

In nuclear medicine, the patterns seen in images represent spatial and temporal arrangements and rearrangements of the physiological or biochemical processes under investigation. How are these patterns best detected and compared?

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Chapter 7

Interpretation of 3D Fusion of Clinical SPECT and MR Brain Images: Preliminary Results

Abstract

A preliminary qualitative interpretation of 3D fusion for clinical cases is conducted. The SPECT and MRI data of two patient groups, *i.e.*, cases diagnosed with the Gilles de la Tourette Syndrome and Attention-Deficit Hyperactivity Disorder, are presented using the Normal Fusion technique. These fusion images are first compared with the 2D SPECT images to assess whether Normal Fusion accurately characterizes the functional data of the cortical surface layer. Then the fusion images of the individual cases are qualitatively evaluated and the two patient groups are compared. The results indicate that the signaling of cortical activity by the Normal Fusion images is in good agreement with 2D SPECT reconstructions and that specific patterns of hypo or hyperactivity are more easily recognized with the Normal Fusion technique.

7.1 Introduction

The routine availability of multiple imaging modalities for patient investigation provides new insights to the clinician, but also poses challenging demands on the extraction and presentation of the multivariate data. The mental integration of multiple tomographic datasets into one consistent 3D representation of the patient is an extremely difficult task which calls for computer assistance. Integration or fusion of image data requires registration of the different sets into the same coordinate frame and presentation of the information in an integrated fashion.

This thesis focusses on techniques for the integrated visualization of functional and anatomical brain data. Evaluation of several of these techniques is presented in Chapter 6 for the localization of abnormalities. Here we perform a preliminary interpretation of integrated visualization using the Normal Fusion images from Chapter 6.

In Figure 4.2 Normal Fusion images of two children, diagnosed, *resp.* with the Gilles de la Tourette Syndrome (TS) and autistic behavior, are presented. The patterns of cerebral blood flow observed in these images prompted this study. In the current chapter two patient groups, *i.e.*, children diagnosed with either TS ($n=6$) or Attention-Deficit Hyperactivity Disorder (ADHD) ($n=6$), are used. Only these two groups were available with a combination of a sufficiently high resolution MRI dataset and HMPAO-SPECT images.

The aim of this chapter is twofold: *i)* To compare the Normal Fusion images with the original 2D SPECT data to determine whether the integrated 3D presentations accurately characterize the SPECT information of the surface layer of the brain. *ii)* To qualitatively investigate patterns of cerebral blood flow in the integrated images.

We will first provide some background on both TS and ADHD, and then give a description of the patient groups and the setup of the study.

7.1.1 The Gilles de la Tourette Syndrome

TS is a chronic neuropsychiatric disorder that has its onset in childhood and is primarily characterized by multiple motor and vocal tics. Virtually any muscle group can be affected by tics, but the onset is usually in the orofacial region (Peterson et al. 1993). A genetic etiology is supported by family-genetic and twin studies, with most likely a sex-influenced autosomal dominant mode of inheritance and variable expressivity as TS, chronic motor tic disorder or obsessive-compulsive disorder (Cohen and Leckman 1994, Robertson 1994). Subjects with TS often exhibit comorbid disorders in addition to the wide range of tics, such as ADHD in children and adolescents and obsessive-compulsive disorder at adult age. About 40% of the children and adolescents with TS have a comorbid ADHD.

A substantial body of data implicates the basal ganglia and related cortical and thalamic structures in the pathophysiology of TS (Leckman et al. 1992). Post-mortem studies have so far not established specific abnormalities, except for one case with

smaller neurons in the putamen and caudate nuclei (Richardson 1982). This suggests hypoplasia of parts of the basal ganglia which may be due to some developmental arrest. In vivo neuroradiologic studies provide support for the involvement of the basal ganglia in the pathophysiology of TS. Structural neuro-imaging by means of 3D reconstructed MRI has demonstrated smaller volumes of the caudate, lenticular and globus pallidus nuclei in TS subjects compared to controls. Furthermore, an absence of the normal volumetric asymmetry (left greater than right) was shown in TS subjects (Peterson et al. 1993, Singer et al. 1993).

A number of SPECT studies have examined the cerebral blood flow in TS (mainly adults) using HMPAO. The first study (Riddle et al. 1992) compared nine controls to nine right-handed adults with TS. A significantly reduced cerebral perfusion in the left putamen and left globus pallidus of the TS subjects was reported. A second study (George et al. 1992) included 20 adolescents and adults with TS and eight normal adults, and found an increased right frontal activity in TS. This finding, however, demands caution because the analysis did not include a correction for multiple comparisons and the frontal perfusion in the controls was unusually low. A third study (Moriarty et al. 1995) including 50 subjects (age range 7 to 65) and 20 controls found significantly lower HMPAO uptake in the left caudate and anterior cingulate area in TS.

