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https://doi.org/10.1016/j.bandl.2021.105046

# Reading abilities and dopamine $D_2/D_3$ receptor availability: An inverted U-shaped association in subjects with schizophrenia

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# Abstract

Reading impairments are prominent trait-like features of cognitive deficits in schizophrenia, predictive of overall cognitive functioning and presumably linked to dopaminergic abnormalities. To evaluate this, we used $^{18}$F-fallypride PET in 19 healthy and 21 unmedicated schizophrenia subjects and correlated dopamine receptor binding potentials in relevant AFNI-derived regions and voxelwise with group performance on WRAT4 single-word reading subtest. Healthy subjects' scores were positively and linearly associated with $D_2/D_3$ receptor availability in the rectus, orbital and superior frontal gyri, fusiform and middle temporal gyri, as well as middle occipital gyrus and precuneus, all predominantly in the left hemisphere and previously implicated in reading, hence suggesting that higher dopamine receptor density is cognitively advantageous. This relationship was weakened in schizophrenia subjects and in contrast to healthy participants followed an inverted U-shaped curve both in the cortex and dorsal striatum, indicating restricted optimal range of dopamine $D_2/D_3$ receptor availability for cognitive performance in schizophrenia.



*Key words*: Cognition; Dopamine; Wide Range Achievement Test; Positron emission tomography; $^{18}$F-fallypride; Reading abilities.

# 1. Introduction

## 1.1 Reading in schizophrenia

Impaired reading is among the most prominent features of the cognitive dysfunction in schizophrenia (Vanova et al., 2020) and is typically assessed with tests of single-word reading. The commonly used word reading subtest of Wide Range Achievement Test (WRAT) measures an individual's ability to pronounce irregularly spelled words and is considered an effective standardized academic skill measurement with high test-retest reliability (Olsen et al., 2015). Reductions in the WRAT reading scores have been demonstrated in subjects with schizophrenia (Revheim et al., 2006) and other psychotic disorders (Shafee et al., 2018) as well as in individuals at high risk for psychotic disorders (Carrion et al., 2015). Together with parental education, the WRAT reading score predicted global cognitive ability in healthy subjects, whereas subjects with schizophrenia show marked deviations from predicted score (Hochberger et al., 2020). Similarly, the WRAT in conjunction with maternal education level was found to predict current cognitive performance in healthy subjects, while 98% of subjects with schizophrenia displayed cognitive functioning below expectations (Keefe et al., 2005). Reading deficits in subjects with schizophrenia are significantly more severe than would be expected from their general cognitive impairment (Revheim et al., 2014) and encompass poor reading comprehension, rapid naming and phonological awareness (Arnott et al., 2011). The WRAT reading score has a higher heritability (0.75) than any of the six Brief Assessment of Cognition in Schizophrenia subtest scores (Hill et al., 2013) and in subjects with schizophrenia reading ability may be a more accurate predictor of premorbid ability than memory or academic achievement (Dalby and Williams, 1985), consistent with evidence that reading deficits in schizophrenia are related to lifetime risk factors (Revheim et al., 2014).

## 1.2 Functional imaging of reading

With the advance of functional neuroimaging neural underpinnings of reading have been relatively well established. Reading ability is thought to include orthographic, phonological and semantic processing components, which requires integration of multiregional cortical networks (Price, 2012). The earliest brain blood flow imaging report showed frontal premotor, anterior Sylvian, and postcentral increases during reading in comparison to rest (Ingvar and Schwartz, 1974), with follow-up addition of frontal eye fields (Ingvar, 1983). Subsequent studies indicate that neuroanatomical basis of reading encompasses cortical regions across all four cerebral lobes (He et al., 2013), including the primary visual cortex in the occipital lobe (Martinez et al., 2012; Pattamadilok et al., 2017), bilateral motor and premotor Brodmann areas 4 and 6, the pars opercularis of the inferior frontal gyrus (area 44), left superior and bilateral middle temporal gyri (areas 22 and 21) (Evans et al., 2016), left fusiform gyrus (areas 37 and 19), temporal pole (area 38) as well as the cerebellum (Turkeltaub et al., 2002). A study by Johns et al. (2008) related individual differences in word decoding skills to regional brain volumes in young adult readers, including the temporal, inferior frontal, and fusiform regions in the left hemisphere. A meta-analysis of 36 fMRI studies confirmed reading task activation in the temporo-occipital, middle temporal and inferior parietal areas in the left hemisphere (Taylor et al., 2013). A recent review of modulation of reading performance by non-invasive brain stimulation (Turker and Hartwigsen, 2021) buttressed the central role of the left inferior frontal and inferior parietal cortex, and also implicated the left posterior parietal and anterior temporal regions as potentially critical to, respectively, orthographical and semantic processing.

## 1.3 Dopamine imaging and reading

We have recently reported a positive relationship between gray matter metabolism and dopamine $D_2/D_3$ receptor availability in healthy human brain, that was weakened in subjects with schizophrenia, and proposed a modulating role of dopaminergic neurotransmission in cognitive task-induced metabolic changes (Mitelman et al., 2020). The role of dopamine in regulation of cognitive functions has been a matter of substantive and growing interest (Nieoullon et al., 2003), particularly in schizophrenia and not least in light of the puzzling inefficacy of $D_2$ antagonists in alleviating its prominent cognitive symptoms (Conn et al., 2020). A double-blind randomized trial of three antipsychotics in adolescents with schizophrenia failed to show a significant effect of treatment on the WRAT reading scores (Frazier et al., 2012). Like reading ability, dopamine receptor availability appears to represent a trait-like feature of schizophrenia with good test-retest reliability (Nyberg et al., 1996; Kodaka et al., 2013; Alakurtti et al., 2015), high heritability (Borg et al., 2016), and interindividual variability mirroring the distribution of behavioral traits in the general population that naturally lends itself to correlational studies (Farde et al., 1997 and 2018). Positron emission tomography with dopamine receptor radioligands has made it feasible to reveal correlations between binding potentials in specific neuroanatomic regions and various cognitive scores (Takano, 2018). This line of research has already, if tentatively, buttressed the role of dopaminergic dysfunction in cognitive deficits in schizophrenia. In the earliest such study, dopamine agonist apomorphine was shown to enhance activation of the anterior cingulate cortex during phonemic fluency task in schizophrenia but not in healthy subjects (Dolan et al., 1995). In our own study using the sample reported here, positive correlations between $D_2/D_3$ receptor availability across many brain areas and an assortment of

executive functions as assessed with the Wisconsin Card Sorting Test were significantly weaker in subjects with schizophrenia than healthy subjects (Vyas et al., 2018).

Dopaminergic modulation of cortical functions has often been presented within the frame of optimal range of dopamine availability, in mathematical terms described by inverted parabola. The inverted U-shaped quadratic relation was initially found in studies of the effects of psychopharmacological manipulation of dopamine $D_1$ receptors in the prefrontal cortex on cognitive performance and working memory in animals (Arnsten et al., 1994 and 1998; Vijayraghavan et al., 2007) and healthy human volunteers (Kimberg et al., 1997; Chen et al., 2020), well-reviewed in Cools and D'Esposito (2011), thus suggesting an optimal range of the binding potential for cognitive skills (Seamans and Yang, 2004). More recently, inverted-U relationship for the frontostriatal circuitry and various cognitive functions was investigated in a number of methodologically diverse studies with correlational design, and confirmed for some (but not all) personality traits. Thus, it was reported for the availability of striatal dopamine transporter and novelty seeking (Liang et al., 2017) and for the balance between catechol-O-methyltransferase (COMT) polymorphisms and prefrontal $D_2$ receptor availability and both working and episodic memory (Papenberg et al., 2020), the latter supporting the role of the dynamics between the availability of dopamine and $D_2$ receptors in the U-shaped relationship. Fewer correlational studies specifically focused on reading abilities. In healthy subjects, a [$^{11}$C]SCH 23390 PET study found an inverted U-shaped relationship between dopamine $D_1$ receptor availability and WCST scores (Takahashi et al., 2008). It was also found that in 188 healthy men optimal scores on a mental health inventory were associated with genotypes in midrange COMT activity, whereas lower scores on the inventory were associated with genotypes in both high or low ranges of COMT activity (Htun et al., 2014). Modulating effect of dopamine

on reading was found to be mediated by dopaminergic polymorphisms COMT Val$^{158}$Met and DAT1 VNTR 9/10, following an inverted U-shaped curve, so that the intermediate prefrontal dopamine levels led to strengthening of the frontostriatal effective connectivity during an overt reading task, which involved the interaction between the left caudate and the frontal Brodmann areas 6, 8, 9, 10, 44, 45, anterior cingulate areas 24 and 32 (Arnold et al., 2016).

Differential relationships between dopaminergic activity and cognitive performance between healthy and schizophrenia subjects have not yet attracted a comparable research interest. A single correlational [$^{123}$I]epidepride SPECT study of dopamine $D_2/D_3$ receptor availability in the frontal cortex and cognitive performance reported a significant quadratic function for Cambridge Neuropsychological Test Automated Battery subtests of verbal fluency, planning, and attention in antipsychotic-naïve subjects with schizophrenia, that did not reach statistical significance in healthy participants (Fagerlund et al., 2013). In a visual information processing set shifting task in this study, healthy subjects displayed an inverted U-shaped relationship whereas it was linear in subjects with schizophrenia, implying differential impact of dopamine receptor availability on task performance in these diagnostic groups. Taken together, this literature points to a possible quadratic relation between the dopaminergic function, including dopamine receptor availability in the striatum and prefrontal cortex, and performance on cognitive tasks, which may be differentially impacted in schizophrenia with its attendant cognitive manifestations.

