.0003), but a word of caution is nevertheless indicated: These two MPAs tended to be found with relatively high frequency in the normal controls in both studies (53% of Dublin controls had high/steeped palate and 40% had epicanthus; 19 and 3% of Malmö controls had these respective MPAs). Furthermore, our patients’ normal siblings showed increased rates of both high/steeped palate (52%) and epicanthus (24%) that were identical to the rates in the patients (52 and 23%, respectively) [38]. Notably, these MPAs did not generally occur in patients and siblings in the same families, suggesting that these MPAs are related to schizophrenia in a broader sense but not necessarily to the actual development of the disease per se.

3.3. MPA’s relationship to other etiological and background factors

MPAs are generally known to result from both genetic and early environmental factors [91, 103], and studies of background factors for MPAs in schizophrenia have shown highly inconsistent results. Family history of psychosis has shown everything from significant positive relationships [79], to independence [2, 29] to significant negative relationships [30]. Similar positive [30, 79], neutral [57] and negative [49] relationships have been found to male gender. Parental social class was unrelated to MPA rate in one study [55], while our (unpublished) study found maternal age to be positively related to patients’ MPA rates. Two of our studies found PCs to be related to increased rates of MPAs in patients [10]. An important question concerns whether the reasons for the occurrence of increased rates of MPAs in individuals later developing schizophrenia are in some manner related to schizophrenia (e.g., reflect schizophrenia-related genetic influence) vs. reflect the same malformation-increasing factors (e.g., increased maternal age) as in the normal population. The significant increase in the same Waldrop-type MPAs in other mental disorders [55, 57] and the inconsistent results to date regarding MPA-background factors in schizophrenia might favor the latter interpretation. Nevertheless, additional study of this question is clearly desirable before drawing any firm conclusions.

3.4. MPAs’ relationship to later characteristics of the patients

If MPAs do (as hypothesized) reflect widespread developmental disturbances occurring at the time of important prenatal brain development, then one might expect to find relationships between increased rates of MPAs in subgroups of patients and increased deviations on neurological, cognitive and psychiatric clinical characteristics. The results to date have been generally negative or inconsistent. With one exception [28], age of onset has consistently been found not to be lower in patients with high MPA rates [40]; and abnormal premorbid personality is not consistently associated with MPAs [2, 32, 57]. Various studies have found MPAs to be unrelated to positive and/or negative symptoms [55, 57, 95], positively related to negative symptoms [80], and positively related to number of admissions [57], but not to chronicity [74] or duration of illness [2, 95]. Results concerning the relationship between increased MPAs and cognitive disorder are similarly inconsistent, with four studies finding no relationship and three others finding positive relationships [40]. Two other studies found a relationship to one particular test, such as trail making B [75] or graphesthesia [57]. Premorbid intelligence was related to MPA level in one study [80] but not in another from the same year [57].

In our own study [40], we found no relationship at all between increased MPAs in schizophrenia patients and their neurological, cognitive or clinical disturbance characteristics. The three studies to date [40, 74, 95] have thus failed to find a relationship between MPAs and adult neurological abnormality. Furthermore, the increased MPA levels in the normal siblings of our patients were not related to the increased cognitive and neurological abnormality found in these siblings [39, 40].

Given the general inconsistency or lack of relationships between MPA level and the particular neurological, cognitive and clinical characteristics of patients with schizophrenia, two basic interpretations suggest themselves: One possibility is that the early abnormal development opera-
tionally represented by these MPAs reflects an early developmental trajectory toward later mental abnormality, but that many other factors intervene during the subsequent decades of the individual’s development, to determine the specific adulthood form of mental abnormality reflected in the individual patients’ psychiatric clinical, cognitive and neurological characteristics. In such a case, any direct specific relationship between early MPAs and later individual characteristics of the patients would be distorted, due to subsequent intervening influences. Another possibility is that the MPAs, observed to characterize, e.g., 60–85% of schizophrenia patients [38,50,51,85], in reality only reflect a small portion of the truly relevant cerebral dysmorphogenesis in schizophrenia, that cerebral dysmorphogenesis is generally pervasive across schizophrenia patients, and that such pervasive dysmorphogenesis (if existing) would, by definition, not identify only a subgroup of patients with specific clinical, cognitive or neurological deviations. A theoretically possible third interpretation of the lack of relationship between MPA level and specific deviations. A theoretically possible third interpretation of the lack of relationship between MPA level and specific characteristics of the individual patients is that the MPAs are entirely irrelevant for schizophrenia, but this seems highly unlikely given the extremely high rates in such patients.

In a final look at early somatic abnormality, we turn to head circumference (HC) at birth.