In summary, the functional and anatomical data support the involvement of the cortico-striato-thalamo-cortical circuits in TS (Alexander and Crutcher 1990).

7.1.2 Attention-Deficit Hyperactivity Disorder

ADHD is a childhood-onset disorder characterized in DSM-IV by hyperactivity, impulsiveness, and poor sustained attention. Three subtypes have been described: predominantly hyperactive/impulsive, predominantly inattentive, and combined types. ADHD is the most prevalent psychiatric disorder in childhood and occurs in 3-5% of all children between 7 and 12 years. Boys are about four times more often affected than girls. The disorder shows a strong persistence over development; the prevalence of ADHD among adolescents is 1.5-2% and among adults 0.5-1%. The diagnosis of ADHD is made on the basis of a clinical picture, currently no laboratory test or set of tests can be used to form a definite diagnosis. (Cantwell 1996)

Psychosocial factors are not thought to play a primary etiological role in ADHD, but family genetic factors have been implicated. Furthermore, some "environmental" etiological factors (including pre and perinatal abnormalities, toxins, sugar intoxication, and orthomolecular theories of great need for vitamins and nutrients in children with ADHD) have been proposed. (Cantwell 1996)

ADHD has an enormous impact on the utilization of medical and health care services. Both in clinical and epidemiologic samples ADHD in children is associated with a high rate of comorbid disorders, such as oppositional and conduct (aggressive) disorders (50%), affective disorders (20%) and learning disorders (30%) (Cantwell

1996). The presence of comorbid aggression has emerged as the most critical factor in exacerbating these developmental risks. Children with ADHD and comorbid aggression are also fairly resistant to successful behavioral and pharmacologic interventions.

Pathophysiology of ADHD has been investigated with MRI (Castellanos et al. 1994, Giedd et al. 1994), SPECT and PET (Lou et al. 1984, Zametkin et al. 1990), implicating the fronto-striatal areas as being abnormal. The MRI study has demonstrated a reduced volume in the rostrum and rostral body of the corpus callosum, and decreased volumes of the caudate nuclei. Steere and Arnstein (1995) interpreted this as an alteration of functioning of the prefrontal and anterior cingulate cortices of the brain in addition to altered premotor function.

SPECT studies revealed focal cerebral hypoperfusion of striatum and hyperperfusion in sensory and sensorymotor areas. The PET study in adult ADHD revealed lower cerebral glucose metabolism in the premotor cortex and in the superior prefrontal cortex (Zametkin et al. 1990). These areas are involved in the control of motor activity and attention.

7.2 Materials and Methods

7.2.1 The patient data

At the University Hospital Utrecht a total of 41 children and adolescents are part of an ongoing study involving MRI and SPECT acquisitions (for acquisition characteristics see Section 6.2.1). From these cases we selected 16 patients on the basis of absence of comorbid disorders according to DSM-IV criteria. Another four cases were removed from the selection owing to the low quality of the cortical SPECT data yielding a total of six TS and six ADHD cases. The age of the TS patients ranged from 8 to 13 years, and the ADHD range was 8 to 11 years. All subjects were on medication, but not during the acquisition of the data. Subjects with TS used either clonidine (N=3) or low doses of neuroleptics (N=3). ADHD subjects were treated with methylphenidate (N=5) or clonidine (N=1).

Ethical concerns about radiation exposure precluded the use of a normal control group. All children and their parents gave their informed consent to participate in this study, which was approved by the ethical committee of the University Hospital Utrecht. Participants were volunteered from children referred to the Outpatient Child Psychiatric Unit, where they underwent extensive diagnostic procedures, including standardized psychiatric examinations, developmental history, and neuropsychological testing.

7.2.2 Setup

For each patient Normal Fusion visualizations were made for the six principal directions supplying a roundabout view of the brain. The images are viewed on screen with an option to manipulate the color encoding of the functional information according to the approach discussed in Chapter 5. For quick comparison of the visualizations for different patients we also used color prints of the Normal Fusion images. For these prints, color encoding was qualitatively set by the principal author (RS, see page vii) by increasing the amount of red to an arbitrary level and then performing the same for the color blue. The author was not one of the raters and made no use of clinical information during these operations.

The quality of the 2D SPECT data was first investigated in the usual way by a nuclear medicine physician (JvI). The Normal Fusion images were subsequently investigated and compared with the 2D SPECT data to evaluate their accuracy for signaling of hypo and hyperperfused areas in the cerebral cortex.

Finally, the Normal Fusion visualization were qualitatively evaluated by the nuclear medicine physician, a neuroradiologist (LM) and a child psychiatrist (JB) so as to interpret the individual cases and to compare the patient groups TS and ADHD.