In this correlational study, we investigated the role of the dopaminergic system in reading in healthy and unmedicated schizophrenia subjects. Three hypotheses were examined: (1) positive correlations between dopamine $D_2/D_3$ receptor availability and reading skills in cortical regions previously associated with functional activation during reading; (2) lower correlations in

subjects with schizophrenia than healthy subjects as reflection of dopaminergic dysfunction in schizophrenia; (3) a narrower inverted U-shaped relationship between dopamine $D_2/D_3$ receptor availability and reading skills in subjects with schizophrenia as evidence of reduction in optimal range of dopaminergic modulation.

## 2. Methods

The Wide Range Achievement Test, 4th Edition (Wilkinson and Robertson, 2006) word reading standard scores were obtained for 19 healthy and 21 schizophrenia subjects (**Table 1**) on a separate occasion within a few days before or after the $^{18}$F-fallypride scan. Schizophrenia subjects were diagnosed with the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1996). Twenty schizophrenia subjects were neuroleptic-naïve, five were previously medicated (two had a lifetime neuroleptic exposure of one week and one subject each –2 weeks, 3 months and 3.8 years), none received neuroleptic medications for the 30-day period prior to the scanning and no subject discontinued antipsychotics specifically for the study.

$T_1$-weighted MRI images were acquired using the 1.5T GE Signa NVi scanner (General Electric, Milwaukee, WI) with TR=24ms, TE=5ms, flip angle=40°, slice thickness=1.2mm, pixel matrix=256×256, field of view=23cm, total slices=128. PET scans were acquired using an ECAT EXACT HR+ scanner in 3D mode (Brix et al., 1997). Scanning and image processing procedures are described in detail in our earlier publications (Buchsbaum et al., 2006; Mitelman et al., 2020). Briefly, the participants were placed in the scanner in supine position with their head fixed. The dynamic acquisition of the data was initiated with a 30-sec bolus injection of $^{18}$F-fallypride, produced according to previously reported methods (Mukherjee et al., 1995) at high specific activity (>2000 Ci/mmole) with a dose of 0.7 mCi/10kg. The data were reconstructed using the ECAT v7.2 OSEM following corrections applied for attenuation, normalization, and

scatter, then spatially aligned using AIR 3.08 software (Woods et al., 1992). Parametric images of $^{18}$F-fallypride binding potential with respect to the non-displaceable compartment ($BP_{ND}$) were generated using the SPM software. The $BP_{ND}$ were calculated using a multilinear variation (Ichise et al., 2002) of the Logan distribution volume ratio (Logan et al., 1996) which employs a reference region (cerebellum) for representation of the kinetics of unbound radioligand in the tissue (Cunningham et al., 1991; Siessmeier et al., 2005). The preprocessing included creation of an image of the first several minutes of $^{18}$F-fallypride uptake after the bolus to represent the admixture of unbound $^{18}$F-fallypride throughout the brain and the bound $^{18}$F-fallypride in the high-density $D_2/D_3$ striatum. The matrices from the data spatially normalized to the Montreal Neurological Institute (MNI) $^{18}$F-fluorodeoxyglucose template (7×9×7 basis functions, 16 nonlinear iterations, 12-parameter affine registration model using FLIRT) were applied to the $BP_{ND}$ parametric images, summed and used to spatially normalize the individual $BP_{ND}$ images. Differences in $^{18}$F-fallypride binding potential between healthy and schizophrenia subjects in this sample have been previously reported (Lehrer et al., 2010; Mitelman et al., 2020), and in addition to several regions in the prefrontal and temporal cortex are higher in healthy than schizophrenia subjects in the hypothalamus, mammillary bodies, and several thalamic nuclei.

Single-word reading was assessed using the WRAT4 (Wilkinson and Robertson, 2006), which involved asking the participants to read aloud a series of letters and words of increasing difficulty (from *see* to *synecdoche*). Standardized scores range from 50 to 145 (mean=100±15). In addition to voxel-by-voxel analyses, the $^{18}$F-fallypride $BP_{ND}$ images in MNI space were sampled in cortical and subcortical structures of the AFNI (Cox, 1996). We started the analyses of correlations between WRAT4 scores and regional $^{18}$F-fallypride $BP_{ND}$ with replications of regional findings from previously published fMRI studies that employed task-induced activation

paradigm. First, we compared voxelwise correlation maps in our sample of healthy participants with cluster coordinates from the largest activation likelihood estimation meta-analysis of 36 studies of reading (Taylor et al., 2013). We then used selected masks of AFNI regions of interest and multiple regression to predict WRAT4 performance from $^{18}$F-fallypride binding by replicating significant findings in the set of multiple areas from several available fMRI publications (Phillipose et al., 2007; Bloemendaal et al., 2015; Evans et al., 2018; Jones et al., 2018). In these analyses, we computed multiple R in healthy and schizophrenia subjects, as well as their difference by Fisher's z-test. Inverted-U hypothesis for the relationship between $^{18}$F-fallypride binding and WRAT4 performance was evaluated by examining the quadratic term of the WRAT4 vs. $^{18}$F-fallypride $BP_{ND}$ fit (i.e. the fit of a parabola with the polynomial $x^2$ term negative).

# 3. Results

Healthy and schizophrenia subjects displayed no significant differences in their performance on WRAT4 tests (**Table 1**), ensuring that correlations between WRAT4 and $^{18}$F-fallypride binding potentials were not confounded by group differences in reading scores. The correlation between BPRS total and WRAT4 reading scores in subjects with schizophrenia was not significant (0.13).

## 3.1. WRAT4 correlations with $^{18}$F-fallypride $BP_{ND}$ in regions previously implicated in reading

We chose the Taylor et al. (2013) meta-analysis that used activation likelihood estimation on 36 fMRI studies of reading (see the first cluster in their table 2) as the starting point in our sample of 19 healthy subjects. Taylor et al. first cluster was large and had three local maxima: left temporal, occipital, and angular. Our largest cluster of correlations between WRAT4 scores and $^{18}$F-fallypride $BP_{ND}$ included their first cluster areas, and both the second and third maxima

in our data were significant at their exact xyz coordinates **(Table 2).** Overlapping with their precise coordinates, significant positive correlations between WRAT4 scores and $^{18}$F-fallypride $BP_{ND}$ in our sample of healthy subjects were in the left frontal lobe (medial superior, rectus, medial orbital gyri), left and right middle temporal gyri, left fusiform gyrus, left middle occipital gyrus, left and right precunei (the correlations were particularly strong in the left gyrus rectus and precuneus).

### 3.2. WRAT4 correlations with $^{18}$F-fallypride $BP_{ND}$ in AFNI regions matching published reports

We matched 11 brain regions whose volumes were correlated with decoding reading skills (Table 5 in Jones et al., 2018) to corresponding AFNI definitions: lateral occipital, supramarginal, superior frontal, lateral orbitofrontal (Brodmann area 47), medial orbitofrontal (Brodmann area 11), superior temporal (Brodmann area 38) gyri in the left hemisphere, and middle temporal, lingual, superior parietal, and postcentral gyri in the right hemisphere. For healthy subjects Jones et al. set of regions yielded multiple R=0.912 ($F_{12, 6}$=2.48, p=0.13) and for subjects with schizophrenia — R=0.549 ($F_{12, 12}$=0.43, p=0.92). The group difference in multiple R was significant (Fisher's z=2.81, p=0.0049), indicating weaker correlations in subjects with schizophrenia.

Using three regions (left inferior frontal, left superior temporal, and right middle temporal) which were activated to a greater extent by reading than subtraction (Evans et al. 2018, page 310, second paragraph), the multiple R for healthy subjects was 0.69 ($F_{4, 14}$=3.17, p=0.047) and for subjects with schizophrenia — 0.540 ($F_{4, 20}$=2.06, p=0.124), and the R difference was not significant. Using the region sensitive to distraction in Bloemendaal et al. (2015) in left Brodmann areas 44/45 yielded R=0.61 ($F_{3, 15}$= 2.94, p=0.067) in healthy subjects and R=0.48 ($F_{3,}$

$_{21}$=2.14, p=0.13) in subjects with schizophrenia, with no significant group differences. Thus, for the cortical regions implicated in these two studies, we found correlations at or approaching the level of significance in our sample of healthy subjects but not in those with schizophrenia and with no significant intergroup differences.

Using six regions from Phillipose et al. (2007) which showed diminished activation associated with reading words in 105 cerebrovascular accidents patients (Brodmann areas 22, 37, 39, 40, 44, and 45), we found that none of the six areas significantly correlated with $^{18}$F-fallypride binding in either healthy or schizophrenia subjects. The same six variable model as presented in their table 1 found that Brodmann area 37 (significant in their sample) yielded nonsignificant t=1.79, p=0.101 in our analyses, with the multiple R for healthy subjects — 0.69 ($F_{7, 11}$=1.39, p=0.30) and for schizophrenia subjects — 0.62 ($F_{7, 17}$=1.48, p=0.24). Restricting the model to their top two Brodmann areas 37 and 40, also failed to reach statistical significance in healthy subjects (multiple R=0.58, $F_{3, 15}$=2.48, p=0.101) and in subjects with schizophrenia (R=0.335, $F_{3, 21}$=0.46, p=0.46), with no significant intergroup differences.

### 3.3. Exploratory correlations between WRAT4 scores and $^{18}$F-fallypride $BP_{ND}$ in AFNI regions

The left lateral temporal lobe (Brodmann areas 20, 21, 22) yielded a significant correlation between WRAT4 scores and $^{18}$F-fallypride $BP_{ND}$ (R=0.449, $F_{3, 15}$=4.08, p=0.026) in healthy subjects but only reached a trend level of significance in subjects with schizophrenia (R=0.26, $F_{3, 21}$=0.53, p=0.07; group difference by Fisher's z p=0.094, one-tailed). For individual Brodmann areas in the left temporal cortex in healthy subjects, correlations with areas 20 (r=0.58, p=0.0096), 36 (r=0.579, p=0.0095), and 38 (r=0.51, p=0.026) reached statistical significance, areas 37 (r=0.417, p=0.052) and 22 (r=0.42, p=0.071) showed a trend toward

statistical significance, and areas 21 (r=0.386, p=0.102), 34 (r=0.385, p=0.103), and 42 (r=0.293, p=0.224) weren't significant. Thus, of the 8 left temporal areas all were in the positive direction, with 3 meeting and 2 approaching $p<0.05$ significance. No right hemisphere correlations in healthy subjects were significant and no correlation for any of the Brodmann areas in any lobe or hemisphere in subjects with schizophrenia approached statistical significance (see full set of correlations in **Tables B.1** and **B.2**).

