

## Effect of fluoxetine on regional cerebral metabolism in autistic spectrum disorders: a pilot study

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### Abstract

The regional metabolic effects of fluoxetine were examined in patients with autism spectrum disorders. Six adult patients with DSM-IV and Autism Diagnostic Interview (ADI) diagnoses of autism ( $n = 5$ ) and Asperger's syndrome ( $n = 1$ ), entered a 16-wk placebo-controlled cross-over trial of fluoxetine. The patients received  $^{18}\text{F}$ -deoxyglucose positron emission tomography with co-registered magnetic resonance imaging at baseline and at the end of the period of fluoxetine administration. After treatment, the patients showed significant improvement on the scores of the Yale–Brown Obsessive–Compulsive Scale – Obsessions subscale and the Hamilton Anxiety Scale; Clinical Global Impressions – Autism scores showed 3 of the patients much improved and 3 unchanged. Relative metabolic rates were significantly higher in the right frontal lobe following fluoxetine, especially in the anterior cingulate gyrus and the orbitofrontal cortex. Patients with higher metabolic rates in the medial frontal region and anterior cingulate when unmedicated were more likely to respond favourably to fluoxetine. These results are consistent with those in depression indicating that higher cingulate gyrus metabolic rates at baseline predict SRI response.

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### Introduction

Although the pathophysiological defect in autism may or may not involve the serotonergic system, serotonin reuptake inhibitors (SRIs) are among the most promising pharmacological treatments for autism and the serotonin system has long been implicated in autistic disorders (Hollander et al., 1998; McDougle et al., 1996). Double-blind studies of clomipramine (Gordon et al., 1993), fluvoxamine (McDougle et al., 1996) and fluoxetine (Hollander et al., 1998), as well as open label studies of fluoxetine (Mehlinger et al., 1990) and sertraline (Steingard et al., 1997), have documented efficacy in treating both global autistic symptoms and symptoms of repetitive behaviours and restricted interests in up to 60% of patients treated. The basis for the apparent effectiveness

of SRIs in a portion of patients with autism is still to be determined. However, evidence from functional imaging studies of autistic patients (Buchsbaum et al., 1992; Haznedar et al., 1997b, 2000) and of the regional metabolic effects of SRIs (Buchsbaum et al., 1997) suggests that the anterior cingulate cortex (ACG) may be an important substrate for this effect.

Metabolism in the ACG, assessed by positron emission tomography (PET), has been found to be significantly increased in SRI-treated depressive patients, especially in treatment responders (Buchsbaum et al., 1997); indeed, elevated ACG and adjacent medial frontal activity at baseline may predict the magnitude of subsequent SRI response in depression (Buchsbaum et al., 1997; Mayberg et al., 1997) as well as clinical response to sleep deprivation (Wu et al., 1999). This finding suggested to us that autistic patients who showed a favourable response to SRI treatment might resemble depressed patients in showing increased metabolism in the ACG before SRI treatment. It is of interest in this regard that Chugani et al. (1997) observed decreased [ $^{11}\text{C}$ ]methyltryptophan uptake, in-

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dicative of decreased unilateral serotonin synthesis, in the frontal lobes of autistic boys compared with their non-autistic siblings. It should be noted that these studies and the imaging studies reviewed in them did not have uniform definitions of the cingulate gyrus and differed in their separation of Brodmann areas 25, 24 and 32 and in their definition of orbital frontal and subgenual cortex. For this reason we assessed these areas in several ways for greater comparability with the literature, to allow systematic exploration, and to demonstrate that the findings were robust across methodological approaches. Based on these observations, we hypothesized that (1) high ACG metabolism in the baseline scan would be linked to a favourable clinical response to fluoxetine and (2) that the ACG and adjacent medial and orbital-frontal cortex would show metabolic rate change after treatment with the SRI fluoxetine.

