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The Nature of Dopamine Dysfunction in Schizophrenia and What This Means for Treatment

Meta-analysis of Imaging Studies

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Context: Current drug treatments for schizophrenia are inadequate for many patients, and despite 5 decades of drug discovery, all of the treatments rely on the same mechanism: dopamine D_2 receptor blockade. Understanding the pathophysiology of the disorder is thus likely to be critical to the rational development of new treatments for schizophrenia.

Objective: To investigate the nature of the dopaminergic dysfunction in schizophrenia using meta-analysis of in vivo studies.

Data Sources: The MEDLINE, EMBASE, and PsycINFO databases were searched for studies from January 1, 1960, to July 1, 2011.

Study Selection: A total of 44 studies were identified that compared 618 patients with schizophrenia with 606 controls, using positron emission tomography or single-photon emission computed tomography to measure in vivo striatal dopaminergic function.

Data Extraction: Demographic, clinical, and imaging variables were extracted from each study, and effect sizes were determined for the measures of dopaminergic function. Studies were grouped into those of presynaptic function and those of dopamine transporter and receptor availability. Sensitivity analyses were conducted to explore the consistency of effects and the effect of clinical and imaging variables.

Data Synthesis: There was a highly significant elevation ($P < .001$) in presynaptic dopaminergic function in schizophrenia with a large effect size (Cohen $d = 0.79$). There was no evidence of alterations in dopamine transporter availability. There was a small elevation in $D_{2/3}$ receptor availability (Cohen $d = 0.26$), but this was not evident in drug-naive patients and was influenced by the imaging approach used.

Conclusions: The locus of the largest dopaminergic abnormality in schizophrenia is presynaptic, which affects dopamine synthesis capacity, baseline synaptic dopamine levels, and dopamine release. Current drug treatments, which primarily act at $D_{2/3}$ receptors, fail to target these abnormalities. Future drug development should focus on the control of presynaptic dopamine synthesis and release capacity.

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SCHIZOPHRENIA REMAINS ONE OF the leading causes of global disease burden in adults despite more than 50 years of drug development.[1] Understanding its neurobiology is critical for future rational drug discovery.[2,3] The dopamine hypothesis of schizophrenia was first proposed more than 30 years ago on the basis of indirect evidence. It received support from studies of postmortem brain tissue that found increased striatal $D_{2/3}$ receptor density and dopamine levels in patients with schizophrenia and from studies of dopamine and its metabolites in cerebrospinal fluid.[4-8] However, postmortem studies are not able to measure some aspects of the dopaminergic function, such as dopamine release, and are potentially biased by the effects of antipsychotic treatment and agonal events, whereas the cerebrospinal fluid studies were inconsistent and unable to provide insights into the regional aspects of dopamine dysfunction.[9-11] The introduction of positron emission tomographic (PET) and single-photon emission computed tomographic (SPECT) imaging enabled the investigation of in vivo cerebral dopamine neurotransmission free of these limitations.[11-13]

Positron emission tomographic imaging and SPECT imaging have been used to investigate dopaminergic parameters in schizophrenia, beginning with studies of

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$D_{2/3}$ receptors[14,15] and later covering presynaptic function, including dopamine synthesis capacity, dopamine release, and transporters[16-19] (see eAppendix [http://www.archgenpsychiatry.com] for further background on these approaches). To our knowledge, there has not been a previous meta-analysis of the presynaptic or dopamine transporter findings in schizophrenia, and since the previous $D_{2/3}$ meta-analysis in drug-free or drug-naive patients,[20] there have been a large number of new studies, which approximately doubles the sample size.

The purpose of our meta-analysis is to synthesize the PET and SPECT imaging findings on dopaminergic function in schizophrenia and to consider their implications for the treatment of schizophrenia. We focus on the striatum because it has the highest density of dopamine projections in the brain[21] and because dopaminergic dysfunction in the striatum can be reliably imaged and has been linked to the severity of symptoms, response to treatment, and the onset of the disorder.[22-25] We group findings into studies of presynaptic dopaminergic function (dopamine synthesis capacity, dopamine release, and synaptic dopamine levels), dopamine transporter availability, and dopamine receptor availability. The studies of dopamine synthesis capacity are grouped with those of dopamine release and synaptic dopamine levels (which use pharmacological challenges that either deplete or release dopamine from presynaptic terminals) because animal[26-28] and in vivo human evidence[29] indicates that they index related aspects of dopaminergic function. However, the results are also given separately for these different methodological approaches for comparison. Researchers can view the study data on, and add future studies to, our open-access database and wiki (http://www.schizophreniadata.com).

METHODS

DATA SOURCES AND STUDY SELECTION

The PubMed, PsycINFO, and MEDLINE electronic databases were searched in their entirety from January 1, 1960, to July 1, 2011. To be included in the meta-analysis, an article needed to report in vivo PET or SPECT imaging findings on striatal dopaminergic function in patients with schizophrenia and a control group, including the mean and standard deviations for both groups. Current antipsychotic treatment was an exclusion criterion for the studies of dopamine receptors because this affects dopamine receptor binding potential[30] (see eFigure 1 for search results and eAppendix for further details on the search and inclusion-exclusion criteria).

