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# $^{99}$mTc HMPAO Cerebral Blood Flow Imaging Reveals Tourette's Network when Compared to Healthy Controls

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## Abstract

**Background:** Published imaging abnormalities in Tourette's syndrome (TS) patients are variable. The objective of this study was to measure changes in Cerebral Blood Flow (CBF) using SPECT HMPAO in adult patients with TS compared to Healthy Controls (HC). Based on prior volumetric MRI, nuclear medicine and post mortem studies our a *priori* hypothesis was that the CBF to the caudate nucleus would be reduced.

**Method:** We measured CBF changes using $^{99}$mTc HMPAO SPECT in 10 adults with TS and 10 matched HC. Following injection of 30 mCi of $^{99}$mTc HMPAO, SPECT images were acquired. Statistical parametric mapping (SPM) analysis was performed using the Neuro-MIM software. Z scores were then generated for significant p values < 0.05.

**Results:** TS subjects were 40 ± 13 years old with an average Yale Global Tic Severity Scale (YGTSS) of 28.4 ± 10.8. A significant decrease in CBF was noted in the caudate nucleus, putamen, the insula, the olfactory cortex and medial temporal lobe structures (amygdala, hippocampus and para-hippocampal gyrus) (Z scores: -2.01, -3.04, -1.89, -2.11, -2.66, -3.0, and -2.82, respectively). On the other hand, significant increases in CBF were noted in the occipital lobe and primary visual cortex regions (Z scores: +1.84, +1.82). Only borderline increases in the motor and somatosensory areas (Z scores: +1.2 and +1.47) were noted.

**Conclusion:** Measurable changes in cerebral blood flow exist in the basal ganglia bilaterally as well as other brain regions in adult TS patients compared to HC. An abnormal blood flow network beyond the basal ganglia may exist and can be imaged in Tourette's. This manifests as CBF decreases in the insula, caudate nucleus, olfactory cortex, and medial temporal lobe structures and increases in the occipital lobe. These findings need to be replicated in a larger cohort.

**Keywords:** SPECT; HMPAO; Tourette; CBF

## Introduction

Tourette's syndrome is a disease characterized by motor and vocal tics. There is a wide variability in behaviors and impact on daily function. Slight differences exist between pediatric and adult TS [1-4]. Imaging reports show some differences regarding anatomical and functional abnormalities in TS patients [3,5]. Imaging would be a very useful biomarker in TS whether it be at baseline or in the long term management of patients. It has been used with some promise to assess post- therapeutic mechanistic changes and possibly earlier signs of behavioral or drug therapy efficacy. At baseline a few anatomical changes have been noted [6-8]. On the other hand functional changes have been described in greater detail using functional MRI, as well as SPECT and PET nuclear medicine techniques [6,8-10]. Yet at times inconsistency in published data is found regarding these baseline routine imaging changes [7,11,12]. The cortico-striatal-thalamic-cortical circuitry (CSTC) has been described in the pathophysiology of TS and other movement disorders [3,7-9,11,13-21]. This pathway/network has been heterogeneously and inconsistently delineated on imaging. However, both volumetric MRI studies and postmortem brain studies point to abnormalities in the caudate nucleus, allowing us to hypothesize that cerebral blood flow (CBF) would be reduced in this basal ganglia structure [22]. Nuclear medicine techniques are routinely used and can accurately explore *in vivo* pathophysiological changes [5,21,23-25]. They have been utilized successfully to observe and measure cerebral blood flow (CBF) in several psychiatric conditions [25-30]. CBF measurements have the benefit of being able to image the whole brain and in a non-targeted fashion, while more specific/targeted radiotracers may give us only a portion of the story. Widely available semi quantitative SPM analysis techniques have revolutionized brain PET and SPECT imaging and can be used to perform comparisons to healthy control databases [1]. Changes in CBF have been noted in TS 20 years ago. Since then imaging has progressed and so have the findings owing to improvements in techniques, software and hardware. In this study, we wanted to measure CBF changes using single photon emission computed tomography (SPECT) with hexamethylpropyleneamine oxime (HMPAO) in adult patients with TS and compare it to healthy controls (HC). Based on prior volumetric MRI, nuclear medicine imaging and post mortem studies our a priori hypothesis was that the CBF to the caudate nucleus would be reduced.