### 3.4. Maps of voxelwise correlations between WRAT4 scores and $^{18}$F-fallypride $BP_{ND}$

In healthy subjects, extensive areas of strong positive correlations were seen in the temporal lobes (more prominent in the left hemisphere) and left posterior prefrontal region (more prominent at the frontal pole; **Fig. 1, Fig. A.1** and **Table A.1**). Subjects with schizophrenia displayed negative correlations in the most dopamine-rich areas — the caudate and putamen, as well as in the posterior frontal lobe (in contrast, healthy subjects displayed positive correlations in these regions, see crosshair in **Fig. 1).** Positive correlations with WRAT4 scores were significantly weaker in subjects with schizophrenia than in healthy subjects in the left superior parietal lobule (the largest cluster), right angular gyrus and precuneus in the parietal lobe, as well as the right orbitofrontal, left rectus and inferior frontal gyri **(Table 3).** The correlations with the right caudate and left putamen were strongly positive in healthy subjects and negative in subjects with schizophrenia, with significant differences by Fisher's z-test.

### 3.5. Inverted parabola relating WRAT4 scores and $^{18}$F-fallypride $BP_{ND}$ in AFNI regions

In subjects with schizophrenia, polynomial regression for the $^{18}$F-fallypride $BP_{ND}$ predicting WRAT4 scores revealed negative coefficients of the quadratic term ($a$), indicative of inverted parabola relationship in many cortical and subcortical regions. This was most marked and statistically confirmed (**Table B.3**) in the bilateral whole caudate nuclei and caudate heads,

left and right nucleus accumbens, left hippocampus, left inferior temporal gyrus, and left temporal Brodmann areas 21, 22, and 37. In contrast, quadratic coefficients in healthy subjects were mainly positive or nearing zero, indicative of the parabolic (U-curved) or linear relationship, failing to reach statistical significance in any region except the left inferior temporal gyrus (inverted parabola). In comparison to healthy participants, subjects with schizophrenia had significantly greater negative quadratic regression term for the left and right hippocampus ($t=-3.12$ and $-2.10$, $F_{2,38}=4.89$ and 2.21, $p=0.025$ and 0.040), left and right anterior cingulate ($t=-2.45$ and $-2.16$, $F_{2,38}=3.37$ and 2.70, $p=0.02$ and 0.04), left and right caudate ($t=-2.24$ and $-2.70$, $F_{2,38}=2.53$ and 3.68, $p=0.09$ and 0.03), and left and right Brodmann area 21 ($t=-1.73$ and $-1.94$, $F_{2,38}=1.76$ and 1.99, $p=0.19$ and 0.15). The full set of data is presented in **Table B.4** and typical curves in **Fig. 2 and Fig. A.2.**

### 3.6. Voxelwise mapping of inverted-U relation between WRAT4 scores and $^{18}$F-fallypride $BP_{ND}$

Voxel–by–voxel maps also revealed much more prominent inverted-U relations between WRAT4 scores and $^{18}$F-fallypride $BP_{ND}$, with particularly stronger negative quadratic coefficients *a* in schizophrenia than healthy subjects in the temporal lobes and visual association cortex (the two largest clusters of significant Fisher's z-scores in **Table 4, Fig. 3, Fig. A.3).** The clusters for subjects with schizophrenia (except for the first multimaximum region) are larger than those in healthy subjects and tend to be differentially located in that there are prominent regions in bilateral occipital association areas, which extend into the posterior portions of the temporal lobes and the fusiform gyri (**Fig. 3, Fig. A.3**).

# 4. Discussion

## 4.1. Reading and dopamine $D_2/D_3$ receptor availability in healthy subjects

In this study, we examined correlations between WRAT4 word reading scores and dopamine $D_2/D_3$ receptor availability in healthy and schizophrenia subjects. Using the cluster coordinates from the largest meta-analysis of fMRI studies of single-word reading to date (Taylor et al., 2013), we confirmed that WRAT4 performance in healthy subjects was positively correlated with dopamine $D_2/D_3$ receptor availability in most of their precise coordinates. These regions included the left frontal lobe (medial superior, rectus, medial orbital gyri), left and right middle temporal gyri, left fusiform gyrus, left middle occipital gyrus, and bilateral precunei. The WRAT4 correlations in our sample were particularly strong with the $D_2/D_3$ receptor availability in the gyrus rectus and precuneus in the left hemisphere. We also found significant positive correlation between WRAT4 scores and $D_2/D_3$ receptor availability in the constellation of coordinates from the left inferior frontal, left superior temporal, and right middle temporal gyri that were activated to a greater extent by reading than subtraction in Evans et al. (2018), and, at trend level, from the region in the left Brodmann areas 44/45 that was sensitive to distraction during reading in Bloemendaal et al. (2015). We failed to obtain similar results for the six regions in the frontal, temporal, and parietal lobes that showed diminished activation during reading in a large sample of patients after cerebrovascular accidents (Phillipose et al., 2007), and for 11 widespread regions in all lobes volumetrically correlated with decoding reading skills (Jones et al., 2018). Thus, dopaminergic role in reading abilities was confirmed in regions previously implicated in reading by increased activation in fMRI studies but not decreased activation in a clinical population after cerebrovascular accidents or volumetric MRI studies, possibly reflecting a differential role of dopaminergic innervation in immediate cognitive functions versus derivative structural features that are adaptive or developmental in origin.

Further exploration of the temporal cortex with AFNI-generated regions of interest revealed significant positive correlations between WRAT4 scores and $D_2/D_3$ receptor availability in healthy subjects in the left lateral temporal lobe (Brodmann areas 20, 21, 22). Individually, of the 8 left temporal Brodmann areas 5 were either significant (20, 36, 38) or approaching statistical significance (22, 37), whereas none were significant in the right temporal lobe. Voxelwise mapping similarly showed extensive areas of strong positive correlations in the temporal lobes (primarily in the left hemisphere) as well as the left posterior prefrontal region and particularly at the left frontal pole.

These results provide evidence for the involvement of dopaminergic innervation in reading and specifically overlapping with precise regions of interest in the frontal and temporal cortex previously associated with activation during reading tasks in fMRI studies. $D_2/D_3$ receptor availability in the left temporopolar Brodmann area 38, the region implicated as critical to semantic processing of single words during reading by research employing targeted modulation with transcranial direct current and magnetic stimulation (reviewed in Turker and Hartwigsen, 2021) and by fMRI (Turkeltaub et al., 2002; Wang et al., 2019), also directly correlated with single-word reading performance in the present study. Likewise in agreement with the potential role of the bilateral posterior parietal cortex in phonological processing during single-word reading, revealed by the review of non-invasive brain stimulation research (Turker and Hartwigsen, 2021), in our present study $D_2/D_3$ receptor availability in both left and right precunei directly correlated with single-word reading performance. In healthy subjects, most cortical regions showed a weak but positive relationship between $D_2/D_3$ receptor availability and WRAT4 score, which is consistent with the concept that higher density of cortical dopamine receptors may be cognitively advantageous. In accordance with available theoretical models

emphasizing the role of mesocortical pathway in prefrontal cognitive functions, earlier investigations employing correlational and pharmacological challenge approaches focused on the prefrontal cognitive tests. However, the mesolimbic and mesocortical pathways support dopaminergic neurotransmission in other cortical regions, including the hippocampus (Edelmann and Lessmann, 2018) and medial temporal cortex. Moreover, dopamine receptors are not confined to directly innervated cortical regions (Lidow et al., 1991), leading to a speculation that extracellular dopamine in the cortex may originate from noradrenergic terminals (Devoto and Flore, 2006). Although density of the dopamine $D_2/D_3$ receptors throughout the cerebral cortex follows a decreasing anteroposterior gradient (Lidow et al., 1989), they are present in most of the cortical regions (Papenberg et al., 2019) and dopaminergic system may therefore be expected to subserve cognitive functions outside the prefrontal cortex. $^{18}$F-fallypride is a high-affinity ligand with high signal-to-noise ratio, hence readily suitable for extrastriatal $D_2/D_3$ assessments across the cortex (Seaman et al., 2019). Indeed, we herein demonstrate that dopamine $D_2/D_3$ receptor availability in both the frontal and temporal cortex is positively associated with a reading task performance, a cognitive function with multiregional integration.

## 4.2. Differential relationship between reading performance and dopamine $D_2/D_3$ receptor availability in healthy and schizophrenia subjects

In contrast to healthy subjects, in patients with schizophrenia no correlation between WRAT4 scores and $D_2/D_3$ receptor availability for any of the AFNI Brodmann areas in any lobe or hemisphere approached statistical significance. No significant correlations were detected in any of the attempted replications for the relevant coordinates gleaned from the previously published reports (described in the preceding section). In replication of the report by Jones et al. (2018), for the grouping of 11 regions in all 4 lobes whose volumes correlated with decoding

reading skills, correlations between WRAT4 scores and $D_2/D_3$ receptor availability were significantly weaker in subjects with schizophrenia than in healthy subjects.