7.3 Results

As a first step the areas of increased and decreased SPECT activity indicated by the Normal Fusion visualizations were compared with the information from the original 2D SPECT images and vice versa. An average number of five cold-spots or areas and seven hot-spots or areas were verified. Upon careful comparison the nuclear medicine physician concluded that the 3D Normal Fusion images accurately characterize the corresponding information from the 2D SPECT images. For some of these comparisons color manipulation of the Normal Fusion images proved of importance.

The second aim, *i.e.*, the study of flow patterns, was evaluated by all observers. Table 7.1 presents an overview of the most relevant observations and Figure 7.1 depicts the Normal Fusion images of four of the cases, two for TS (TS1 and TS3) and two for ADHD (ADHD2 and ADHD3). The opinion of the observers was that the Normal Fusion images presented a valuable and fast overview of a large part of the functional information of the grey matter. In combination with the individual anatomy, Normal Fusion images were considered helpful in the recognition of perfusion characteristics of grey matter and in the generation of hypotheses for cortical involvement in these groups.

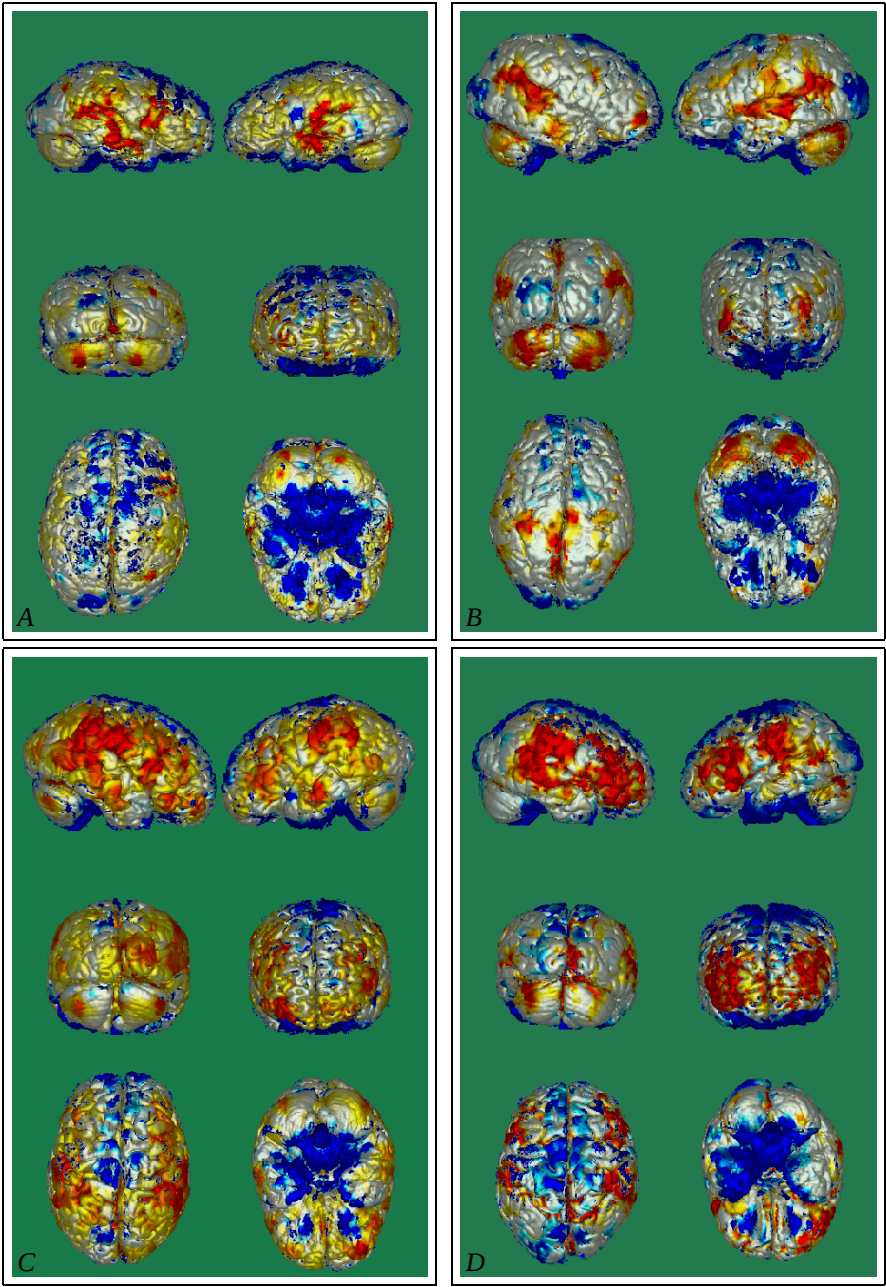


Figure 7.1 Examples of the Normal Fusion visualizations for the TS (top row) and ADHD (bottom row) groups. Frame (A) is case TS1, (B): TS3, (C): ADHD2, and (D): ADHD3 (see Table 7.1).