DATA EXTRACTION

The main outcome measure was the difference in the dopaminergic imaging parameter between healthy controls and patients with schizophrenia. The following additional information was extracted from all the studies: authors, year of publication, population characteristics of the control and patient groups (group size, age, sex, antipsychotic use, diagnosis, and symptom ratings), characteristics of the PET or SPECT imaging (radiotracer and other methodological factors reported), scanner characteristics (scanner type and resolution), and modeling method.

DATA ANALYSIS

Separate meta-analyses were conducted for the studies of presynaptic dopaminergic function, dopamine receptors, and dopamine transporters. The standardized effect sizes of the individual studies were entered in a random-effects meta-analytic model.[31,32] The summary effect sizes (Cohen *d*) were computed using a restricted maximum-likelihood estimator.[33] Publication bias was assessed using funnel plots. Heterogeneity was assessed by calculating the I^2 value (I^2 values <50% indicate low to moderate heterogeneity, whereas I^2 values >50% indicate moderate to high heterogeneity).[34] Leave-one-out sensitivity analyses were conducted. Sources of bias and heterogeneity were evaluated using meta-regression (for publication year and age) and subgroup analyses (for antipsychotic treatment, illness duration, and imaging approach). A significance level of $P<.05$ (2-tailed) was used for all analyses (see eAppendix for further methodological details).

RESULTS

PRESYNAPTIC DOPAMINERGIC FUNCTION

A total of 17 studies described in 15 publications (3 studies reported in 1 article[25]) met inclusion criteria. We excluded one of our articles[35] from the main analysis because it reports additional data on the same subjects included in a previous report,[36] although the data are used in subanalyses in which there is no subject duplication, and another article was excluded because the comparator group was siblings.[37] Overall, the studies include a total of 231 patients and 251 controls. Study details are reported in eTables 1 and 2. There was a significant elevation in schizophrenia, with a summary effect size of $d=0.79$ (95% CI, 0.52-1.07; $z=5.65$; $P<.001$; **Figure 1**).

HETEROGENEITY AND SENSITIVITY ANALYSES

The I^2 value was 39.92% (95% CI, 0.00%-77.03%), indicating low to moderate heterogeneity between studies. Although the regression test for funnel plot asymmetry was not significant ($z=1.52$, $P=.13$), a visual inspection of the funnel plot revealed asymmetry, indicating possible publication bias. The trim-and-fill analysis indicated that there were 3 potentially missing studies on the left side of the funnel plot (all with large standard errors and small effect sizes; eFigure 2). Nevertheless, the summary effect size remained large and highly significant after correcting for these putatively missing studies (corrected effect size: $d=0.67$ [95% CI, 0.37-0.94]; $z=4.55$, $P<.001$; $I^2=48.83\%$ [95% CI, 10.17%-81.01%]).

The summary effect size reached significance in all cases in the leave-one-out analysis, with summary effect sizes varying from $d=0.73$ to $d=0.86$ (all $P<.001$). Meta-regression indicated that there was no influence of year of publication ($\beta=-0.02$; $F_{1,13}=0.99$; $P=.34$) or subject age ($\beta=0.004$; $F_{1,12}=0.015$; $P=.90$). In case current antipsychotic drug treatment confounded the results, the meta-analysis was rerun exclusively for studies of drug-free or drug-naive patients. This showed a significant elevation in drug-free or drug-naive patients compared with

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Study	Year	Standard Effect	(95% CI)	z Score	P Value
Reith et al[19]	1994	1.5194	(0.3748-2.6640)	2.6018	.009
Hietala et al[44]	1995	0.9004	(−0.1639 to 1.9647)	1.6581	.10
Dao-Castellana et al[45]	1997	0.3508	(−0.7480 to 1.4495)	0.6257	.53
Breier et al[43]	1997	0.8766	(0.0201-1.7330)	2.0060	.045
Lindström et al[46]	1999	1.0054	(0.1152-1.8957)	2.2136	.03
Hietala et al[47]	1999	1.0246	(0.1486-1.9005)	2.2924	.02
Laruelle et al[25]	1999	0.9132	(0.4207-1.4058)	3.6342	<.001
Elkashef et al[38]	2000	−0.1313	(−0.8375 to 0.5749)	−0.3644	.72
Abi-Dargham et al[36]	2000	1.0847	(0.3849-1.7844)	3.0382	.002
Meyer-Lindenberg et al[40]	2002	1.8245	(0.4779-3.1711)	2.6556	.008
McGowan et al[48]	2004	1.5549	(0.7028-2.4070)	3.5766	<.001
Kumakura et al[39]	2007	0.0990	(−0.7595 to 0.9576)	0.2261	.82
Nozaki et al[49]	2009	0.1329	(−0.5046 to 0.7704)	0.4087	.68
Howes et al[41]	2009	1.1849	(0.2484-2.1215)	2.4797	.01
Kegeles et al[42]	2010	0.6136	(−0.0549 to 1.2821)	1.7989	.07
Summary		**0.7919**	**(0.5173-1.0666)**	**5.6518**	**<.001**