Significant voxel-by-voxel correlations in subjects with schizophrenia were also scarce, with a notable exception of the dopamine-rich striatal structures. Thus, the correlations with the right caudate and left putamen were strongly positive in healthy subjects and negative in subjects with schizophrenia, with significant differences by Fisher's z-test. This finding may be especially salient since the relationship between the caudate and WRAT4 scores in subjects with schizophrenia also followed a significant inverted-U curve. Cluster correlations were significantly weaker in subjects with schizophrenia than in healthy subjects in the left superior parietal lobule, right angular gyrus and precuneus in the parietal lobe, as well as in the right orbitofrontal, left rectus and inferior frontal gyri in the frontal lobe. Overall, healthy subjects tended to show positive correlations between regional $^{18}$F-fallypride binding potential and WRAT4 reding scores while these correlations were nonsignificant or negative in unmedicated subjects with schizophrenia, and this finding is similar to our earlier results for executive functions (Vyas et al., 2018). As a normally positive association between gray matter metabolism and dopamine $D_2/D_3$ receptor availability is also diminished in subjects with schizophrenia (Mitelman et al., 2020), the disrupted modulating role of dopamine in metabolic responses to cognitive tasks may prove a general phenomenon in schizophrenia, so that similar results could conceivably be expected for other cognitive skills implicated in its psychopathology. Higher dopamine binding potential may also be interpreted as lower concentrations of endogenous dopamine in the synapse, which in healthy subjects would be associated with better reading performance. Presynaptic hyperdopaminergic state and attendant downregulation of dopamine

receptors in schizophrenia may thus be responsible for disruption of normal modulatory role of dopamine in cognitive functions such as reading.

The WRAT4 single-word reading scores showed no significant differences between healthy and schizophrenia subjects in our sample, nor did the scores correlate with the illness severity (judged by nonsignificant correlation between WRAT4 and BPRS). A recent report by Dondé et al. (2019), which likewise found intact single-word reading (in contrast to impaired reading fluency and phonological processing) in medicated subjects with schizophrenia, surmised this to point to a relatively preserved premorbid reading abilities, which unevenly deteriorate with progression to overt illness. Earlier studies similarly documented preserved single-word reading abilities in schizophrenia, which contrasted with impairments in other cognitive domains (Dalby and Williams, 1986; Harvey et al., 2000; Kravariti et al., 2009) and indeed in more complex reading tasks, including passage reading for assessment of accuracy and fluency, which depend on phonological processing, orthographic mapping, and automatic visual recognition (Revheim et al., 2014). Using WRAT4 reading scores as a measure of presumed premorbid cognitive functioning (Johnstone & Wilhelm, 1996), Heinrichs et al. (2015) found that except for the processing speed cognitively normal subjects with schizophrenia did not differ from cognitively intact controls (cognitive normalcy defined by falling within normal range on the MATRICS Consensus Cognitive Battery, not specifically measuring reading skills). More typical schizophrenia subjects with cognitive impairment and underperforming controls both displayed similar discrepancies from WRAT4-estimated premorbid functioning, with no between-groups differences. The authors concluded that schizophrenia subjects with typical cognitive profile are therefore indistinguishable from underperforming controls (Heinrichs et al., 2015). Our results, however, suggest that WRAT4 reading scores may lack sensitivity for

differentiation of diagnostic groups and may not serve as a reliable estimate of premorbid cognitive level. Subjects with schizophrenia appear to be capable of functionally compensating for underlying dopaminergic abnormalities within the range of relatively simple reading tasks exemplified by single-word reading, a capacity that begins to crumble with progression to reading passages and more sophisticated tests of reading abilities. Indeed, our patients proved capable of functional compensation across the range of illness severity as single-word reading performance in our study did not correlate with BPRS. On the other hand, the finding that WRAT4 reading scores in subjects with schizophrenia were not different from healthy subjects in our present study can be viewed as controlling reading performance between groups and exposing variation in underlying dopaminergic mechanisms related to physiological differences in processing rather than performance. Still, it cannot be definitively ruled out that comparable WRAT4 results may indicate that our group of unmedicated subjects with schizophrenia differs from other groups of schizophrenia patients in cognitive performance and attentional facilities. The fact that 15 out of 21 of our schizophrenia subjects were in the optimal range of receptor binding potential for WRAT4 performance may explain why the WRAT4 reading scores did not differ from healthy participants and may account for their longer survival in an unmedicated state before the initial hospitalization (**Table 1**).

### 4.3. Inverted-U relationship between reading performance and dopamine $D_2/D_3$ receptor availability

We report a differential quadratic relation for the dopamine $D_2/D_3$ receptor availability predicting reading performance in healthy and schizophrenia subjects, with markedly more widespread and stronger inverted-U pattern in the latter. The concave (inverted-U) pattern in subjects with schizophrenia was especially prominent in AFNI-generated regions of the bilateral caudate and nucleus accumbens, left hippocampus, and left temporal cortex (fusiform, superior

and middle temporal gyri), whereas the quadratic relation in healthy subjects was predominantly convex (U-shaped) and failed to reach statistical significance, being better described by linear fit. The group differences in the fitting curves, with significantly greater negative quadratic regression term in subjects with schizophrenia than in healthy subjects, were registered bilaterally in the hippocampus, caudate nucleus, anterior cingulate and middle temporal gyri, indicating the narrower negative parabola (inverted-U curve) relating dopamine $D_2/D_3$ receptor availability and reading performance in subjects with schizophrenia in these regions. Similarly, on voxel-by-voxel maps inverted-U curves gathered in larger clusters with significantly stronger fit in subjects with schizophrenia than in healthy subjects across all lobes, with particularly large clusters of differences in the temporal lobes and visual association cortex.

These results are notably consistent with the only published comparison of quadratic relation between dopamine $D_2/D_3$ receptor availability in the frontal cortex and cognitive performance on frontal lobe related tasks in healthy and schizophrenia subjects (Fagerlund et al., 2013). Using [$^{123}$I]epidepride SPECT, these authors similarly reported significant quadratic relations for verbal fluency, planning, and attention in subjects with schizophrenia but not in healthy controls, and specifically an inverted U-shaped relation for rapid visual information processing signal detection measure in schizophrenia with no association in healthy controls (see figure 1 in their report). Taken together with our present findings, this suggests that a negative quadratic relation for dopamine $D_2/D_3$ receptor availability and cognitive performance is not a universal feature of normal cognitive functioning but rather task-dependent, and in some cognitive domains may be more characteristic of cognitive functioning in schizophrenia. Based on our current results it appears that for the reading performance, dependent on multiregional integration with but a partial involvement of the prefrontal cortex, inverted U-shaped quadratic

relations with dopamine $D_2/D_3$ receptor availability are widespread and common in subjects with schizophrenia whereas linear relations are more typical of healthy cognitive functioning. Indeed, this may be the modus operandi outside the prefrontal cortex, as our study found for the hippocampus, temporal and visual association cortex, as well as the caudate and nucleus accumbens in the striatum. This is also congruent with the study of the differential effects of the COMT $Val^{158}$Met polymorphism within the prefrontal cortex on cognitive preparation for overt reading by Arnold et al. (2016) who in healthy subjects found linear relationship in the left inferior frontal gyrus and inverted U-shaped relationship in the mesial prefrontal regions, concluding that "different cognitive subprocesses appear to be differently modulated by dopamine".

Beginning with the series of pioneering studies by Goldman-Rakic and her group in the 1990s (Williams and Goldman-Rakic, 1995), the main focus of research on the dopaminergic role in regulation of cognitive functions had been on the more ubiquitous $D_1$ receptors and the prefrontal cortex. The inverted-U curve, proposed to formalize the observation of optimal level of cognitive performance in relation to dopaminergic influences, accordingly applied specifically to the $D_1$ receptors (Seamans and Yang, 2004; Cools and D'Esposito, 2011). In order to interpret the proposed quadratic relationship over the simple linear correlation the scope of dopaminergic influences on cognition had to be broadened as the relationship naturally lent itself to dualistic explanations invoking dialectically opposed forces. Several such dualistic models were thus introduced in the following decades, attempting to explain the relationship as a dynamic balancing act between two opposing influences, with less optimal performance at the extremes. In Bilder et al. (2004), the dialectics of striatal phasic release of dopamine and prefrontal cortical tonic release take centerstage, cognitively expressed as dimensional tug-of-war between adaptive

flexibility (phasic release) and stability (tonic release). Others ascribe the duality to the opposing functions of the dopamine $D_1$ and $D_2$ receptors, with high and low signal-to-noise processing ratios, respectively, forming a dimension between stability ($D_1$) and flexibility ($D_2$) (Durstewitz and Seamans, 2008). A more recent study contends that the nature of the relationship is simply determined by the balance between the availability of dopamine and dopamine receptors in particular cortical region (Papenberg et al., 2020). Our present findings lend support to the variegated mechanics of dopaminergic modulation of cognitive performance that depends on specifics of the cognitive task, cortical region and dopamine receptor type involved. As pertains to the dopamine $D_2/D_3$ receptors (and in contrast the $D_1$ type), our findings suggest that inverted U-shaped relationship may not be the universal feature of normal $D_2$ physiology but rather a characteristic of particular cognitive processes in pathological conditions, such as schizophrenia. The narrower negative parabola relating the dopamine $D_2/D_3$ receptor modulation of reading performance in subjects with schizophrenia (implied by significantly greater negative quadratic coefficients in schizophrenia than in healthy subjects) may be a function of the restricted range of optimal cognitive performance in response to dopaminergic influences in the context of excessive striatal dopaminergic activity in schizophrenia.