4. Head circumference (HC) at birth

HC reflects the growing mass within the skull and the elasticity of the skull, and is thus standardly measured for purely clinical reasons by both obstetricians and pediatricians early in children’s lives. Abnormally small or large HC is one of the Waldrop scale MPAs, and has been measured in adulthood in most studies of schizophrenia patients. As MPAs are intended to reflect early prenatal development, researchers have apparently assumed that adult head circumference will adequately reflect prenatal cerebral development. However, findings from our recent study (II) seriously challenge this assumption. We found no correlation at all (r = 0.06, n.s.) between HC at birth and HC in adulthood for schizophrenia patients in study II, and a vast majority of the patients changed ‘head size group’ (small, medium, large) from neonatal age to adulthood [12]. This may very well reflect the fact that two-thirds of normal head growth takes place during the first two years of postnatal life [72]. Furthermore, in schizophrenia research, at least two studies (including ours) show disproportionately large HC in adult male schizophrenia patients [4,12].

The questionable value of adult HC as a measure of prenatal cerebral development has intensified scientific attempts to measure HC at birth, employing prospectively recorded information in medical records available in Sweden and Japan. Our group was the first to find that schizophrenia patients have significantly reduced HC at birth, compared with demographically similar comparison neonates from the same hospital delivery series [63]. Of particular importance, the reduced HC was not the result of the reduced gestational age frequently characterizing schizophrenia patients, and patients’ HC was shown to be disproportionately small in relation to body length. A reduction in HC at birth in schizophrenia was subsequently confirmed by four other studies of schizophrenia patients [12,34,37,47], while another recent study failed to find a significant reduction in patients [35]. In two of the subsequent studies [12,47], HC was reduced even with gestational age controlled, confirming our original finding. We later found that reduced HC at birth also significantly characterized patients with other similar psychosis diagnoses (schizo-affective disorder, unspecified functional psychosis) [64].

Attempts have been made to determine the origins of this reduction in prenatal cerebral development. The possibility that reduced HC at birth had resulted from extended head compression during prolonged labor (suggested by Schwarzkopf et al. [88]) was disproven, when no systematic relationship was found between length of labor and HC at birth in schizophrenia patients [63]. Our original findings suggested the influence of some nongenetic factor, as reduced HC at birth was significantly characteristic of schizophrenia patients with a negative family history of psychosis [63]. In contrast, Kunugi et al. [46] found reduced HC to be more characteristic of family-history-positive than family-history-negative cases, although HC was significantly reduced in both subgroups. Investigations in first degree relatives of patients have yielded no certain evidence of a genetic component, in that siblings of schizophrenia patients do not have reduced HC at birth [Cantor-Graae et al., unpub], and newborn offspring of women with schizophrenia do not show disproportionately small HC at birth [68]. Recent results from Japan [37] show, however, that HC for schizophrenia patients (which was smaller than that for control cases) was not smaller than HC for their own siblings. With respect to possible trauma during gestation, we found no relationship between reduced HC and identifiable PCs [63], although Hultman et al. [34] found that female patients with small HC had more OCs (of unspecified timing). On the other hand, our results show a very strong relationship between reduced HC and first-born status in schizophrenia patients [11], and four different studies [34,47,63,64] found reduced HC to be most characteristic of female patients (compared with same-sexed controls). In our recent study II, reduced HC at birth showed no relationship to other measures of prenatal disturbance such as MPAs and dermatoglyphic anomalies in schizophrenia patients [11]. Clearly, the origins and significance of this potentially valuable measure of prenatal cerebral development require further investigation.

In summary, considerable evidence has been amassed for the role of various forms of early somatic trauma and

dysmorphogenesis in the later development of schizophrenia. That OCs, MPAs and reduced HC at birth are in some manner related to this development is by now confirmed beyond the shadow of a doubt. However, the particular manner in which this occurs, how these factors relate to other seemingly important putative etiological factors, and what particular transitory or lasting effects these have on both the early developing brain and the brain of the adult patient with manifest schizophrenia remain to be solved. Special studies such as that demonstrating a strong relationship between LDCs/prolonged labor and diminished hippocampi in ill twins in monozygotic pairs discordant for schizophrenia [67] may be especially instructive in these attempts. While scientific interest in many schizophrenia-related phenomena frequently seems to blossom and quickly fade over time, the increasingly intense research on OCs, MPAs and head circumference at birth witnessed in schizophrenia research during the past several years would clearly demarcate this area as one of the most vital spheres of activity in international schizophrenia research.

Acknowledgements

Our research has been supported by grants from the Swedish Medical Research Council (No. 3793); the Theodore and Vada Stanley Foundation, USA; the NIH (No. MH18857); the Medical Faculty, Lund University; and the Söderström–König Foundation, Sweden.

References


