Molecular Cloning: A Laboratory Manual (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, ed. 2, 1989)]. The following primers were used for PCR and sequencing (6). Exon 2: forward, nt 771 to 791; reverse, nt 1154 to 1173; exon 3: forward, nt 1260 to 1277; reverse, nt 1517 to 1534; exon 6: forward, nt 3323 to 3341; reverse, nt 3544 to 3561; exon 8: forward, nt 4439 to 4456; reverse, nt 4671 to 4690. Forward primers were biotinylated. PCR amplifications were carried out with 2.5 U Taq of DNA polymerase (Gibco BRL) with 30 cycles at 95°C, 45 s; 55°C, 45 s; 72°C, 45 s. PCR products were purified (Magic PCR Preps, Promega), and single-stranded DNA was isolated with streptavidin-coated magnetic beads (Dynal) and sequenced with the reverse primers (Sequenase, U.S. Biochemicals). For SSCP analysis, 1 μCi of ^{32}P-labeled dCTP (deoxycytidine triphosphate) was added to the PCR reaction, and the PCR products were subjected to electrophoresis through a Mutation Detection Enhancement (MDE, AT Biochem) gel in the presence of 10% glycerol at room temperature.

14. RT-PCR was carried out through use of a GeneAmp RNA PCR kit (Perkin-Elmer) (40 cycles at 95°C, 1 min; 55°C, 1 min; 72°C, 1 min). On the basis of human *TGK* cDNA sequence (*12*), the following primers were used: MH4 (nt −49 to −28) and DH4 (nt +818 to +844); DH3 (nt +742 to +758) and DH6 (nt +1667 to +1693); and DH5 (nt +1622 to +1649) and DH7 (nt +2579 to +2604). The reaction products were subcloned into the pGEM-7Z vector and sequenced (Sequenase, U.S. Biochemicals).
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21. PCR fragments were amplified from genomic DNA of all family members and either digested with restriction enzymes or hybridized to allele-specific oligonucleotides (ASOs). Restriction site polymorphisms were used to characterize the mutations at +1399 (Cfo I site destroyed) and +3459 (Msp I site destroyed) in LI-3, and at +3366 (Msp I site created) in LI-2. ASOs were used to characterize the mutations at +950 (normal: 5′-GCCGTTCCTTCTGG-3′; mutant: 5′-GCCGTTACTTCTGG-3′) in LI-3, and at +4640 (normal: 5′-TTCTGTCTGGTGAGC-3′; mutant: 5′-TTCTGTCGGTGAGC-3′) in LI-1. Nucleotide changes are underlined.
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Sex Differences in Regional Cerebral Glucose Metabolism During a Resting State

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Positron emission tomography was used to evaluate the regional distribution of cerebral glucose metabolism in 61 healthy adults at rest. Although the profile of metabolic activity was similar for men and women, some sex differences and hemispheric asymmetries were detectable. Men had relatively higher metabolism than women in temporal-limbic regions and cerebellum and relatively lower metabolism in cingulate regions. In both sexes, metabolism was relatively higher in left association cortices and the cingulate region and in right ventro-temporal limbic regions and their projections. These results are consistent with the hypothesis that differences in cognitive and emotional processing have biological substrates.

Sex differences in behavior have been documented across species. In humans, certain sex differences in cognitive and emotional processing are increasingly recognized to have biological substrates. Women perform better than men on some verbal tasks, whereas men excel in certain spatial and motor tasks (*1*). Such differences have been linked to sex hormones (*2*). In the domain of emotional regulation, men are more likely to express affect instrumentally, such as through physical aggression, whereas women use symbolic mediation, such as through vocal means (*3*). Women also have a higher incidence of depression (*4*) and outperform men in emotional discrimination tasks (*5*). In the human brain, sex differences have been found in the size and morphology of the corpus callosum (*6*), preoptic anterior hypothalamic areas (*7*), the bed nucleus of the stria terminalis volume (*8*), sylvian fissure morphology (*9*), the percentage of cortical gray matter tissue, and cerebral blood flow (CBF) rate (*10*).

Theories on brain regulation of human behavior are based primarily on animal experiments, clinical-pathologic correlations, and neurobehavioral studies in healthy persons (*11*). Studies indicate that emotional processing is primarily regulated by the limbic system and closely related areas (*12*), and cognitive functions have been linked to neocortical association areas (*13*). Furthermore, the cerebral hemispheres differ in cognitive and perhaps in emotional processing, with the left specialized for verbal analytic cognition and the right for spatial processing (*14*). There is also evidence for right hemisphere predominance in emotional processing (*15*).

Neuroimaging permits in vivo studies of brain anatomy and physiology pertinent to these issues. Neuroanatomic studies have suggested larger volumes of tissue in left cortical regions implicated in language (*16*), whereas few systematic asymmetries have been reported in neurophysiologic imaging studies (*17*). We examined the regional topography of physiologic activity in healthy young adults using positron emission tomography (PET). Our purpose was to evaluate sex differences in the distribution of cerebral metabolism in limbic regions and to investigate systematic asymmetries that may help us to understand aspects of functional hemispheric specialization.