### 4.4. Reading abilities and dopaminergic system in the context of other cognitive skills

We chose WRAT4 reading subtest because single-word reading has been widely reported in imaging studies in healthy subjects and in neurocognitive publications in subjects with schizophrenia as described in the Introduction. The present report is based on the AFNI dataset containing 208 regions of interest and 116 cognitive task scores from 30 tasks, so that a search for correlations significant with Bonferroni correction (0.05/116*208), $p < 2.07 \times 10^{-6}$, appears inexpedient. For this reason, we focused on replicating existing functional brain imaging

activation correlates of the reading tasks. Taking into account that reading is a skill with several cognitive components, correlations between the WRAT4 reading and other neuropsychological tasks may be expected. A sample exploration of six representative cognitive tasks in healthy subjects (Digit Span Forward and Backwards, Wisconsin Cart Sorting Test total correct, Stroop color-word interference, Block Design and Trail Making Test Part B) and $^{18}$F-fallypride $BP_{ND}$ in three representative AFNI-defined areas involved in reading performance (left inferior temporal, left middle temporal, and left inferior frontal gyri) yielded 18 correlation coefficients (range = 0.54 to −0.34, mean = 0.17). Comparison with correlations between WRAT4 reading scores and $^{18}$F-fallypride $BP_{ND}$ in the left inferior temporal gyrus (r=0.55), left middle temporal gyrus (r=0.43), and left inferior frontal gyrus (r=0.29) suggests a stronger positive relationship between single-word reading and dopamine $D_2/D_3$ receptor binding potential in these regions than for other cognitive skills.

To examine the specificity of the inverted-U relationship between dopamine binding potential and reading performance across other brain regions and cognitive tasks we evaluated significant ($t<-1.72$) quadratic tests for 18 neuropsychological measures and $^{18}$F-fallypride $BP_{ND}$ in 18 AFNI regions of interest. The neuropsychological measures were Digit Span Forward and Backwards, Wisconsin Cart Sorting Test (perseverative errors and total correct/errors scores), Stroop Color and Word Test (color, word, color-word), COWAT C, F, and L, Block Design and Trail Making Test Parts A and B, Nine-Hole Peg Test (right and left hands), CVLT (total, semantic clustering, and learning slope). The 18 AFNI regions were the caudate nucleus, caudate head, nucleus accumbens, hippocampus, Brodmann areas 20, 21, 22, 37, and the middle temporal gyrus in each hemisphere. Of these 324 t-tests, 70 were significant at $t<-1.72$, and since we are evaluating the inverted-U (a directional hypothesis), we would expect only 162. Of the 70

significant tests, 17 were for healthy subjects and 53 for subjects with schizophrenia. Of the tasks and regions with significant quadratic tests, the COWAT and Trail Making Test Part B were the most highly represented across the temporal lobe and hippocampus in subjects with schizophrenia. The inverted U-shaped association between $D_2/D_3$ receptor availability in subjects with schizophrenia thus appears to be relatively specific to reading and related verbal fluency tests (Shareef, Östberg & Hedenius, 2019) and much less to most other assessed cognitive skills.

The accuracy of the MNI/Talairach system is important to consider as a caveat in understanding the replication of ALE coordinates for single-word reading in the Taylor et al. (2013) meta-analysis. Of the 23 area MNI xyz coordinates listed as salient by these authors, 10 reached statistical significance ($p<0.05$, one-tailed) in healthy subjects, 19 were in the positive, hypothesized direction for the correlation and 20 were in the left hemisphere. Except for the cingulum/precuneus designation for two regions, all the regional labels from established templates matched. Examination of the xyz centers and standard deviation (table 3 in Scheperjans et al., 2008) using MNI space with 1mm slices showed the center of the posterior cingulate at x=−13 (SD=2), y=−40 (SD=5) and z=51 (SD=4). Using the AAL atlas (2mm even number spacing, Rolls et al., 2020), the posterior cingulate/anterior precuneus border is between 44 and 46 at x=−13 and between 40 and 42 for x=−4 — the x dimension in the table 2 in Taylor et al (2013). A standard deviation of 5 suggests a 10mm band for 66% of subjects. Using a very conservative 3mm distance for a penumbra of statistical confirmation adds 4 more xyz confirmations (14 of 23 regions in Taylor et al. table 2).

In summary, the present $^{18}$F-fallypride PET study using the region-of-interest and voxelwise approaches found that single-word reading is normally positively associated with dopamine $D_2/D_3$ receptor availability in a widespread constellation of cortical regions previously

implicated in reading by increased activation in fMRI studies. This association is significantly weaker and uniquely follows an inverted U-shaped pattern in antipsychotic-naïve subjects with schizophrenia despite their comparable single-word reading test performance as compared to healthy controls. These findings may signify a mediating role of the dopaminergic system in reading abilities and their impairments with dopaminergic dysfunction in schizophrenia.

## Acknowledgments

The project was approved by the institutional review boards of the Kettering Health Network, Wright State University and Icahn School of Medicine at Mount Sinai. Major support was provided by Wallace-Kettering Neuroscience Institute. Use of imaging resources was supported by the United States Air Force, Air Force Research Laboratory (AFRL/HEOP), and Air Force Materiel Command, under cooperative agreement F33615-98-2-6002.

## Authors disclosure

The authors declare that they have no conflict of interests. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

# References


Alakurtti, K., Johansson, J. J., Joutsa, J., Laine, M., Backman, L., Nyberg, L., Rinne, J. O. (2015). Long-term test-retest reliability of striatal and extrastriatal dopamine D2/3 receptor binding: Study with [(11)C]raclopride and high-resolution PET. *Journal of Cerebral Blood Flow Metabolism*, 35(7), 1199−1205.

Arnold, C., Gispert, S., Bonig, H., von Wegner, F., Somasundaram, S., Kell, C. A. (2016). Dopaminergic modulation of cognitive preparation for overt reading: Evidence from the study of genetic polymorphisms. *Cerebral Cortex*, 26(4), 1539−1557.

Arnott, W., Sali, L., & Copland, D. (2011). Impaired reading comprehension in schizophrenia: Evidence for underlying phonological processing deficits. *Psychiatry Research*, 187(1-2), 6−10.

Arnsten, A. F. (1998). Catecholamine modulation of prefrontal cortical cognitive function. *Trends in Cognitive Sciences*, 2(11), 436−447.

Arnsten, A. F., Cai, J. X., Murphy, B. L., Goldman-Rakic, P. S. (1994). Dopamine D1 receptor mechanisms in the cognitive performance of young adult and aged monkeys. *Psychopharmacology (Berl)*, 116(2), 143−151.

Bilder, R. M., Volavka, J., Lachman, H. M., Grace, A. A. (2004). The catechol-o-methyltransferase polymorphism: Relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. *Neuropsychopharmacology*, 29(11), 1943−1961.

Borg, J., Cervenka, S., Kuja-Halkola, R., Matheson, G. J., Jonsson, E. G., Lichtenstein, P., Henningsson, S., Ichimiya, T., Larsson, H., Stenkrona, P., Halldin, C., Farde, L. (2016). Contribution of non-genetic factors to dopamine and serotonin receptor availability in the adult human brain. *Molecular Psychiatry*, 21(8), 1077−1084.

Buchsbaum, M. S., Christian, B. T., Lehrer, D. S., Narayanan, T. K., Shi, B., Mantil, J., Kemether, E., Oakes, T. R., Mukherjee, J. (2006). D2/D3 dopamine receptor binding with [F-18]fallypride in thalamus and cortex of patients with schizophrenia. *Schizophrenia Research*, 85(1-3), 232−244.

Carrion, R. E., Cornblatt, B. A., McLaughlin, D., Chang, J., Auther, A. M., Olsen, R. H., Javitt, D. C. (2015). Contributions of early cortical processing and reading ability to functional status in individuals at clinical high risk for psychosis. *Schizophrenia Research*, 164(1-3), 1−7.

Chen, P. S., Jamil, A., Liu, L. C., Wei, S. Y., Tseng, H. H., Nitsche, M. A., Kuo, M. F. (2020). Nonlinear effects of dopamine D1 receptor activation on visuomotor coordination task performance. *Cerebral Cortex*, 30(10), 5346−5355.

Conn, K. A., Burne, T. H. J., & Kesby, J. P. (2020). Subcortical dopamine and cognition in schizophrenia: Looking beyond psychosis in preclinical models. *Frontiers in Neuroscience*, 14, 542.

Cools, R., & D'Esposito, M. (2011). Inverted-U-shaped dopamine actions on human working memory and cognitive control. *Biological Psychiatry*, 69(12), e113−125.

Cox, R. W. (1996). AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research*, 29(3), 162−173.

Cunningham, V. J., Hume, S. P., Price, G. R., Ahier, R. G., Cremer, J. E., Jones, A. K. (1991). Compartmental analysis of diprenorphine binding to opiate receptors in the rat in vivo and its comparison with equilibrium data in vitro. *Journal of Cerebral Blood Flow and Metabolism*, 11(1), 1−9.

Dalby, J. T., & Williams, R. (1986). Preserved reading and spelling ability in psychotic disorders. *Psychological Medicine*, 16(1), 171−175.

Devoto, P., & Flore, G. (2006). On the origin of cortical dopamine: Is it a co-transmitter in noradrenergic neurons? *Current Neuropharmacology*, 4(2), 115−125.

Dolan, R. J., Fletcher, P., Frith, C. D., Friston, K. J., Frackowiak, R. S., Grasby, P. M. (1995). Dopaminergic modulation of impaired cognitive activation in the anterior cingulate cortex in schizophrenia. *Nature*, 378(6553), 180−182.

Dondé, C., Martinez, A., Pejman, S., Patel, G.H., Kraut, R., Kantrowitz, J.T., Javitt, D.C. (2019). Neural and functional correlates of impaired reading ability in schizophrenia. *Scientific Reports*, 9:16022.

Durstewitz, D., & Seamans, J. K. (2008). The dual-state theory of prefrontal cortex dopamine function with relevance to catechol-o-methyltransferase genotypes and schizophrenia. *Biological Psychiatry*, 64(9), 739−749.

Edelmann, E., & Lessmann, V. (2018). Dopaminergic innervation and modulation of hippocampal networks. *Cell Tissue Research*, 373(3), 711−727.

Evans, T. M., Flowers, D. L., Luetje, M. M., Napoliello, E., Eden, G. F. (2016). Functional neuroanatomy of arithmetic and word reading and its relationship to age. *Neuroimage*, 143, 304−315.