## Methods

### Subjects

Six outpatient adults with autism spectrum diagnoses (5 men, mean age =  $30.5 \pm 8.6$  yr) were recruited from outpatient clinics, by advertisement, and from patient advocacy group sources and scanned exactly as described in our earlier report, which included one of the current patients (Haznedar et al., 1997b). Patients were diagnosed on the basis of DSM-IV criteria (American Psychiatric Association, 1994) and the Autism Diagnostic Inventory (ADI) as applied by a trained diagnostician from structured information collection (Lord et al., 1992) for autism ( $n = 5$ ) or Asperger's syndrome ( $n = 1$ ). Patients with other neurological disorders, including seizures and head trauma, were excluded. All patients were verbal and IQ scores ranged from 53 to 119 (mean = 95). The clinical assessment measures used to evaluate response to fluoxetine included the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS; Goodman et al., 1989), the Hamilton Rating Scales for Anxiety (HRSA; Hamilton, 1959) and Depression (HRSD; Hamilton, 1960, 1967), and Global Clinical Impression (GCI). All patients provided written informed consent to participate in the study which was approved by the local IRB.

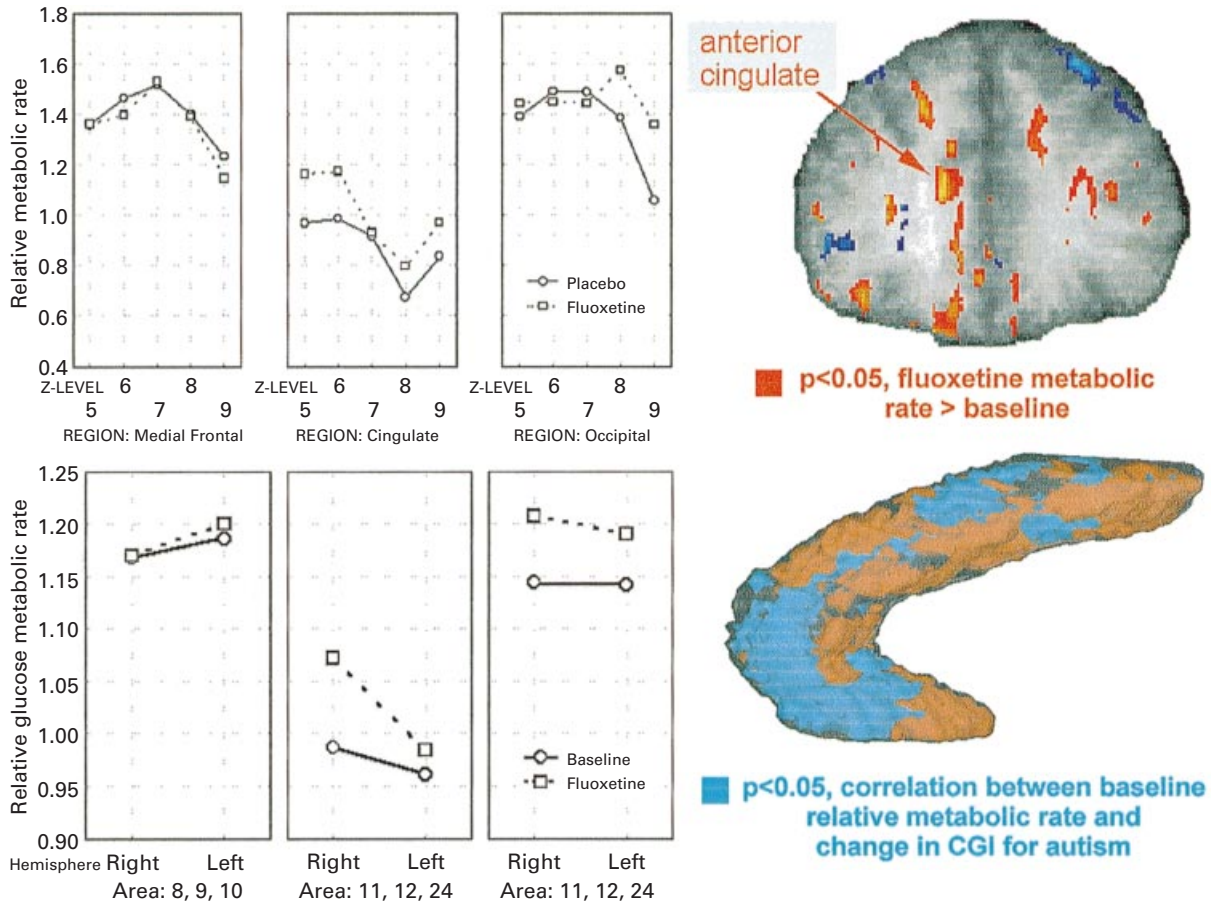
Patients were drug-free for at least 2 wk before beginning a single-blind 1-wk placebo washout. No patients were on fluoxetine, neuroleptics, or MAO inhibitor before washout. Each subject then received fluoxetine for 8 wk and placebo for 8 wk in a randomized cross-over design. Starting doses of 10 mg/d were titrated up, depending on tolerability, by 10 mg/wk, to a maximum of 40 mg/d; 5 subjects were maintained on this dose without any reported side-effects, while 1 subject