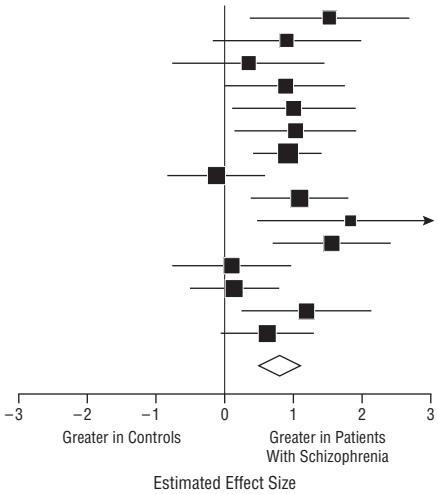

Figure 1. Studies of presynaptic dopaminergic function.[19,25,36,38-49] The forest plot shows the effect sizes and 95% CIs of the difference between patients with schizophrenia and controls, by study. There was evidence of a significant elevation in schizophrenia with a summary effect size of d=0.79 (diamond).

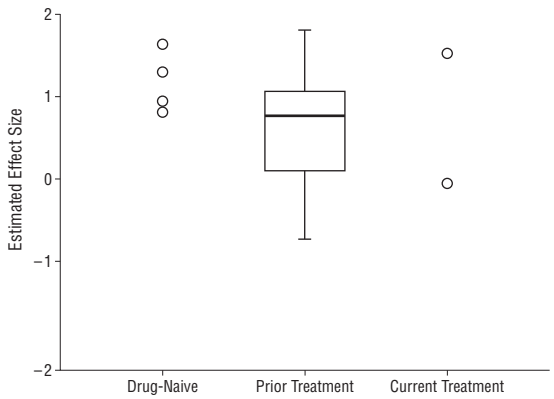

Figure 2. Effect sizes for studies of presynaptic dopaminergic function, by antipsychotic treatment history. In the box plot, the horizontal line represents the median, the whiskers indicate the lowest and highest data points that are within 1.5 the interquartile range, and data outside this range (circles if present) are regarded as potential outliers.

controls (n=13, d=0.69 [95% CI, 0.36-1.01]; z=4.14; P<.001; I^2=46.46% [95% CI, 0.00%-85.31%]). The effect sizes for the studies grouped by antipsychotic treatment are shown in **Figure 2**.

The effect sizes grouped by imaging method are shown in eFigure 3. There was a significant elevation in schizophrenia when the meta-analysis was restricted to the studies using radiolabeled L-3,4-dihydroxyphenylalanine (dopa) (n=11; d=0.78 [95% CI, 0.38-1.18]; z=3.82; P=.0001; I^2=52.62% [95% CI, 3.19%-84.02%]). The effect sizes were similarly positive in the studies of dopamine release (d=1.35 in Abi-Dargham et al,[50] d=0.88 in Breier et al,[43] and d=0.91 in the Laruelle et al[25] report combining 3 cohorts) and in the studies of synaptic dopamine levels (d=1.09 and d=0.61), but there were too few studies to rerun the meta-analysis separately for these approaches.

DOPAMINE TRANSPORTER

Eleven studies met inclusion criteria, providing data on a total of 152 patients and 132 healthy controls. Study details are shown in eTables 3 and 4. There was no evidence of a significant difference between patients with schizophrenia and controls (d=−0.34 [95% CI, −0.75 to 0.07]; z=−1.64; P=.10; **Figure 3**).

HETEROGENEITY AND SENSITIVITY ANALYSES

The I^2 value was 64.04% (95% CI, 25.22%-88.99%), indicating moderate to large heterogeneity between studies. There was no evidence for publication bias (regression test for funnel plot asymmetry: z=−1.75; P=.08; no missing studies estimated by trim-and-fill analysis; see eFigure 4 for the funnel plot) and no significant effect of year of publication (β=−0.01; $F_{1,9}$=0.04; P=.85) or age (β=0.02; $F_{1,9}$=0.25; P=.63) on the effect size. The subgroup analyses found no group differences (eAppendix).

DOPAMINE RECEPTORS

$D_{2/3}$ Receptors

Twenty-two studies met inclusion criteria, providing data on 337 patients and 324 healthy controls (data from Wong et al[15] form part of a subsequent larger data set[62]). The population characteristics and methodological details of the studies are shown in eTables 5 and 6. There was a significant elevation in schizophrenia with a summary effect size of d=0.26 (95% CI, 0.001-0.52; z=1.97; P=.049; **Figure 4**).