Item	Feature	TS						ADHD					
		1	2	3	4	5	6	1	2	3	4	5	6
I	R hyper over L				+	+	+	+	+	+	+	+	
II	FTP confl R					+	+		+	+	+	+	+
III	FS hypo L	+p		+	+p	+p	+p	+p	+p	+p	+p		+
	R	+p		+	+p	+p	+p	+p	+p	+p	+p		
IV	Occ/Cerebellum L	<	<	<	≈	<	<	<	≈	<	<	<	<
	R	<	<	<	<	<	≈	<	>	≈	<	<	<

Table 7.1 The overall results of the qualitative analysis of the Normal Fusion images. R = right, L = left, hyper = hyperperfusion, hypo = hypoperfusion, FTP = fronto-temporo-parietal region, confl = confluent, FS = frontal superior gyrus, Occ = occipital, '+' = present, '<' = lower than 1, '≈' = approximately 1, '>' = higher than 1, The 'p' scores in item III indicate that the hypoperfused area extended over the parietal lobe. For an explanation of the features we refer to the text.

The evaluation of the cortical activity of the individual cases and subsequent comparison between the TS and ADHD patient groups (see Figure 7.1) yielded interesting results (see Table 7.1), from which the following items were deduced:

- I. Hyperperfusion of right cerebral areas in comparison with the corresponding left cerebral areas for the ADHD group (n=5/6).
- II. A pattern of confluent regions of hyperperfusion in the right fronto-temporo-parietal area for the ADHD patients (n=5/6).
- III. Hypoperfusion in the left and/or right frontal superior gyri in a majority of cases (n=10/12). In most of these cases (n=8/10) the hypoperfused area was not limited to the FS, but extended over the parietal lobe. This area largely corresponds with the distribution area of the cerebral anterior artery.
- IV. The occipital lobe and the cerebellum are frequently used as a reference area. We found that the ratio of the occipital lobe over the cerebellum (Occ/cerebellum) is not consistent for the TS and ADHD patients. In most cases (n=8/12) the occipital lobe has a lower perfusion than the cerebellum, which is in accordance with the general belief that the cerebellum signals the highest activity for the brain. However, the other cases (n=4/12) indicate that at least one of these regions is not suited as a general reference area.

7.4 Discussion

The comparison of the information as provided by the Normal Fusion images with that of the original 2D SPECT data calls for several comments. Analysis of functional data such as SPECT is typically enhanced by color manipulation and this also applies to Normal Fusion presentations. The use of the color manipulation capabilities on screen is favored over the printed images for investigation of the data. However, the printed images were of considerable value for quick comparison between multiple

cases. Furthermore, we advise against the stand-alone presentation of the Normal Fusion images for viewing of the data. In our opinion the correlation with the 2D SPECT information is vital for verification of the observations performed with the volumetric display (see also (Webb et al. 1987, Wallis 1992)).

The results indicate that the signaling of cortical activity by the Normal Fusion images is in good agreement with 2D SPECT reconstructions. The visual comparison of the Normal Fusion images with the 2D SPECT data revealed that understanding of the latter was improved by the integrated volumetric display. Detection of 3D patterns is problematic in a 2D SPECT display, especially when the patterns are not in one of the three orthogonal directions. In this respect, the 'signaling' function of Normal Fusion is greatly appreciated, because specific patterns of hypo or hyperactivity are more easily recognized.

In the presented patient datasets, Normal Fusion visualization facilitated the recognition of the above described (Section 7.3) abnormal flow patterns. Assessment of the individual cases and comparison between the two patient groups yielded a few noteworthy features. For example, our observations indicate that the use of the cerebellum or the visual cortex as a reference area as has been implemented in several publications (George et al. 1992, Moriarty et al. 1995, Hashikawa et al. 1995) appears a questionable choice for these patient groups (see also (Lamoureux et al. 1990, Crosson et al. 1994) on the use of the cerebellum as reference area). Until quantitative SPECT will become available (Beekman et al. 1996), the use of overall SPECT activity as a reference seems more appropriate (Crosson et al. 1994).

In comparing the two patient groups, the ADHD cases presented a relatively homogeneous pattern of surface activity. The TS group was quite diverse.

In this preliminary, qualitatively evaluation the Normal Fusion technique presents a quick and accurate characterization of the cortical cerebral blood flow in clinical cases. Recognition of (possibly disease-related) abnormal flow patterns is facilitated. However, the absence of a normal group and the low number of cases prevent definite conclusions to be drawn from this study.