had the dose decreased to 20 mg/d by week 5 because of frontal headaches.

### Imaging procedures

Positron emission tomography (PET; GE model-2048, Milwaukee, WI; resolution 4.5 mm in plane) with  $^{18}\text{F}$ -deoxyglucose as tracer was performed at baseline and after the 8-wk medication period (a sham scan was obtained following the placebo period; the PET laboratory was entirely physically separate from the clinical care group and information was rigorously segregated). Co-registration to structural anatomical images was performed as described previously (Haznedar et al., 1997b). Parameters for magnetic resonance imaging (MRI) axial acquisitions (1.5 T GE Signa 5 × system) were as follows: TR = 24 ms, TE = 5 ms, flip angle =  $40^\circ$ , contiguous 1.2-mm slices.

Specific regions of interest identified in the hypotheses were defined using either standardized stereotaxic methods or structure tracing on the co-registered MRI. For anterior cingulate, medial frontal and parietal-occipital comparison control areas, we examined the atlas of Talairach and Tournoux (1988) and selected the centres of structures identified in the hypothesis for assessment (hypothesis-driven reverse Talairach-Tournoux coordinate method). Next, a  $3 \times 3$  pixel box was applied stereotaxically to each PET scan (top left panel of Figure 1) and relative metabolic rate data obtained (see Wu et al., 1999 and Haznedar et al., 1997a for details). The Brodmann areas of the prefrontal region were assessed on coronal slices perpendicular to the anterior-posterior commissure (AC-PC) line obtained by resectioning. A radial strip method was applied and Brodmann areas were assessed stereotaxically on the basis of a whole human brain post-mortem histological atlas (Perry et al. unpublished observations) examined as described elsewhere (Hazlett et al., 1998). This atlas has 33 proportional coronal slices which correspond very closely to the 33 coronal slices of the Talairach and Tournoux atlas from +65 mm to -95 mm at 5 mm steps. Brodmann areas were identified on proportionately spaced coronal stained sections. The section drawings were digitized and the brain edge, midline and centroid for each hemisphere were identified using the same software on both the drawings and similarly spaced MRI co-registered to PET. Thirty sectors were drawn (centroid to cortical rim) and relative metabolic rates in each sector were assessed selecting only pixels segmented as grey matter on the co-registered MRI. The sectors for each Brodmann areas were identified from the drawings and the mean for each area computed across slices. The Perry and Talairach-Tournoux atlases differ slightly: the Perry atlas was considered 33 slices at