Heterogeneity and Sensitivity Analyses

The I^2 value was 63.93% (95% CI, 39.65%-84.81%), indicating moderate to large heterogeneity between stud-

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Study	Year	Standard Effect	(95% CI)	z Score	P Value
Laakso et al[51]	2000	0.0928	(−0.8317 to 1.0172)	0.1967	.84
Laruelle et al[52]	2000	−0.3836	(−0.9674 to 0.2002)	−1.2879	.20
Laakso et al[53]	2001	−0.9534	(−1.9876 to 0.0807)	−1.8070	.07
Lavalaye et al[54]	2001	0.0655	(−0.8112 to 0.9423)	0.1465	.88
Hsiao et al[55]	2003	0.2097	(−0.5926 to 1.0121)	0.5123	.61
Yang et al[56]	2004	0.0445	(−0.7737 to 0.8627)	0.1066	.92
Yoder et al[57]	2004	−0.0156	(−0.8921 to 0.8610)	−0.0348	.97
Mateos et al[58]	2005	−1.6997	(−2.5722 to −0.8272)	−3.8183	<.001
Mateos et al[59]	2007	−1.2643	(−1.9963 to −0.5322)	−3.3849	<.001
Schmitt et al[60]	2008	−0.4463	(−1.1703 to 0.2776)	−1.2083	.23
Arakawa et al[61]	2009	0.7214	(−0.2007 to 1.6436)	1.5334	.13
Summary		**−0.3376**	**(−0.7412 to 0.0661)**	**−1.6392**	**.10**

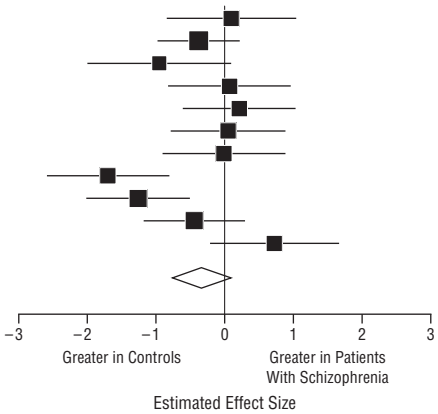

Figure 3. Studies of dopamine transporter availability.[51-61] The forest plot shows the effect sizes and 95% CIs of the difference between patients with schizophrenia and controls, by study. The 95% CI for the summary effect size (diamond; d=0.34) includes 0, indicating no significant difference between patients with schizophrenia and controls.

Study	Year	Standard Effect	(95% CI)	z Score	P Value
Crawley et al[67]	1986	0.8889	(0.0665-1.7113)	2.1185	.03
Farde et al[14]	1990	0.3447	(−0.2968 to 0.9862)	1.0532	.29
Martinot et al[68]	1990	0.1116	(−0.6892 to 0.9124)	0.2732	.78
Martinot et al[64]	1991	0.3969	(−0.3000 to 1.0939)	1.1163	.26
Tune et al[62]	1993	1.6024	(0.8974-2.3075)	4.4548	<.001
Hietala et al[69]	1994	0.3337	(−0.4963 to 1.1637)	0.7879	.43
Martinot et al[65]	1994	0.0000	(−0.8765 to 0.8765)	0.0000	.99
Pilowsky et al[70]	1994	−0.1042	(−0.7244 to 0.5161)	−0.3292	.74
Pedro et al[71]	1994	0.0927	(−0.6667 to 0.8522)	0.2393	.81
Nordström et al[66]	1995	0.7003	(−0.3790 to 1.7796)	1.2717	.20
Laruelle et al[72]	1996	0.5116	(−0.2412 to 1.2644)	1.3319	.18
Okubo et al[63]	1997	0.2188	(−0.4460 to 0.8836)	0.6450	.52
Breier et al[43]	1997	0.0000	(−0.8181 to 0.8181)	0.0000	.99
Abi-Dargham et al[50]	1998	0.0457	(−0.6701 to 0.7614)	0.1251	.90
Abi-Dargham et al[36]	2000	0.3154	(−0.3420 to 0.9727)	0.9402	.35
Yang et al[56]	2004	−0.1397	(−0.9588 to 0.6795)	−0.3342	.74
Talvik et al[73]	2006	−0.2016	(−0.8661 to 0.4630)	−0.5945	.55
Corripio et al[74]	2006	2.3291	(1.3689-3.2892)	4.7543	<.001
Schmitt et al[75]	2009	−0.9150	(−1.6895 to −0.1404)	−2.3153	.02
Kessler et al[76]	2009	−0.4429	(−1.2888 to 0.4030)	−1.0261	.03
Kegeles et al[77]	2010	0.0735	(−0.5800 to 0.7271)	0.2205	.83
Kegeles et al[42]	2010	0.0155	(−0.5825 to 0.6134)	0.0507	.96
Summary		**0.2587**	**(0.0010-0.5165)**	**1.9674**	**.05**