Fagerlund, B., Pinborg, L. H., Mortensen, E. L., Friberg, L., Baare, W. F., Gade, A., Svarer, C., Glenthoj, B. Y. (2013). Relationship of frontal D(2/3) binding potentials to cognition: A study of antipsychotic-naive schizophrenia patients. *International Journal of Neuropsychopharmacology*, 16(1), 23−36.

Farde, L., Gustavsson, J. P., & Jonsson, E. (1997). D2 dopamine receptors and personality traits. *Nature*, 385(6617), 590.

Farde, L., Plaven-Sigray, P., Borg, J., Cervenka, S. (2018). Brain neuroreceptor density and personality traits: Towards dimensional biomarkers for psychiatric disorders. *Philosophical Transactions of the Royal Society of London B Biological Sciences*, 373(1744).

First, M.B, Spitzer, R. L., Gibbon, M., Williams, J. B. (1996). Structured clinical interview for DSM-IV. Washington, DC: American Psychiatric Association.

Frazier, J. A., Giuliano, A. J., Johnson, J. L., Yakutis, L., Youngstrom, E. A., Breiger, D., Sikich, L., Findling, R. L., McClellan, J., Hamer, R. M., Vitiello, B., Lieberman, J. A., Hooper, S. R. (2012). Neurocognitive outcomes in the treatment of early-onset schizophrenia spectrum disorders study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 51(5).

Harvey, P.D., Moriarty, P.J., Friedman, J.I., White, L., Parella, M., Mohs, R.C., Davis, K.L. (2000). Differential preservation of cognitive functions in geriatric patients with lifelong chronic schizophrenia: less impairment in reading compared with other skills areas. *Biological Psychiatry*, 47, 962−968.

He, Q., Xue, G., Chen, C., Chen, C., Lu, Z. L., Dong, Q. (2013). Decoding the neuroanatomical basis of reading ability: A multivoxel morphometric study. *Journal of Neuroscience*, 33(31), 12835−12843.

Heinrichs, R.W., Pinnock, F., Muharib, E., Hartman, L., Goldberg, J., McDermid Vaz, S. (2015). Neurocognitive normality in schizophrenia revisited. *Schizophrenia Research*, 2(4), 226−232.

Hill, S. K., Reilly, J. L., Keefe, R. S., Gold, J. M., Bishop, J. R., Gershon, E. S., Tamminga, C. A., Pearlson, G. D., Keshavan, M. S., Sweeney, J. A. (2013). Neuropsychological impairments in schizophrenia and psychotic bipolar disorder: Findings from the bipolar-schizophrenia network on intermediate phenotypes (B-SNIP) study. *American Journal of Psychiatry*, 170(11), 1275−1284.

Hochberger, W. C., Thomas, M. L., Joshi, Y. B., Swerdlow, N. R., Braff, D. L., Gur, R. E., Gur, R. C., Light, G. A., Consortium of Genomics in Schizophrenia, investigators (2020). Deviation from expected cognitive ability is a core cognitive feature of schizophrenia related to neurophysiologic, clinical and psychosocial functioning. *Schizophrenia Research*, 215, 300−307.

Hollingshead, A. B. (1957). Two Factor Index of Social Position. Yale University Press, New Haven.

Htun, N. C., Miyaki, K., Zhao, C., Muramatsu, M., Sato, N. (2014). Epistasis effects of COMT and MTHFR on inter-individual differences in mental health: Under the inverted U-shaped prefrontal dopamine model. *Biochemical and Biophysical Research Communications*, 451(4), 574−579.

Ichise, M., Toyama, H., Innis, R. B., Carson, R. E. (2002). Strategies to improve neuroreceptor parameter estimation by linear regression analysis. *Journal of Cerebral Blood Flow and Metabolism*, 22(10), 1271−1281.

Ingvar, D. H. (1983). Serial aspects of language and speech related to prefrontal cortical activity. A selective review. *Human Neurobiology*, 2(3), 177−189.

Ingvar, D. H., & Schwartz, M. S. (1974). Blood flow patterns induced in the dominant hemisphere by speech and reading. *Brain*, 97(2), 273−278.

Johns, C. L., Jahn, A. A., Jones, H. R., Kush, D., Molfese, P. J., Van Dyke, J. A., Magnuson, J. S., Tabor, W., Mencl, W. E., Shankweiler, D. P., Braze, D. (2018). Individual differences in decoding skill, print exposure, and cortical structure in young adults. *Language, Cognitiion and Neuroscience*, 33(10), 1275−1295.

Johnstone, B. & Wilhelm, K.L. (1996). The longitudinal stability of the WRAT-R reading subtest: is it an appropriate estimate of premorbid intelligence? *Journal of International Neuropsychological Society*, 2, 282−285.

Keefe, R. S., Eesley, C. E., & Poe, M. P. (2005). Defining a cognitive function decrement in schizophrenia. *Biological Psychiatry*, 57(6), 688−691.

Kimberg, D. Y., D'Esposito, M., & Farah, M. J. (1997). Effects of bromocriptine on human subjects depend on working memory capacity. *Neuroreport*, 8(16), 3581−3585.

Kodaka, F., Ito, H., Kimura, Y., Fujie, S., Takano, H., Fujiwara, H., Sasaki, T., Nakayama, K., Halldin, C., Farde, L., Suhara, T. (2013). Test-retest reproducibility of dopamine D2/3 receptor binding in human brain measured by pet with [11C]MNPA and [11C]raclopride. *European Journal of Nuclear Medicine and Molecular Imaging*, 40(4), 574−579.

Kravariti, E., Morgan, K., Fearon, P., Zanelli, J.W., Lappin, J.M., Dazzan, P., Morgan, C., Doody, G.A., Harrison, G., Jones, P.B., Murray, R.M., Reichenberg, A. (2009). Neuropsychological functioning in first-episode schizophrenia. *The British Journal of Psychiatry*, 195, 336−345.

Lehrer, D.S., Christian, B.T., Kirbas, C., Chiang, M., Sidhu, S., Short, H., Wang, B., Shi, B., Chu, K.W., Merrill, B., Buchsbaum, M.S. (2010). 18F-fallypride binding potential in patients with schizophrenia compared to healthy controls. *Schizophrenia Research*, 122(1-3), 43−52.

Liang, C. S., Ho, P. S., Yen, C. H., Chen, C. Y., Kuo, S. C., Huang, C. C., Yeh, Y. W., Ma, K. H., Huang, S. Y. (2017). The relationship between the striatal dopamine transporter and novelty seeking and cognitive flexibility in opioid dependence. *Progress in Neuropsychopharmacology and Biological Psychiatry*, 74, 36−42.

Lidow, M. S., Goldman-Rakic, P. S., Gallager, D. W., Rakic, P. (1991). Distribution of dopaminergic receptors in the primate cerebral cortex: Quantitative autoradiographic analysis using [3H]raclopride, [3H]spiperone and [3H]sch23390. *Neuroscience*, 40(3), 657−671.

Lidow, M. S., Goldman-Rakic, P. S., Rakic, P., Innis, R. B. (1989). Dopamine D2 receptors in the cerebral cortex: Distribution and pharmacological characterization with [3H]raclopride. *Proceedings of National Academy of Sciences of the United States of America*, 86(16), 6412−6416.

Logan, J., Fowler, J. S., Volkow, N. D., Wang, G. J., Ding, Y. S., Alexoff, D. L. (1996). Distribution volume ratios without blood sampling from graphical analysis of PET data. *Journal of Cerebral Blood Flow and Metabolism*, 16(5), 834−840.

Martinez, A., Revheim, N., Butler, P. D., Guilfoyle, D. N., Dias, E. C., Javitt, D. C. (2012). Impaired magnocellular/dorsal stream activation predicts impaired reading ability in schizophrenia. *Neuroimage Clinical*, 2, 8−16.

Mitelman, S. A., Buchsbaum, M. S., Christian, B. T., Merrill, B. M., Buchsbaum, B. R., Mukherjee, J., Lehrer, D. S. (2020). Positive association between cerebral grey matter metabolism and dopamine D2/D3 receptor availability in healthy and schizophrenia subjects: An (18)F-fluorodeoxyglucose and (18)F-fallypride positron emission tomography study. *World Journal of Biological Psychiatry*, 21(5), 368−382.

Nieoullon, A., & Coquerel, A. (2003). Dopamine: A key regulator to adapt action, emotion, motivation and cognition. *Current Opinion in Neurology*, 16 Suppl 2, S3−9.

Nyberg, S., Farde, L., & Halldin, C. (1996). Test-retest reliability of central [11C]raclopride binding at high D2 receptor occupancy. A PET study in haloperidol-treated patients. *Psychiatry Research*, 67(3), 163−171.

Olsen, J. P., Fellows, R. P., Rivera-Mindt, M., Morgello, S., Byrd, D. A., Manhattan, H. I. V. Brain Bank (2015). Reading ability as an estimator of premorbid intelligence: Does it remain stable among ethnically diverse HIV+ adults? *Clinical Neuropsychology*, 29(7), 1034−1052.

Papenberg, G., Jonasson, L., Karalija, N., Johansson, J., Kohncke, Y., Salami, A., Andersson, M., Axelsson, J., Wahlin, A., Riklund, K., Lindenberger, U., Lovden, M., Nyberg, L., Backman, L. (2019). Mapping the landscape of human dopamine D2/3 receptors with [(11)C]raclopride. *Brain Structure and Function*, 224(8), 2871−2882.

Papenberg, G., Karalija, N., Salami, A., Rieckmann, A., Andersson, M., Axelsson, J., Riklund, K., Lindenberger, U., Lovden, M., Nyberg, L., Backman, L. (2020). Balance between transmitter availability and dopamine D2 receptors in prefrontal cortex influences memory functioning. *Cerebral Cortex*, 30(3), 989−1000.