## Methods

We measured CBF changes in 10 adults with TS using SPECT HMPAO compared to HC. After local Yale IRB approval, 10 patients were recruited with appropriate consenting per protocol. All patients

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were injected with approximately 30 mCi of $^{99m}$Tc HMPAO. Following an uptake phase of about 60 minutes, where patients rested, eyes open in a dimly lit room per our standard protocol, imaging was performed. 360° SPECT images were acquired with a dual headed Symbia T2 camera, using a circular orbit with auto contouring at 30 seconds per frame. Reconstruction of images was performed using a 3D Flash iterative algorithm. Reconstructed SPECT datasets were co-registered to a commercial HC database using the Neuro-MIM software. Z scores were then generated for significant p values <0.05. Significant Z scores were determined to be < -1.5 or > +1.5. In addition to the caudate nuclei, 25 regions of interest were analyzed in an exploratory fashion. Experienced technologists performed data acquisition and pre-processing. An experienced nuclear medicine physician performed post-processing SPECT data and interpretation of studies. All patients underwent brain MRI acquisitions without contrast per Yale neuroradiology standard clinical protocol.

## Results

Our cohort's mean age was 40 ± 13 years old [29-58]. We had 9 males and 1 female. The average YGTSS total tic severity score was 28.4 ± 10.8. Two subjects reported clinically significant OCD symptoms (Y-BOCS ≥ 12). Eight subjects reported significant ADHD symptoms at baseline (Connor's ADHD rating scale ≥ 18). However only 3 subjects reached a diagnostic threshold for comorbid OCD and 1 subject reached a diagnostic threshold for comorbid ADHD. A summary of our cohort and medication status is found in Table 1. All MRI studies were reviewed and reported clinically by a neuroradiologist. Qualitative reads did not detect any abnormalities in any of our patients. However we noted a few changes in CBF (Figures 1 and 2).

### Basal ganglia structures

At baseline significantly reduced CBF was observed in the TS subjects in the caudate nucleus (z=-1.9, p<0.05). Reduced CBF in the globus pallidus (z=-1.3, p<0.05), putamen (z=-2.01, p<0.05) and thalamus (z=-1.2, p<0.05) was observed at trend levels (Figures 3 and 4).

### Sensorimotor cortical structures

There was increased CBF in precentral (z=+1.2, p<0.05) and post central (z=+1.5, p<0.05) gyri in TS subjects compared to healthy controls at trend levels.

### Temporal lobe structures

TS subjects showed a significant decrease in CBF in several temporal lobe structures compared to healthy controls. Significantly reduced CBF in TS subjects was observed in amygdala (z=-2.7, p=0.004), hippocampus (z=-3.0, p=0.001), para hippocampal gyrus (z=-2.8, p=0.003) and the medial temporal lobe as an overall structure (z=-3.1, p=0.001).

### Other cortical structures

Significant CBF reductions in TS subjects were also observed in the insula (z=-3.0, p=0.001), olfactory cortex (z=-2.1, p=0.02) and significant increases in the visual cortex (z=+1.82, p<0.05). In summary, on HMPAO SPECT scans we demonstrated several baseline differences between TS subjects and healthy controls. Consistent with our a priori hypothesis a significant decrease in CBF was noted in the caudate nucleus as well as the putamen. In addition, significant decreases were seen in the olfactory cortex, the insula, and medial temporal lobe structures including the amygdala, hippocampus and para-hippocampal gyrus (Z scores: -1.89, -2.01, - 3.04, -2.11, -2.66, -3.0, and -2.82 respectively). Borderline abnormal decreases were noted in the globus pallidus, thalamus and anterior cingulate gyrus (Z scores: -1.34, -1.23, and -1.46 respectively). On the other hand, significant increases in CBF were noted in the occipital lobe and primary visual

| Age | Sex | ADHD | OCD | Antipsychotic | Alpha-2 | SSRI | Benzo | Other |
|---|---|---|---|---|---|---|---|---|
| 51 | M | - | X | - | - | Fluvoxamine | Clonazepam | - |
| 42 | M | - | - | - | - | - | - | - |
| 30 | M | - | - | - | Clonidine | - | - | Loratidine |
| 26 | M | - | - | - | - | - | - | - |
| 53 | M | X | - | - | - | - | Clonazepam | Atomoxetine |
| 29 | M | - | X | - | - | - | - | - |
| 62 | M | - | - | - | - | - | - | - |
| 29 | M | - | - | Pimozide | - | - | - | - |
| 31 | M | - | - | - | - | Sertraline | - | Propranolol |
| 45 | F | - | X | - | - | Sertraline | - | Buproprion |