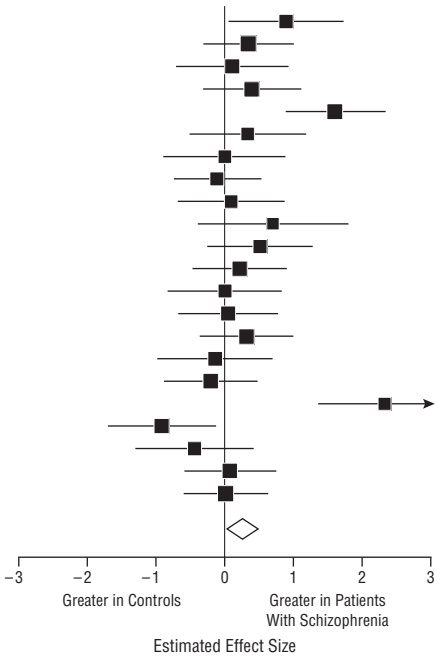

Figure 4. Studies of $D_{2/3}$ receptor availability.[14,36,42,43,50,56,62-77] The forest plot shows the effect sizes and 95% CIs of the difference between patients with schizophrenia and controls, by study. There was evidence of a small increase in D_2 receptor availability in schizophrenia with a summary effect size (diamond) of d=0.26.

ies. There was no evidence for publication bias (regression test for funnel plot asymmetry: z=1.32; P=.19; no missing studies estimated by trim-and-fill analysis; see eFigure 5 for the funnel plot) and no significant effect of year of publication (β=−0.03; $F_{1,19}$=2.27; P=.15) or age (β=0.01; $F_{1,18}$=0.34; P=.57) on the effect size.

In the leave-one-out analysis, the effect sizes varied from d=0.18 to d=0.32 (with P values from .11 to .01, respectively) and were not significant on 14 of the 22 iterations. We repeated the meta-analysis, including a study[78] initially excluded owing to the relatively short antipsychotic drug washout period, and found a nonsignificant effect size of d=0.25 (95% CI, −0.01 to 0.51; z=1.8753; P=.06; I^2=62.75% [95% CI, 38.65%-84.13%]). The subgroup analyses identified no significant difference between patients and controls in studies exclusively of antipsychotic-naive patients or in studies that used benzamide radiotracers, whereas significant differences were found in studies that included patients who had received prior antipsychotic treatment or that used butyrophenone radiotracers (see eAppendix for these analyses and comparisons of illness duration between subgroups).

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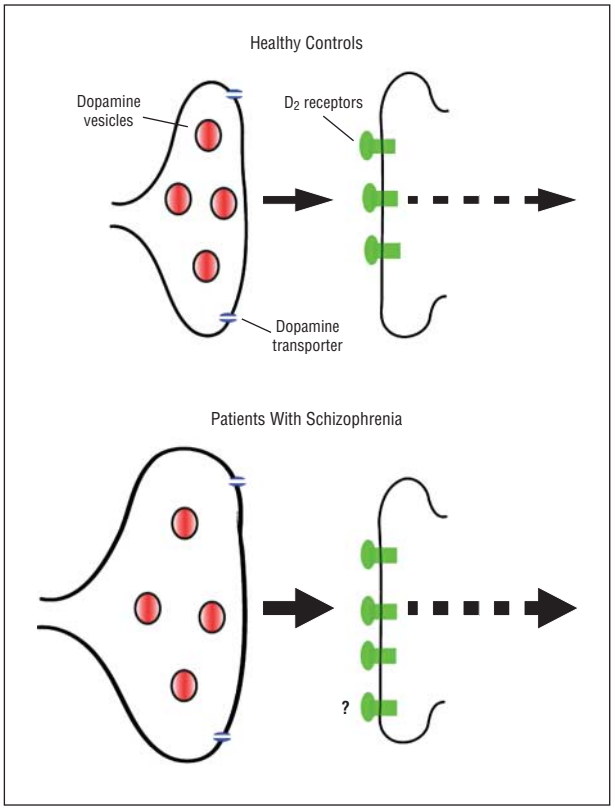

Figure 5. Schematic diagram summarizing the findings from our meta-analyses of dopamine function in schizophrenia. The diagram shows that the major dopaminergic abnormality in schizophrenia is presynaptic. The main findings from our meta-analyses are that presynaptic dopaminergic function is altered in schizophrenia, with a large effect size (d=0.79), and that there is no difference in dopamine transporter availability and a small elevation in $D_{2/3}$ receptor availability, although the latter finding was not consistent.

Other Dopamine Receptors

We identified 4 studies of D_1 receptor availability in untreated patients,[63,79-81] too few to permit meta-analysis. None of these found a significant difference in striatal D_1 availability between patients with schizophrenia and controls, although one study[81] found a trend toward an increase in antipsychotic-naive patients but not drug-free patients (see eAppendix for overview).

STRIATAL SUBREGIONS

We repeated the meta-analyses for the caudate and putamen separately. In the studies of presynaptic function, there was a significant elevation in schizophrenia for the putamen (see eAppendix for details: d=0.51 [95% CI, 0.14-0.88]; z=2.72; P=.007) but not the caudate. There were no significant differences in the caudate or putamen between patients and controls in the studies of dopamine transporter or $D_{2/3}$ receptor availability (see eAppendix for details).