**Figure 1.** Analyses of fluoxetine effects on relative metabolic rate based on three different methods (by Talairach–Tournoux positioned ROIs, cortical surface stereotaxis, and significance probability mapping, SPM) confirm fluoxetine’s regional effect. *Left upper panel:* Regions of interest (ROI) positioned using the Talairach–Tournoux atlas box positions at z-levels 32, 28, 20, 12, –4 (labelled respectively 5, 6, 7, 8, and 9) in middle frontal (x–y pairs at the 5 slice levels respectively, 36,42; 35,41; 31,46; 38,51; 40,50), cingulate (6,9; 6,–22; 8,25; 8,33; 8,36) and parietal–occipital regions (5,–65; 5,–65; 5,–72; 5,–68; 6,–90) show fluoxetine effect in the cingulate but not parietal control regions; three-way MANOVA ( $F_{8,40} = 2.19$ ,  $p = 0.049$ ) with repeated measures for drug treatment (baseline, fluoxetine), region (medial frontal, cingulate, and occipital) and z-slice level. Relative metabolic rate was measured in  $3 \times 3$  pixel square boxes in left and right hemispheres positioned using a method closely similar to the linear proportional method of Talairach and Tournoux (Haznedar et al., 1997a,b). *Left lower panel:* Cortical surface stereotaxic method analysis confirms fluoxetine effect in medial frontal, posterior dorsolateral, and cingulate regions (4-way MANOVA for drug treatment, hemisphere, Brodmann area grouping region (anterior dorsolateral prefrontal, orbital and medial frontal, and medial frontal/posterior prefrontal), and individual Brodmann area;  $F_{2,8} = 9.18$ ,  $p < 0.0085$ ). *Right upper image:* SPM mapping for coronal section also confirms cingulate increases with fluoxetine (Talairach and Tournoux; x, y, z = 12, 35, 17) confirmed with method of Friston et al. (1991) (figure patch threshold  $t = 2.571$ , 2-tailed  $p < 0.05$ , maximum  $t = 9.68$ , greater than corrected  $t = 3.814$  for  $p < 0.05$ ). SPM mapping for 3-D anterior cingulate gyrus shows significant correlation between metabolic rate on the baseline scan and CGI improvement after fluoxetine treatment (figure patch threshold  $r = 0.805$ ,  $p < 0.05$ ,  $r$  patch average =  $-0.884$ , maximum  $r = -0.99$ , resampling  $p < 0.05$ ).

5-mm intervals in a brain extending from +70 mm to –100 mm while the Talairach and Tournoux atlas extends to –102 mm and includes a very small –100 mm slice. Since neither our method nor Perry et al. (unpublished observations) include the posteriormost atlas slice nominally touching –102 mm and mathematically of zero diameter as a tangent plane while Talairach and

Tournoux do include a 10-mm diameter section at this position, the correspondence approaches an identical method. This method complemented the  $3 \times 3$  pixel boxes by following the outer edge of the brain radially on the co-registered MRI and providing larger regions of interest covering the entire Brodmann area, but lacks the standardized reporting nomenclature of the hypothesis-

driven reverse Talairach–Tournoux coordinate method. The caudate and putamen were reliably traced (Shihabuddin et al., 1998) on the co-registered MRI at  $z = 12, 4$ , and  $-4$  (Talairach and Tournoux, 1988), and relative metabolic rate calculated as counts in the area divided by mean counts assessed within the whole brain as traced on axial MRI slices matching the PET.

For the 3-D exploration of the cingulate gyrus, M.M.H. and A.S. outlined the ACG on axial MRI slices (intertracer intraclass correlation coefficient for ten subjects volume = 0.87). Outlining began with the plane showing the appearance of the cingulate sulcus and ended dorsally (25–30 planes higher) with the plane showing the disappearance of the corpus callosum. The ACG was outlined from the deepest recess of the cingulate sulcus, moving medially and then in an inferior direction until reaching the callosal recess. The two recesses were connected with a straight line, and this triangular area also included the cingulum.

### Statistical analyses

A priori hypotheses were tested with targeted multivariate analysis of variance (MANOVA) comparisons for regions of interest (ROIs) and exploratory analyses covering larger adjacent areas were carried out with 2-D and 3-D significance probability mapping (SPM) (see Haznedar et al., 1997b). To test hypothesis 1 (increased metabolism in the ACG and neighbouring orbital-frontal cortex predicts clinical response after fluoxetine), we chose the coordinates of these two regions from the Talairach and Tournoux atlas (1988). To test hypothesis 2 (differential metabolic response to fluoxetine in orbito-frontal and dorsolateral cortex), we used these same stereotaxic values plus additional parieto-occipital control (or contrast) areas to evaluate the specificity of the findings. A second analysis using Brodmann areas obtained stereotaxically was also carried out to assess the robustness of the finding in this small sample.