**Table 1:** Clinical and medication characteristics.

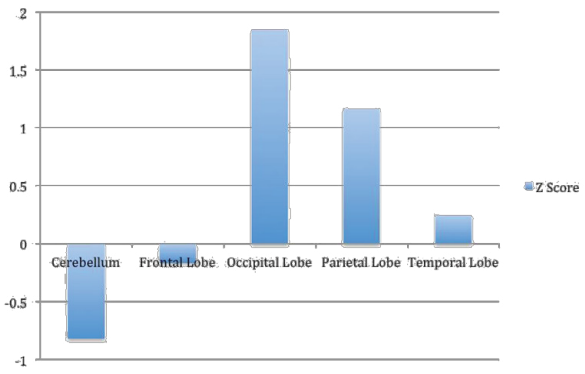


**Figure 1:** Z-Scores of blood flow in the cerebellum and different cerebral lobes.

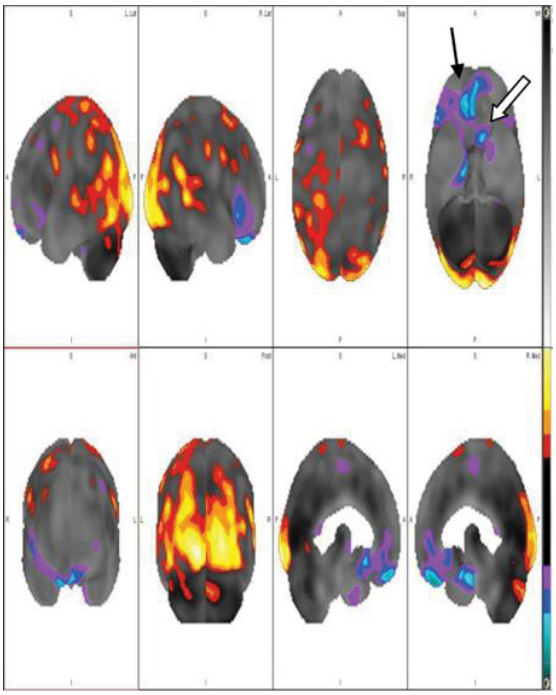

**Figure 2:** Surface map projection of Z scores of a patient with TS compared to HC showing increases in CBF in the occipital lobe and decreases in the orbitofrontal region (thin black arrow) and basal ganglia (thick white arrow).

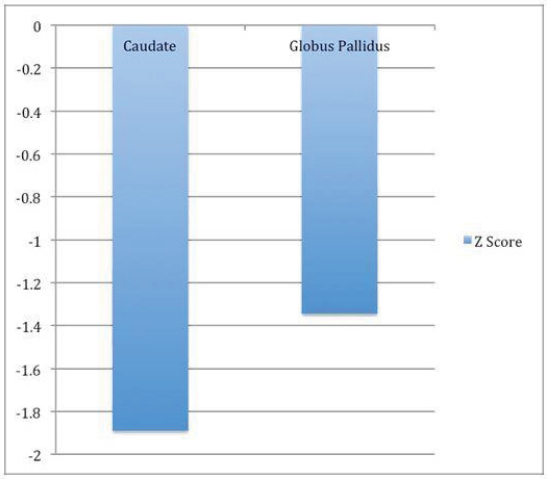


**Figure 3:** Z-Scores of cerebral blood flow in basal ganglia structures for p<0.05. Significant changes are noted in the caudate nucleus.

cortex regions (Z scores: +1.84, +1.82) and borderline increases in the motor and somatosensory areas (Z scores: +1.2 and +1.47) (Table 2).

## Discussion

Our data reveals a quite extensive area of CBF changes beyond the basal ganglia as well as beyond the conventionally described CSTC pathway. This suggests a widespread network of blood flow changes either directly related to the intrinsic Tourette's disease process or linked to comorbidities and compensation mechanisms. Currently published imaging data in TS is a bit variable. Morphologic CT and MRI data are sparse and have seldom showed conflicting anatomic

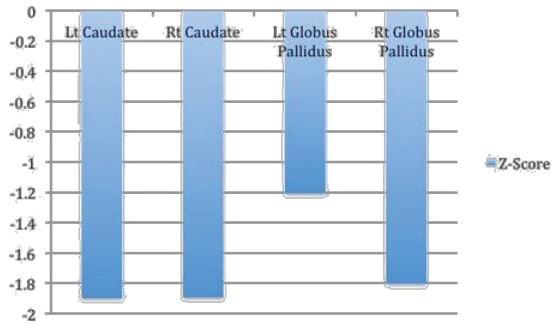


**Figure 4:** Figure 2. Z-Scores of cerebral blood flow in basal ganglia structures bilaterally for p<0.05. Left versus Right sided Z score changes in BG structures. There was no significant difference between left or right as previously described in the right caudate, if anything a slight trend was seen in the right globus pallidus not caudate nucleus.