COMMENT

The main findings from our meta-analyses are that presynaptic dopaminergic function is altered in schizophrenia, with a large effect size (d=0.79), and that there is no difference in dopamine transporter availability and a small elevation in $D_{2/3}$ receptor availability, although the latter finding was not consistent. These findings are summarized schematically in **Figure 5**.

METHODOLOGICAL CONSIDERATIONS

One methodological consideration common to all meta-analyses is that they are limited by the quality of the studies that are included. We included all relevant studies and did not apply quality screening because this may introduce other biases, although this involves pooling findings from studies using different radiotracers, scanners, and methods of data collection and pharmacokinetic analysis. We have summarized these variables (eTables 1-6) to enable readers to make judgments about individual studies. Although including all studies has the advantage of reducing selection biases and increasing the generalizability of findings, there is a risk of diluting effects.

There was low to moderate heterogeneity in the studies of presynaptic dopaminergic function, which suggests that there is consistency across studies. However, there was moderate to large heterogeneity in the studies of dopamine transporter and $D_{2/3}$ receptor availability. Potential sources for this were evaluated in secondary analyses and are discussed herein. Nevertheless, because the random-effects model used in the meta-analyses does not assume homogeneity of effects, our findings should be robust to heterogeneity.

Presynaptic Dopaminergic Function

Although the trim-and-fill analysis indicated that there may be missing studies, the elevation in patients remained large and highly significant after correcting for putatively missing studies. There was a highly significant and large effect size in all the iterations of the leave-one-out analysis, which indicates that the elevation in presynaptic dopaminergic function was not dependent on the inclusion of any one study. We found a large positive effect size when the meta-analysis was restricted to studies that used radiolabeled dopa to index dopamine synthesis capacity, and although there were insufficient studies to permit separate meta-analyses, there were similar positive effect sizes in the studies that used α-methylparatyrosine or amphetamine challenges, which suggests that the elevation is consistent across technique. The elevation was evident when studies of patients currently receiving antipsychotic treatment were excluded from the meta-analysis, which indicates that antipsychotic treatment is unlikely to explain the effect. We cannot, however, exclude the possibility that prior treatment had a persistent effect in the studies of drug-free patients, although Figure 2 indicates that, in absolute terms, the effect sizes were at least as great in the studies of drug-naive patients as in the studies of patients who had received prior treatment, which suggests that this is not the case.

The radiolabeled dopa studies used several different analytic and imaging methods, including the simple ratio approach that does not account for many of the complexities of radiolabeled dopa analysis and is highly

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dependent on scanning duration,[82] factors that may contribute to the negative effect size in the only study to use this approach.[38] Nevertheless, that the elevation in schizophrenia was evident across studies using a variety of methods and analytic approaches suggests it is robust.

The elevation in presynaptic dopaminergic function could be due to an increased density of dopamine terminals in the striatum. However, this interpretation is unlikely for 2 reasons: first, there is no evidence of a similar elevation in dopamine transporter availability in our meta-analysis or in the vesicular monoamine transporter (both in vivo markers of dopamine neuron terminal density),[83,84] and, second, dopamine neuron numbers are not elevated in postmortem samples.[85] Thus, this indicates that the increased dopamine synthesis capacity and dopamine release reflect functional changes rather than increased neuronal density. Although elevated dopamine synthesis capacity could reflect increased enzyme activity in compensation for reduced dopa or dopamine levels, this interpretation is not consistent with the evidence that synaptic dopamine levels and dopamine release, respectively, are also increased and positively correlated.[35] Together, the presynaptic studies thus suggest that there is increased dopaminergic activity reflected in increased dopamine synthesis capacity and increased dopamine release.[35] This is consistent with evidence of increased turnover of striatal dopamine in schizophrenia.[39] Further work is needed to determine whether dopamine synthesis capacity is related to dopamine release in schizophrenia, as has been found for synaptic dopamine and dopamine release,[35] and whether other aspects of dopaminergic function (eg, conversion of tyrosine to dopa, and dopamine catabolism) are also abnormal.

Dopamine Transporter Availability

There was no evidence of publication bias. Antipsychotic treatment is unlikely to explain our finding because most of the patients in the dopamine transporter studies were drug-naive, and the lack of difference between patients and controls was also evident when the studies of treated patients were excluded. A likely source of the heterogeneity between studies is the number of different radiotracer imaging approaches used, although we were not able to formally assess this. Differences in clinical characteristics, such as variation in the severity and phase of illness and in drug-free intervals, are evident between studies (eTables 3 and 4) and may be a further source of heterogeneity between studies.