The significance probability mapping technique is similar to other approaches (Friston et al., 1991) but uses MRI-based region-alignment and adds conservative resampling to assess statistical significance. We chose the  $y = 35$  mm coronal slice for its central position in the part of the cingulate anterior to the corpus callosum as the slice to explore. Continuous edges were manually drawn around the brain. Nine midline points equally spaced in the  $z$  direction were identified. Slices were then adjusted by the number of rows and columns so that every slice contained an equal number of pixels with every edge pixel aligned and midline pixels positioned in a vertical strip at edge centre. Co-registered PET images were similarly standardized and  $t$  tests carried out for each pixel. We

provided the  $t$  tests corrected for multiple use as in Poline and Mazoyer (1993) and resampling as in Haznedar et al. (1997b). For resampling we examined random draws with replacement of the 6 individuals assigned to placebo or medication. For each such permutational sample we computed the paired  $t$  test and examined the largest cluster of contiguous pixels obtained with a  $p < 0.05$  threshold. The volume of this cluster (number of pixels multiplied by the mean value above the threshold) was tabled. After 5000 samples the resulting histogram was examined and the 95% limit obtained. This method has been published elsewhere (Siever et al., 1999).

Changes on behavioural tests were assessed with paired  $t$  tests, two-tailed. Correlations between metabolic rate and regional brain metabolic rate were assessed with product-moment correlation coefficients, and tested two-tailed. Three-dimensional correlations between metabolic rate and ratings were similarly calculated and displayed in Figure 1.

### Results

As shown in Table 1, fluoxetine-treated autistic patients showed significant improvement on the Y-BOCS – Obsessions Scale and the HRSA; CGI improvement scores showed an apparently bimodal distribution, with 3 out of 6 patients much improved (CGI improvement rating of 2; 2 autistic, 1 Asperger's syndrome) and half unchanged (rating of 4), but the sample was too small to achieve reasonable power for non-normality testing.

We examined correlations between frontal and ACG metabolic rate at baseline and clinical response in the patients to test the hypothesis that greater clinical response as assessed by the CGI baseline Autism score was associated with higher metabolic rates in the left medial frontal cortex (Talairach–Tournoux  $z$ -level =  $-4$ ;  $r < -0.88$ ,  $p < 0.05$ , 2-tailed), right medial frontal cortex ( $z$ -level =  $+26$ ;  $r = -0.77$ ,  $p < 0.05$ , 1-tailed) and right ACG ( $z$ -level =  $-4$ ;  $r = -0.59$ ,  $p < 0.10$ ) (Figure 1). Improved HRSD scores were also predicted by right ACG metabolism in the baseline scan ( $z$ -level =  $+26$ ,  $r = -0.83$ ,  $p < 0.05$ , 2-tailed;  $z$ -level =  $+26$  and  $+8$ ,  $r = -0.80$  and  $-0.74$ ,  $p < 0.05$ , 1-tailed).

Fluoxetine-treated patients showed significantly increased relative metabolism in frontal ROIs of the right but not the left hemisphere (Figure 1), most marked in the ACG and largely absent in parietal-occipital regions. Analysis of the prefrontal cortex by Brodmann areas confirmed a significant differential fluoxetine effect in the ACG and ventral frontal areas with a three-way treatment by region by slice level interaction (Figure 1).

Metabolic rate was also significantly increased in the striatum, especially on the right (medication condition  $\times$

**Table 1.** Clinical change with fluoxetine

Scale	Baseline		Fluoxetine		Difference			
	Mean	S.D.	Mean	S.D.	Mean	S.D.	<i>t</i>	<i>p</i>
Y-BOCS obsessions	9.67	3.44	5.67	4.17	4.00	3.35	2.92	0.03
Y-BOCS compulsions	6.83	4.88	6.67	4.37	0.17	2.23	0.18	0.86
Y-BOCS total	16.50	7.50	12.33	8.29	4.17	4.31	2.37	0.06
CGI autism	4.00	0.63	3.00	1.10	1.00	1.26	1.94	0.11
Hamilton anxiety	6.17	5.42	1.67	2.42	4.50	3.51	3.14	0.03
24-item HRSD	9.00	7.54	5.17	4.49	3.83	3.87	2.43	0.06

**Table 2.** Individual patient response

Patient no.	Dx	Est. IQ	Y-BOCS			CGI base severity	CGI improvement end fluoxetine	Responder
			Base	End	Change			
1	Aut	53	16	11	5	5	2	+
2	Asp	100	31	8	23	3	2	+
3	Aut	74	16	10	6	5	2	+
4	Aut	119	5	7	-2	4	4	-
5	Aut	108	32	26	6	4	4	-
6	Aut	116	6	9	-3	4	3	-

+, Responder; -, non-responder.

hemisphere interaction,  $F_{1,4} = 14.4$ ,  $p = 0.019$ ). The effect was largest in the ventral putamen, but the medication condition  $\times$  structure  $\times$  level  $\times$  hemisphere interaction was significant only at a trend level ( $F_{2,8} = 3.07$ ,  $p = 0.10$ ).