| Region | Z Score |
|---|---|
| Caudate nucleus | -1.89 |
| Globus pallidus | -1.34 |
| Thalamus | -1.23 |
| Cerebellum | -0.82 |
| Frontal lobe | -0.16 |
| Parietal lobe | 1.16 |
| Temporal lobe | 0.25 |
| Occipital lobe | 1.85 |
| Amygdala | -2.66 |
| Hippocampus | -3 |
| Para hippocampal gyrus | -2.82 |
| Superior temporal Gyrus | 0.76 |
| Medial temporal lobe | -3.12 |
| Para central lobule | 0.005 |
| Post central gyrus | 1.47 |
| Precentral gyrus | 1.2 |
| Supplementary motor area | 0.13 |
| Anterior cingulate gyrus | -1.46 |
| Posterior cingulate gyrus | -1.14 |
| Cuneus | 0.79 |
| Precuneus | -0.99 |
| Fusiform gyrus | 0.21 |
| Insula | -3 |
| Lingual gyrus | -0.5 |
| Olfactory cortex | -2.11 |
| Primary visual cortex | 1.82 |
| Orbitofrontal Region | -0.86 |

**Table 2:** Regional Average Z scores values for p<0.05.

changes. These have been shown to include most commonly asymmetric volume changes in the basal ganglia [4,6]. Other contradictory structural changes have been reported to include the prefrontal, orbitofrontal, limbic and somatosensory cortices [6,7,11,14,15,31-33]. These reports have not been consistent in the adult or pediatric populations [19,34-36]. These anatomical findings are well summarized by Church et al. [6]. On the other hand functional MRI techniques have been more revealing [16,17,37,38]. SPECT and PET imaging has also explored noninvasively several pathways in TS patients including the metabolic, dopaminergic, serotoninergic and cannabinoid pathways [15,31,39-48]. Reports are also variable and at times contradictory for all pathways. These studies have imaged a specific process and do not allow a global view of functional changes. Therefore, they have offered