Dopamine Receptor Availability

There was no evidence of publication bias. There was no significant difference between patients and controls on 14 of the 22 iterations of the leave-one-out analysis, which indicates that the finding of a difference in the meta-analysis is not robust. In the sensitivity analyses, we could not detect a difference between patients and controls when the meta-analysis was restricted to purely drug-naive patients or when it was restricted to patients who had received prior treatment scanned with benzamide radiotracers. The 2 studies[64,65] that used ergot radiotracers included a mixture of drug-naive and previously treated patients and found no difference between patients and controls, in line with the findings with benzamide radiotracers. However, when the meta-analysis was restricted to butyrophenone radiotracers, there was an elevation in patients. Interestingly, this was not evident in the one butyrophenone study[66] exclusively of drug-naive patients. These further analyses thus suggest that the imaging approach used and the inclusion of patients who had received prior antipsychotic treatment are likely to contribute to the inconsistency in the meta-analysis. Other differences in clinical characteristics may also contribute to this inconsistency: in particular, duration of illness (which was shorter in the drug-naive patients), whether illness duration included the prodrome, and the nature and severity of symptoms (eTable 6).

There are differences in the pharmacokinetic properties of the different radiotracers and in the analytic methods used to characterize them and their pharmacodynamics,[86-88] so it is not possible to disentangle which of these factors might underlie the effect of imaging approach on our findings. For example, in comparison with the benzamide radiotracer raclopride, in membrane, slice, and cell preparations, the butyrophenone radiotracers *N*-methylspiperone and spiperone have shown paradoxical binding decreases following dopamine depletion[89,90] and either increases or no overall change following stimulated release.[89-91] Some studies,[91] although not all,[92] have found that spiperone has a greater tendency to bind to internalized receptors than does raclopride. *N*-methylspiperone and spiperone also have a higher affinity for $D_{2/3}$ receptors than does raclopride (K_d values for *N*-methylspiperone and spiperone are in the picomolar range and, those for raclopride are in the nanomolar range), and they have slower kinetics,[86] which makes it more difficult to obtain quantitative estimates from short-duration PET studies and necessitates the use of a different kinetic model for analysis.[15,93]

When evaluating the sensitivity analyses, it is also important to consider that the risk of type II errors increases when the number of studies is reduced, and there is an inevitable decrease in the precision of the estimate. This is reflected in the wide confidence intervals for the drug-naive and drug-free groupings, and therefore the finding of a lack of a significant difference in the drug-naive studies needs to be seen in the context of the reduced power to find such a difference. Finally, elevated baseline synaptic dopamine in schizophrenia could potentially make group differences harder to detect. Nevertheless, overall, one can conclude that, although there was a small elevation in $D_{2/3}$ receptor availability, it was not a consistent finding and was not present in drug-naive patients, although some caveats remain.

IMPLICATIONS FOR THE DOPAMINE HYPOTHESIS OF SCHIZOPHRENIA

Our findings provide in vivo evidence to support the dopamine hypothesis of schizophrenia. Early versions of this hypothesis could only conjecture the nature of the abnormality.[94] This meta-analysis provides evidence

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to specify that the major dopaminergic abnormality in schizophrenia is a presynaptic one, affecting dopamine synthesis capacity and release, and that, in contrast, the overall effect on $D_{2/3}$ receptor availability is small. This view is supported by findings of elevated dopamine synthesis capacity in drug-naive individuals in the prodrome to schizophrenia[24] and of a further increase associated with the onset of the psychotic disorder.[95] There is also evidence of specificity because this presynaptic dopaminergic dysfunction is not seen in nonpsychotic affective and anxiety disorders (see review by Howes et al[16]). Although we were unable to examine symptoms in our meta-analyses, the challenge studies[17,36] link elevated dopamine release to positive rather than negative symptoms.

Although our findings support proposals that dopaminergic dysfunction is a final common pathway to psychosis, they do not address the issue of what drives the presynaptic striatal alterations. One candidate is decreased D_1-mediated dopaminergic neurotransmission in the frontal cortex (see Fusar-Poli et al[96] and Meyer-Lindenberg et al[40] and review by Heinz et al[97]). Another candidate, supported by preclinical models and some human findings,[98-100] is glutamatergic dysfunction.

Our finding that dopamine transporter availability is unaltered indicates that there is no elevation in transporter levels that might compensate for elevated dopamine release. It may also explain the later age of onset of schizophrenia in women than men, because women tend to have higher dopamine transporter availability than men, which naturally declines with age in both sexes.[101] Although our findings indicate that transporter availability is unaltered, it remains possible that transporter *function* is altered in schizophrenia.

Because we focused on the striatum, it is not possible to know whether our presynaptic findings are specific to the striatum or whether they are also relevant to dopaminergic projections to other brain regions, and future work will need to evaluate the extrastriatal dopamine system. Our analyses of striatal subregions suggest that the presynaptic elevation may be localized to the putamen. However, these findings should be considered as exploratory because not all studies provided data and because the resolution of scanners varied markedly (eTable 1). The putamen localization contrasts with recent findings focusing on functional, as opposed to purely anatomical, subregions of the striatum, which have suggested that the dopaminergic dysfunction is localized in a part of the caudate nucleus that is linked to associative cortical regions.[41,42] Unfortunately, there were too few studies for the functional subregions to be examined in our meta-analysis, and therefore studies using high-resolution scanners are warranted to examine subregional effects further.