Pattamadilok, C., Chanoine, V., Pallier, C., Anton, J. L., Nazarian, B., Belin, P., Ziegler, J. C. (2017). Automaticity of phonological and semantic processing during visual word recognition. *Neuroimage*, 149, 244−255.

Price, C. J. (2012). A review and synthesis of the first 20 years of PET and fMRI studies of heard speech, spoken language and reading. *Neuroimage*, 62(2), 816−847.

Revheim, N., Butler, P. D., Schechter, I., Jalbrzikowski, M., Silipo, G., Javitt, D. C. (2006). Reading impairment and visual processing deficits in schizophrenia. *Schizophrenia Research,* 87(1-3), 238−245.

Revheim, N., Corcoran, C. M., Dias, E., Hellmann, E., Martinez, A., Butler, P. D., Lehrfeld, J. M., DiCostanzo, J., Albert, J., Javitt, D. C. (2014). Reading deficits in schizophrenia and individuals at high clinical risk: Relationship to sensory function, course of illness, and psychosocial outcome. *American Journal of Psychiatry*, 171(9), 949−959.

Rolls, E. T., Huang, C., Lin, C., Feng, J., Joliot, M. (2020). Automated anatomical labelling atlas 3. *Neuroimage*, 206:116189.

Scheperjans, F., Eickhoff, S. B., Homke, L., Mohlberg, H., Hermann, K., Amunts, K., Zilles, K. (2008). Probabilistic maps, morphometry, and variability of cytoarchitectonic areas in the human superior parietal cortex. *Cerebral Cortex*, 18(9), 2141−2157.

Seaman, K. L., Smith, C. T., Juarez, E. J., Dang, L. C., Castrellon, J. J., Burgess, L. L., San Juan, M. D., Kundzicz, P. M., Cowan, R. L., Zald, D. H., Samanez-Larkin, G. R. (2019). Differential regional decline in dopamine receptor availability across adulthood: Linear and nonlinear effects of age. *Human Brain Mapping*, 40(10), 3125−3138.

Seamans, J. K., & Yang, C. R. (2004). The principal features and mechanisms of dopamine modulation in the prefrontal cortex. *Progress in Neurobiology*, 74(1), 1−58.

Shafee, R., Nanda, P., Padmanabhan, J. L., Tandon, N., Alliey-Rodriguez, N., Kalapurakkel, S., Weiner, D. J., Gur, R. E., Keefe, R. S. E., Hill, S. K., Bishop, J. R., Clementz, B. A., Tamminga, C. A., Gershon, E. S., Pearlson, G. D., Keshavan, M. S., Sweeney, J. A., McCarroll, S. A., Robinson, E. B. (2018). Polygenic risk for schizophrenia and measured

domains of cognition in individuals with psychosis and controls. *Translational Psychiatry*, 8(1), 78.

Shareef, Z., Östberg, P., & Hedenius, M. (2019). Verbal fluency in relation to reading ability in students with and without dyslexia. *Applied Psycholinguistics*, 40(2), 445−472.

Siessmeier, T., Zhou, Y., Buchholz, H. G., Landvogt, C., Vernaleken, I., Piel, M., Schirrmacher, R., Rosch, F., Schreckenberger, M., Wong, D. F., Cumming, P., Grunder, G., Bartenstein, P. (2005). Parametric mapping of binding in human brain of D2 receptor ligands of different affinities. *Journal of Nuclear Medicine*, 46(6), 964−972.

Takahashi, H., Kato, M., Takano, H., Arakawa, R., Okumura, M., Otsuka, T., Kodaka, F., Hayashi, M., Okubo, Y., Ito, H., Suhara, T. (2008). Differential contributions of prefrontal and hippocampal dopamine D(1) and D(2) receptors in human cognitive functions. *Journal of Neuroscience*, 28(46), 12032−12038.

Takano, H. (2018). Cognitive function and monoamine neurotransmission in schizophrenia: Evidence from positron emission tomography studies. *Frontiers in Psychiatry*, 9, 228.

Taylor, J. S., Rastle, K., & Davis, M. H. (2013). Can cognitive models explain brain activation during word and pseudoword reading? A meta-analysis of 36 neuroimaging studies. *Psychological Bulletin*, 139(4), 766−791.

Turkeltaub, P. E., Eden, G. F., Jones, K. M., Zeffiro, T. A. (2002). Meta-analysis of the functional neuroanatomy of single-word reading: Method and validation. *Neuroimage*, 16(3 Pt 1), 765−780.

Turker, S. & Hartwigsen, G. (2021). Exploring the neurobiology of reading through non-invasive brain stimulation: A review. *Cortex*, 141, 497−521.

Vanova, M., Aldridge-Waddon, L., Jennings, B., Puzzo, I., Kumari, V. (2020). Reading skills deficits in people with mental illness: A systematic review and meta-analysis. *European Psychiatry*, 64(1):e19.

Vijayraghavan, S., Wang, M., Birnbaum, S. G., Williams, G. V., Arnsten, A. F. (2007). Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. *Nature Neuroscience*, 10(3), 376−384.

Vyas, N. S., Buchsbaum, M. S., Lehrer, D. S., Merrill, B. M., DeCastro, A., Doninger, N. A., Christian, B. T., Mukherjee, J. (2018). D2/D3 dopamine receptor binding with [F-18]fallypride correlates of executive function in medication-naive patients with schizophrenia. *Schizophrenia Research*, 192, 442−456.

Wang, K., Leopold, D.R., Banich, M.T., Reineberg, A.E., Willcutt, E.G., Cutting, L.E., Del Tufo, S.N., Thompson, L.A., Opfer, J., Kanayet, F.J., Lu, Z.L., Petrill, S.A. (2019). Characterizing and decomposing the neural correlates of individual differences in reading ability among adolescents with task-based fMRI. *Developmental Cognitive Neuroscience*, 37:100647.

Wilkinson, G. S., & Robertson, C. (2006). The Wide Range Achievement Test – Fourth Edition. Lutz, FL: Psychological Assessment Resources.

Williams, G. V., & Goldman-Rakic, P. S. (1995). Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. *Nature*, 376(6541), 572−575.

Woods, R. P., Cherry, S. R., & Mazziotta, J. C. (1992). Rapid automated algorithm for aligning and reslicing PET images. *Journal of Computer Assisted Tomography*, 16(4), 620−633.

**Fig. 1**. Voxelwise correlations between WRAT4 and $^{18}$F-fallypride $BP_{ND}$.

MNI z=28 (top), z=3 (bottom). *Left*: healthy subjects show positive correlations in the caudate, putamen, and prefrontal cortex. *Middle*: schizophrenia subjects show diminished correlations, with some negative correlations in the caudate. *Right*: Fisher's z-test shows lower correlations in schizophrenia subjects in the caudate and putamen.

Color bar for group correlations shows r from=−0.38 ($p<0.05$, 1-tailed) to r=0.77 and r<−0.693 ($p<0.0005$, 1-tailed). Color bar for Fisher's z-test shows $z>1.96$ ($p<0.05$, 2-tailed) to $z>4$ ($p<0.00003$, 2-tailed).

**Fig. 2.** Voxel-by-voxel Fisher's z-test (right) comparing quadratic regression t-values for WRAT4 vs. $^{18}$F-fallypride $BP_{ND}$ between schizophrenia (left) and healthy subjects (middle).

**Fig. 3.** Quadratic function with full fit for WRAT4 vs. $^{18}$F-fallypride $BP_{ND}$ in AFNI regions.

**Table 1.** Demographic and clinical characteristics of study participants.

*Hollingshead Two-Factor Index of Social Position for family of origin (Hollingshead 1957)

**Table 2.** Voxelwise replication of Taylor et al (2013, table 2) activation likelihood estimation meta-analysis of reading words vs. pseudowords.

* Distance between our and Taylor et al. clusters. Note that of the 23 entries in Taylor et al., in our data 20 were positive (i.e. in the hypothesized direction) and 10 had a significant r value at their exact reported location. Three more were within 2mm away from their significant voxel, approximately the limit of accuracy as only even Talairach coordinate values are reported by Taylor et al. Since the distance is from the edge of our cluster to the center of the Taylor et al. cluster, it is very likely that the clusters overlap.

**Table 3.** Clusters of significant Fisher's z differences (negative z-scores indicate greater correlations in healthy than schizophrenia subjects).

**Table 4.** Cluster analysis for WRAT4 scores predicting $^{18}$F-fallypride $BP_{ND}$*.

* Values for Brodmann areas are within 2 mm from MRIcro Brodmann template.

# Supplementary Material

## Appendix A.

**Figure A.1**. Maps of t-values for test of quadratic term in polynomial prediction of WRAT4 reading scores from $^{18}$F-fallypride binding potentials in subjects with schizophrenia (left) and healthy subjects (right). Blue and purple colors (negative t-values) indicate inverted U-shaped relationship (threshold $p<0.05$). Color bar values (two-tailed): −2.00 is $p<0.05$, −3.31 is 0.002, and −5.31 is <0.00001. In subjects with schizophrenia, note significant areas in the anterior cingulate, striatum, and hippocampus. See **Table A.1** for specific clusters.

**Figure A.2.** One-tailed test of quadratic regression hypothesis in temporal and frontal lobes in schizophrenia subjects. AFNI regions: left Brodmann area 21 ($t=1.76$, $p=0.095$), right Brodmann area 21 ($t=1.91$, $p=0.072$), left Brodmann area 22 ($t=1.85$, $p=0.064$), right Brodmann area 10 ($t=32.30$, $p=0.034$).

**Figure A.3**. Product-moment correlations between WRAT4 word reading scores and $^{18}$F-fallypride binding potentials in healthy and schizophrenia subjects, their Fisher's z comparisons, and t-values for group differences in quadratic term regression. Note predominately yellow and red areas indicating positive correlations in healthy subjects and predominately blue areas indicating negative correlations in subjects with schizophrenia. In the latter, these areas in the temporal lobe (2$^{nd}$ row) show an inverted U-shaped relationship between reading scores and $^{18}$F-fallypride binding, confirmed with a significant t in quadratic regression ANOVA.