insight into a small portion of the story but not the whole picture since all these probes cannot practically be imaged at the same time. Radiotracer distribution has been found to be quite different in specific structures in between studies. For example, dopamine radiopharmaceuticals are found to be increased in the basal ganglia in some studies and decreased in others [26,47,49-51]. The benefit of using nonspecific probes such as measuring overall cerebral blood flow changes can allow us to detect primary and secondary changes. Hence CBF imaging offers an idea about global changes. Regarding SPECT CBF changes in TS, a few studies have been reported with some discrepancies in results. Our study, on the other hand benefits from the latest advanced semi-quantitative techniques, much higher resolution of the newest SPECT cameras and better co-registration tools when comparisons are made to normal databases. Image reconstruction techniques have also dramatically improved with iterative algorithms being robust and currently standard of care. We believe the findings in our study offer a clear correlation with the natural pathophysiology of the disease. Not surprisingly we found changes in the caudate nucleus, which are expected in TS as the basal ganglia are the cornerstone of movement control and tic development. Changes in CBF with HMPAO/ECD in the caudate nucleus and other structures have been described in the past [10,28-30, 52,53]. Less robust techniques have described more globally decreased CBF in the basal ganglia or even asymmetry more so on the right side in some studies [53], while others have described it on the left [10,54]. Our study unlike others was able to discriminate between changes in CBF in other basal ganglia structures such as the globus pallidus where only borderline significance was noted. Our study did not find any asymmetry in caudate uptake. Prior reports may have been confounded by psychiatric comorbidities or suboptimal techniques. Changes we found in the insula, thalamus and anterior cingulate gyrus are felt to be related to the thalamo cortical pathway. Involvement of these structures has also been described with other neuroimaging studies [10, 46,54-56]. Our study shows that these changes although present are not prominent semi-quantitatively. Cingulum changes have been described in other studies as it is essential for brain connectivity and emotional and non-emotional integration of information. In other clinical examples of elevated anterior cingulate cortex activity it may contribute to tics, obsessive-compulsive behaviors, and aberrant social behavior. Conversely, reduced cingulate activity following infarcts or surgery can contribute to behavioral disorders including akinetic mutism, diminished self-awareness and depression, motor neglect and impaired motor initiation, reduced responses to pain, and aberrant social behavior. Overall, anterior cingulate cortex appears to play a crucial role in initiation, motivation, and goal-directed behaviors [57]. We also found changes in the primary motor and somatosensory cortices. Although our findings were not greatly significant statistically they are in accordance with other MRI and clinical reports involving the somatosensory cortex in some way in TS. These changes noted in pre and postcentral gyri have been noted to be more pronounced in other dystonia's and movement disorders [14,31]. Although discordant, several authors found that there may be changes in grey matter volumes in the primary somatosensory cortex, theorized in one report that it may be related to premonitory urges [7,11, 15,33,38,58]. This discordance may due to differences in methods as measurement of grey matter volume and thickness is not standardized today and is used only in research. On other hand SPECT and PET semi-quantitative techniques –as used in our study- are routinely performed clinically and have been well validated. This prompts us to believe that our findings in the primary somatosensory and visual cortices should not be disregarded. TS patients may use compensatory mechanisms, for example they may recruit the somatosensory and orbital cortices in order to overcome slower task performance or other limitations [3,7,32]. Functional changes in the pre and post-central gyrus have been also described with functional MRI7, [38] Visual cortex involvement in the TS network was of some surprise, and although not fully explained it may still fit with the larger somatosensory changes. Whether these changes are intrinsic to the disease or adaptive/maladaptive is unknown. This is less likely artefactual from patient preparation during the uptake phase of the radiotracer because it was quite consistent and prominent in nearly all patients. Although increases in CBF in the occipital lobe, SMA and primary somatosensory cortices have been described in the past [15,40,41,46] they did not reach statistical significance in our study. We could not reproduce any SMA changes, but the occipital lobe/primary visual and primary somatosensory cortices changes were present. The traditionally proposed rationale is that these represent outflow tracts in movement disorders. These changes may be at the origin or in part directly involved in the disease pathophysiology. This may be the lead to changes in other neurotransmitters or simply an accompanying factor. On the other hand changes in CBF may also be a consequence of abnormal neurotransmission. Lastly a hypothesis has been generated that behavioral and cerebral functional changes are frequently induced by patients to inhibit their tics. CBF changes may then be in part attributed to symptom control chemical changes as these patients develop a variety of mechanisms intended to control motor movements/tics potentially by accentuating the somatosensory pathways. In order to understand our findings we need to look at the pathophysiology of tics and TS. Berardelli [3] describes extensively changes that are seen. He concludes that when advanced visual information is reduced, patients with tics and TS become progressively slower in completing motor sequences. Therefore one could assume that our group showing increased CBF in the occipital lobe and primary visual cortex may be a compensatory adaptive mechanism that allows for proper voluntary movement initiation. Dysfunction in the basal ganglia-thalamo-cortical projections would affect the sensorimotor integration explaining changes we've noted in CBF in these regions. The limbic cortical circuits including the amygdala and other medial temporal lobe structures will also be affected as confirmed in our study. Diffusion tensor imaging (DTI) is functional MRI sequence that detects the white matter fibers that connect different parts of the brain. Church et al. [6] suggests in a review paper that DTI is pointing towards functional changes in the corpus callosum, somatosensory and motor cortex and the caudate [6]. Additionally, we have found decreases in CBF in the olfactory cortex. This has never been reported before with any imaging technique in TS. However, this finding is not surprising as deficits in the sense of smell are quite common in Parkinson's and changes in olfaction have been described in several other movement disorders including some hints in TS. The challenge in TS patients and other movement disorders is that these may frequently be subclinical. Advanced and appropriate testing is required to uncover olfactory changes clinically and patient reports are usually not reliable. Lack of significant frontal or prefrontal changes in our study may be due to a less prominent comorbid psychiatric profile of our patients.

## Limitations

Our sample size was small which may limit the ability to detect smaller changes in CBF. The presence of confounding comorbidities, although less likely in our cohort may also affect CBF, which can be altered in some psychiatric disorders. None of our subjects reported significant depression or anxiety symptoms as assessed by HDRS and HARS. The effects of medications on CBF were not assessed although

this is also a lesser confounding factor in our cohort as seen in Table 1. The intrinsic properties of SPECT with its limited spatial resolution can be overcome by performing PET CBF studies, however current PET CBF is not readily available. Those studies are much more difficult to perform logistically. However a follow-up PET CBF study would be of great value. Lastly we have not performed any partial volume averaging corrections to account for any grey matter volume changes. This would most likely not impact most of our findings that are strongly positive but may improve detection of changes in areas that were borderline abnormal.

## Conclusion

Measurable reductions in cerebral blood flow exist bilaterally in the caudate nuclei and the putamen of TS patients compared to healthy controls. Our study also shows CBF decreases in the insula, olfactory cortex, and medial temporal lobe structures and CBF increases in the occipital lobe. If replicated a network involving all these structures should be explored in greater detail.

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