IMPLICATIONS FOR TREATING SCHIZOPHRENIA

The current drug treatments for schizophrenia were discovered prior to the notions of dopamine as a neurotransmitter and prior to our ability to measure its function in vivo in humans. They were the outcome of empiricism and serendipity, rather than rational drug design based on pathophysiology. It has transpired that the major mode of action of all currently licensed antipsychotic drugs is to block D_2 receptors.[9,102] However, our meta-analysis indicates that, by blocking D_2 receptors, current drugs are acting downstream of the locus of the largest dopaminergic abnormality in the disorder. Thus, although antipsychotics suppress overall neurotransmission, they fail to target the major dopaminergic abnormality. Furthermore, our finding that the $D_{2/3}$ alterations were not present in drug-naive patients suggests that $D_{2/3}$ receptor alterations are not intrinsic to the illness but are secondary to prior antipsychotic treatment. Although studies are needed to test this after accounting for the factors already discussed, this interpretation is consistent with animal evidence that antipsychotics result in $D_{2/3}$ receptor upregulation[103] and with evidence that withdrawing antipsychotic drugs in humans uncovers elevated $D_{2/3}$ receptor availability.[104] It is not surprising that when antipsychotics are stopped (usually by the patient), when there is nothing to suppress the dysregulated presynaptic dopaminergic system, and when there is a potentially supersensitive postsynaptic receptor system, then there is a high risk of relapse.

Our findings indicate that, rather than focusing exclusively on postsynaptic receptors, future treatments should target the presynaptic control of dopamine synthesis and release. Interestingly, one of the first effective drug treatments for schizophrenia was reserpine,[105] and more recent data show that use of α-methylparatyrosine is associated with a rapid and profound reduction in psychotic symptoms.[36] Because both of these drugs deplete the store of presynaptic dopamine, there is thus proof of principle that, by acting on the presynaptic dopaminergic system, we can treat the psychosis. However, although presynaptic dopamine depletion seems logical from a pathophysiological perspective, it raises a technical challenge because dopamine and norepinephrine share part of the same synthetic pathway. Thus, treatments that interfere with dopamine also risk affecting norepinephrine synthesis, leading to undesirable adverse effects. Therefore, future efforts at presynaptic modulation will need to go beyond the simple depletion of dopamine or blockade of its synthesis because the cost-benefit ratio of this is unlikely to be therapeutically viable. Future efforts will also probably need to show some regional selectivity if they are to avoid altering dopamine neurotransmission in the frontal cortex and potentially worsening negative symptoms and cognitive impairments, both of which have been linked to frontal cortical D_1 receptor availability in schizophrenia.[63]

Interestingly, patients who respond less well to antipsychotic drugs have been found to show lower synaptic dopamine levels,[36] and findings indicate that treatment-resistant patients show normal dopamine synthesis capacity.[106] These findings suggest that psychotic symptoms in some patients may be unrelated to dopaminergic function, at least as indexed by these imaging techniques.

Although we did not find a major alteration in dopamine transporter or $D_{2/3}$ receptor availability, there could nevertheless be other functional alterations. In fact, this is indirectly suggested by findings that patients with schizophrenia are supersensitive to the psychoto-

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genic effects of the D_2 receptor agonist apomorphine when given at high doses.[107] Interestingly, when apomorphine is given at low doses, which are thought to have a preferential presynaptic action to reduce dopaminergic transmission, it has an antipsychotic effect.[108] D_2 receptors may exist in forms with differing affinities for dopamine, and it has been proposed that there is an excess of the high-affinity form in schizophrenia.[107] However, the first in vivo study[109] in schizophrenia using a radiotracer selective for the high-affinity form found no evidence of alterations, although a significant caveat is that this radiotracer also shows appreciable binding to D_3 receptors. Notwithstanding this, other aspects of $D_{2/3}$ receptor function (such as internalization or signal transduction) or the function of other dopamine receptors could be abnormal in schizophrenia and warrant investigation in patients. If these or other aspects of D_2 function are abnormal, this would suggest new drug targets, and even if D_2 function is unaltered, finding new ways to intervene at this level could still be useful to counteract the effects of presynaptic dysfunction on dopamine neurotransmission.

An attractive feature of the present findings is that the pathophysiological target (ie, increased dopamine synthesis capacity and dopamine release) can now be measured in preclinical models and humans using exactly the same molecular imaging techniques as has been done for dopamine transporters and $D_{2/3}$ receptors.[110] So, although most of the animal models used to develop antipsychotics in the past have had to rely on indirect measures (such as amphetamine-induced locomotion or conditioned avoidance response abolition), the present findings provide a pathophysiological target that can be directly measured in animals. With advances in small animal imaging and experimental human studies, it should be possible to induce the precise presynaptic abnormality in animal models and to measure the response to new medications in animals and in experimental human models in the same way.

In conclusion, there is consistent evidence of presynaptic dysfunction in schizophrenia with a large effect size but no evidence of a compensatory increase in dopamine transporter availability to buffer the system. $D_{2/3}$ receptor upregulation is small and not detected in antipsychotic-naive patients. These findings suggest that drug development should target the presynaptic regulation of dopamine synthesis and release.

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