**Table A.1**. Cluster analysis of negative t-values* for test of quadratic term in polynomial prediction of WRAT4 reading scores from $^{18}$F-fallypride binding potentials in healthy and schizophrenia subjects (see in conjunction with **Fig. A.1**).

* Negative t-values indicate inverted U-shaped relationship.

## Appendix B.

**Table B.1**. Correlations between WRAT4 reading scores and $^{18}$F-fallypride binding potentials for AFNI ROI in healthy subjects and patients with schizophrenia.

**Table B.2**. Summary of significant multiple R for regional bihemispheric groupings of AFNI Brodmann areas.

**Table B.3**. Linear and quadratic regression for WRAT4 reading scores vs $^{18}$F-fallypride binding potentials in AFNI regions in healthy (H) and schizophrenia (S) subjects. Negative quadratic coefficient and significant p for quadratic term indicate hypothesized inverted U-shaped relationship for $^{18}$F-fallypride binding predicting WRAT4 reading scores.

**Table B.4**. Comparison of linear and quadratic regression coefficients for WRAT4 reading scores vs $^{18}$F-fallypride binding potentials in AFNI regions in healthy and schizophrenia subjects. Significant "t quad" with negative value indicates inverted U-shaped curve. Multiple R-squared, F, p, and df are shown for entire model (intercept, x, and $x^2$).

**Table 1.** Demographic and clinical characteristics of study participants.

| | Schizophrenia ($n$ = 21) | **Healthy subjects ($n$ = 19)** | **Statistics** |
|---|---|---|---|
| Age | 32.5±12.9 years<br>Range: 18−53 | 29.2±9.3 years<br>Range: 19−48 | $t$ = 1.16 $df$ = 38 $p$ = 0.25 |
| Sex (males/females) | 15/6 | 12/7 | Fisher's Exact test = 0.74 |
| Ethnicity (white/African American African-Jamaican/African-Caribbean/Mixed) | 19/2/0/0/0 | 16/0/1/1/1 | $\chi^2$ = 6.24 $p$ = 0.18 |
| **Social class*** | 41.90±15.74 | 35.74±9.30 | $t$ = 1.47 $df$=38 $p$ = 0.15 |
| **Right-handed** | 19 | 16 | Fisher's Exact test = 0.3 |
| **Duration of illness median/mean** | 128/259.9±257.8 weeks | | |
| **Age of onset** | 26.86±11.14<br>Range: 13−45 | | |
| **BPRS Total Score** | 45.00±5.34 | | |
| **WRAT4 Reading Score** | 95.48±12.04 | 99.90±9.69 | $t$ = −1.27 $df$=38 $p$ = 0.21 |

*Hollingshead Two-Factor Index of Social Position for family of origin (Hollingshead 1957)

**Table 2.** Voxelwise replication of Taylor et al (2013, table 2) activation likelihood estimation meta-analysis of reading words vs. pseudowords

| Area in Taylor et al table 2 | MNI x | y | z | Template region | r WRAT vs. fallypride (exact Taylor et al coordinates) | Distance* | Nearest significant voxel r | x | y | z | Template region |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1a | -50 | -66 | 18 | Left middle temporal | .162 | 2mm | 0.392 | -52 | -63 | 18 | Left superior temporal |
| 1b | -46 | -72 | 38 | Left middle occipital | .436 | | | | | | |
| 1c | -52 | -58 | 30 | Left angular | .189 | | | | | | |
| 2a | -32 | -26 | -12 | Left parahippocampal | .189 | 3mm | 0.423 | -31 | -29 | -13 | Left parahippocampal |
| 2b | -22 | -34 | -14 | Left fusiform | .448 | | | | | | |
| 3a | -6 | -48 | 32 | Left posterior cingulate | .140 | 9mm | 0.380 | 0 | -53 | 32 | Left precuneus |
| 3b | 2 | -56 | 24 | Right precuneus | .463 | | | | | | |
| 4a | -8 | 28 | -10 | Left medial orbitofrontal | .124 | 2mm | 0.394 | -9 | 28 | -12 | Left medial orbitofrontal |
| 4b | -4 | 26 | -18 | Left rectus | .644 | | | | | | |
| 5 | -64 | -54 | -10 | Left middle temporal | .389 | | | | | | |
| 6 | 54 | -64 | 20 | Right middle temporal | .432 | | | | | | |
| 7 | -18 | 38 | 44 | Left superior frontal | -.156 | 27mm | 0.448 | -1 | 59 | 44 | Left superior frontal |
| 8 | -38 | 18 | 44 | Left middle frontal | -.333 | 4mm | -0.389 | -37 | 14 | 37 | Left middle frontal |
| 9 | -24 | 24 | 52 | Left middle frontal | -.199 | | | | | | |
| 10a | -4 | -34 | 34 | Left posterior cingulate | .204 | 13mm | 0.402 | 2 | -45 | 38 | Left precuneus |
| 10b | 2 | -36 | 38 | Right middle cingulate | .048 | 9mm | 0.402 | 2 | -45 | 38 | Left precuneus |
| 11 | -10 | -54 | 18 | Left precuneus | .023 | 6mm | 0.457 | -4 | -54 | 18 | Left precuneus |
| 12 | -12 | 46 | -8 | Left medial orbitofrontal | -.263 | 9mm | 0.459 | -20 | 50 | -11 | Left superior frontal |
| 13 | -4 | -56 | 44 | Left precuneus | .620 | | | | | | |
| 14 | -30 | -22 | -26 | Left fusiform | .392 | | | | | | |
| 15 | -52 | 34 | 6 | Left inferior frontal | .298 | 7mm | 0.387 | -51 | 41 | 6 | Left inferior frontal |
| 16 | -54 | -36 | 16 | Left superior temporal | .114 | 7mm | 0.470 | -54 | -36 | 9 | Left superior temporal |
| 17 | -2 | 56 | 4 | Left medial superior frontal | .358 | 1mm | 0.404 | -2 | 57 | 4 | Left medial superior frontal |

* Distance between our and Taylor et al. clusters. Note that of the 23 entries in Taylor et al., in our data 20 were positive (i.e. in the hypothesized direction) and 10 had a significant r value at their exact reported location. Three more were within 2mm away from their significant voxel, approximately the limit of accuracy as only even Talairach coordinate values are reported by Taylor et al. Since the distance is from the edge of our cluster to the center of the Taylor et al. cluster, it is very likely that the clusters overlap.

**Table 3.** Clusters of significant Fisher's z differences (negative z-scores indicate greater correlations in healthy than schizophrenia subjects).

| | Region | x | y | z | Volume | Fisher's z |
|---|---|---|---|---|---|---|
| 1 | Left superior parietal gyrus | -23 | -75 | 56 | 2492 | -3.38 |
| 2 | Left rectus gyrus | 0 | 58 | -15 | 980 | -3.86 |
| 3 | Right caudate | 21 | 21 | 13 | 881 | 4.27 |
| 4 | Left inferior frontal gyrus | -45 | 26 | 2 | 785 | -3.32 |
| 5 | Right angular gyrus | 56 | -51 | 34 | 680 | -3.61 |
| 6 | Right precuneus | 4 | -60 | 13 | 598 | -3.08 |
| 7 | Left putamen | -23 | 15 | 9 | 502 | 4.40 |
| 8 | Right orbitofrontal gyrus | 17 | 73 | -4 | 323 | -3.71 |
| 9 | Left inferior temporal gyrus | -41 | -11 | -34 | 99 | -3.18 |
| 10 | Left inferior frontal gyrus | -30 | 26 | -17 | 70 | -3.02 |

**Table 4.** Cluster analysis for WRAT4 scores predicting $^{18}$F-fallypride $BP_{ND}$.

| Region* | x | y | z | Volume | |
|---|---|---|---|---|---|
| **Comparison of healthy and schizophrenia subjects** | | | | | |
| | | | | | Fisher's z |
| BA 19 | 41 | -89 | -5 | 1966 | -4.206 |
| BA 37 | -49 | -65 | -5 | 1088 | -3.433 |
| BA 32 | 11 | 49 | 27 | 704 | -3.721 |
| BA 45 | -57 | 29 | 7 | 584 | -4.621 |
| BA 8 | 3 | -19 | 49 | 569 | -3.463 |
| BA 39 | -33 | -57 | 29 | 450 | -4.365 |
| BA 18 | 3 | -57 | -7 | 442 | -3.217 |
| BA 17 | -3 | 71 | 3 | 438 | -3.194 |
| **Schizophrenia subjects** | | | | | |
| | | | | | t |
| BA 32 | 15 | 37 | 7 | 3609 | -5.605 |
| BA 25 | 13 | 13 | -1 | 3593 | -4.983 |
| BA 39 | -31 | -55 | 29 | 2419 | -4.411 |
| BA 43 | -59 | -3 | 25 | 1762 | -3.766 |
| BA 18 | 39 | -85 | -5 | 1407 | -4.102 |
| BA 11 | 17 | 51 | -15 | 965 | -4.467 |
| BA 22 | -57 | 29 | 7 | 490 | -5.440 |
| BA 18 | 9 | -55 | -9 | 336 | -3.580 |
| **Healthy subjects** | | | | | |
| | | | | | t |
| BA 6 | 37 | 1 | 23 | 5784 | -4.592 |
| BA 22 | 67 | -7 | 11 | 644 | -4.691 |
| BA 11 | 23 | 39 | -15 | 520 | -3.953 |
| Thalamus | 9 | -9 | 13 | 417 | -3.936 |
| BA 36 | -27 | -1 | -39 | 353 | -3.783 |
| BA 2 | -49 | -35 | 59 | 240 | -3.971 |
| BA 18 | 17 | -93 | 5 | 162 | -3.609 |

***** Values for Brodmann areas are within 2 mm from MRIcro Brodmann template.