## Discussion

Metabolic changes in the ACG, medial and orbitofrontal region and striatum were linked to therapeutic response to fluoxetine in patients with autism spectrum disorders, consistent with (1) earlier findings of baseline abnormalities in ACG metabolism in autism (Haznedar et al., 1997b); (2) metabolic changes in the medial frontal and cingulate following SRI administration (e.g. Buchsbaum et al., 1997) and (3) baseline cingulate metabolism prediction of SRI response (Buchsbaum et al., 1997; Mayberg et al., 1997). Like depressed patients, individuals with autism spectrum disorders who had relatively high metabolic rates in the ACG before treatment compared to other patients were more likely to show a clinical response to SRI treatment than were those with normal or low metabolic rates at baseline. In both autism and depression, baseline metabolic rates tended to be lower than normal,

yet individuals with relatively increased rates were more likely to show a therapeutic response.

The anterior cingulate and medial prefrontal cortex have been hypothesized to modulate internal emotional response. Devinsky et al. (1995) distinguished the emotional role of Brodmann areas (BA) 25–32 from the attentional role of BA 24. Note that the area of strongest correlation between metabolic rate in the placebo scan and clinical response to fluoxetine is the emotional area (BA 25, Figure 1).

Although all clinical scores showed improvement (albeit statistically significant for only two scales) after fluoxetine, there were individual differences in therapeutic responsiveness as reflected by the CGI scores. Accumulation of larger numbers of patients than were available for this preliminary report will be necessary to demonstrate that a subgroup exists, confirm bimodal distributions, and evaluate how well brain imaging methods can identify these individuals. Because of the small sample, type II error may have prevented us from demonstrating differential effects among components of the striatum, significant correlations with some behavioural scales, and group medication effects with the HRSD. It is hoped that extending these studies will shed further light on patterns of regional brain metabolism that may prove predictive of response to treatment with SRIs. It is clear from the clinical

literature (Hollander et al., 1998; McDougle et al., 1996) that only a subgroup of autistic patients show a significant clinical response to SRIs, so biological correlates of individual differences in serotonergic responsivity are of interest. The observation of decreased [ $^{11}\text{C}$ ]methyl-tryptophan uptake (Chugani et al., 1997), indicative of decreased serotonin synthesis in frontal regions, but increased serotonin synthesis in cerebellar regions, may be useful in pursuing these differences. The areas of decreased serotonin synthesis in the frontal cortex are rich in 5-HT-1d inhibitory autoreceptors (Pascual et al., 1996), whereas brain regions with increased 5-HT synthesis, such as cerebellum lack 5-HT inhibitory autoreceptors. The severity of repetitive behaviours as measured by the Y-BOCS parallels the growth hormone response to the 5-HT-1d agonist sumatriptan in autism (Hollander et al., 2000). This suggests that a specific component of the serotonin system may play a role in mediating one specific behavioural component of autism, repetitive behaviours, which might help to sort out the heterogeneity in autism. The current study may also further help by identifying a subgroup of patients with increased metabolic activity in frontal and anterior cingulate regions who are most responsive to the serotonin enhancing effects of SRIs such as fluoxetine.

We plan to extend these studies in larger numbers of patients with both autism and Asperger's syndrome, as the small number of patients in each subgroup precluded meaningful analysis of differences in responsiveness that may distinguish two presumably related diagnostic groups that are included within the spectrum of autistic disorders. Our patients were all verbal and relatively high-functioning, so studies in patients with a greater degree of impairment are needed. Nevertheless, our results are not dissimilar to those reported by McDougle et al. (1996) in a trial with fluvoxamine in 30 adults with autistic disorder who found that approx. 50% of adult patients were global treatment responders. Our pilot study adds to the literature in this area by reporting potential predictors of therapeutic response derived from functional brain imaging and suggests that heterogeneity in medication response in autism may be related to individual differences in the function of the limbic system.

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