We studied 61 healthy right-handed volunteers (37 men and 24 women) recruited by advertising. The mean age ± SD was 27.3 ± 6.5 years for men and 27.7 ± 7.4 for women, and the mean years of education ± SD were 14.4 ± 2.0 and 14.9 ± 2.1, respectively. Participants underwent comprehensive medical, neurologic, and psychiatric screenings (*18*). Informed consent was obtained after the nature and possible consequences of the study were explained.

Subjects were scanned after an overnight fast. A radial artery line and a contralateral antebrachium venous line were kept patent with physiological saline. Approximately 185 megabequerels (5 mCi) of ^{18}F-labeled 2-fluoro-2-deoxy-D-glucose (FDG) were administered intravenously while subjects lay in a quiet, dimly lit room with eyes open and ears unoccluded. Subjects were instructed to stay quiet and relaxed without either exerting mental effort or falling asleep (*19*). For determination of the input function, arterial samples were obtained over 90 min. Activity of ^{18}F in 250-μl aliquots was measured in a dose calibrator after a 3- to 4-hour decay interval. Image acquisition began 40 min after isotope administration with the subjects positioned in a custom-molded, head holder of rigid foam that was aligned by two laser beams situated at right angles. The PENN-PET scanner (*20*) has a fixed gantry,

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a 9-cm axial field of view, and an image spatial resolution of 5.5 mm full width at half maximum in all directions. Tissue activity concentration per unit time was calculated with scanner calibration and dead-time correction factors (*21*). Calibrated blood activity concentration values and metabolism were calculated with lumped and rate constants (*22*).

We cross-registered PET images with corresponding magnetic resonance images by using established procedures (*23*). Templates with regions of interest (ROIs) were custom-fitted to magnetic resonance image slices by investigators trained to an inter-rater reliability criterion of >0.85 (intra-class correlation) for 39 of the 42 regions. Of these, 36 were included in the statistical analysis (Fig. 1). We calculated two indices that are based on count rates: (i) region: whole brain (R:WB) ratios averaging the two hemispheres and (ii) a laterality index [percent (left minus right):mean (left, right)].

Average metabolism calculated from WB counts did not differ between men (mean ± SD, 4.66 ± 0.97 ml per 100 g of tissue mass per minute) and women (4.62 ± 1.09), $t(58) < 1$. This is consistent with cerebral glucose metabolism studies (*24*) but contrasts with studies of CBF, where women have higher rates. Analysis of the regional distribution of metabolic activity (Fig. 2A) revealed that, in both men and women, metabolism was lowest in the corpus callosum and highest in the basal ganglia (*25*). A sex × region analysis of variance (testing the hypothesis of gender differences in regional metabolism) yielded a sex × region interaction of $F(35,2065) = 3.55$, $P < 0.001$. The groups had identical relative metabolism in all nonlimbic frontal, parietal, and occipital regions, but sex differences were prevalent in temporal-limbic regions, basal ganglia, brainstem, and cerebellum. Whereas men had higher relative metabolism in lateral and ventro-medial aspects of temporal lobe regions, they had lower relative metabolism in the middle and posterior cingulate gyrus. The number of regions showing significant sex differences (*17*) is larger than would be expected by chance (2/36 at the 0.05 level), $z = 10.6$, $P < 0.0001$. The raw absolute metabolic rates were only higher in men than in women for the occipital temporal region, temporal pole, hippocampus, amygdala, and orbital frontal cortex ($P < 0.05$).

To examine individual differences in this pattern, we calculated a "female-typical" score by standardizing (z transformation; mean = 0, SD = 1) the regional metabolic rates and subtracting metabolism in the temporal-limbic regions from cingulate metabolism (Fig. 3). Only 17 of the 61 subjects (13 men and 4 women) had scores opposite to their respective sex-typical indices, $\chi^2(1) = 12.7$, $P < 0.001$. This could not be explained by sex differences in anxiety because the two groups did not differ in reported anxiety (*26*), either for trait (men, 32.4 ± 6.9; women, 32.2 ± 7.8), $t(59) < 1$, or state (34.6 ± 6.8 and 36.6 ± 6.9, respectively), $t = 1.09$ (*27*).

Examination of the laterality of metabolism indicated that asymmetries were ubiquitous in both men and women (Fig. 2B). Of 36 regions, 20 deviated from symmetry at the 0.01 significance level, with five additional differences significant at $P = 0.05$. Some of the asymmetries seem related to functional brain organization. Consistent with the dextrality of our subjects, metabolism was relatively higher in the left hemisphere for premotor, motor, and sensorimotor cortex and both brainstem regions (midbrain and pons), which control contralateral motor functions, and higher in the right for cerebellum, which influences motor functions ipsilaterally. The higher left hemispheric values observed in medial and inferior frontal, parietal, superior, and inferior temporal cortices and cingulate gyrus may reflect the role of these regions in

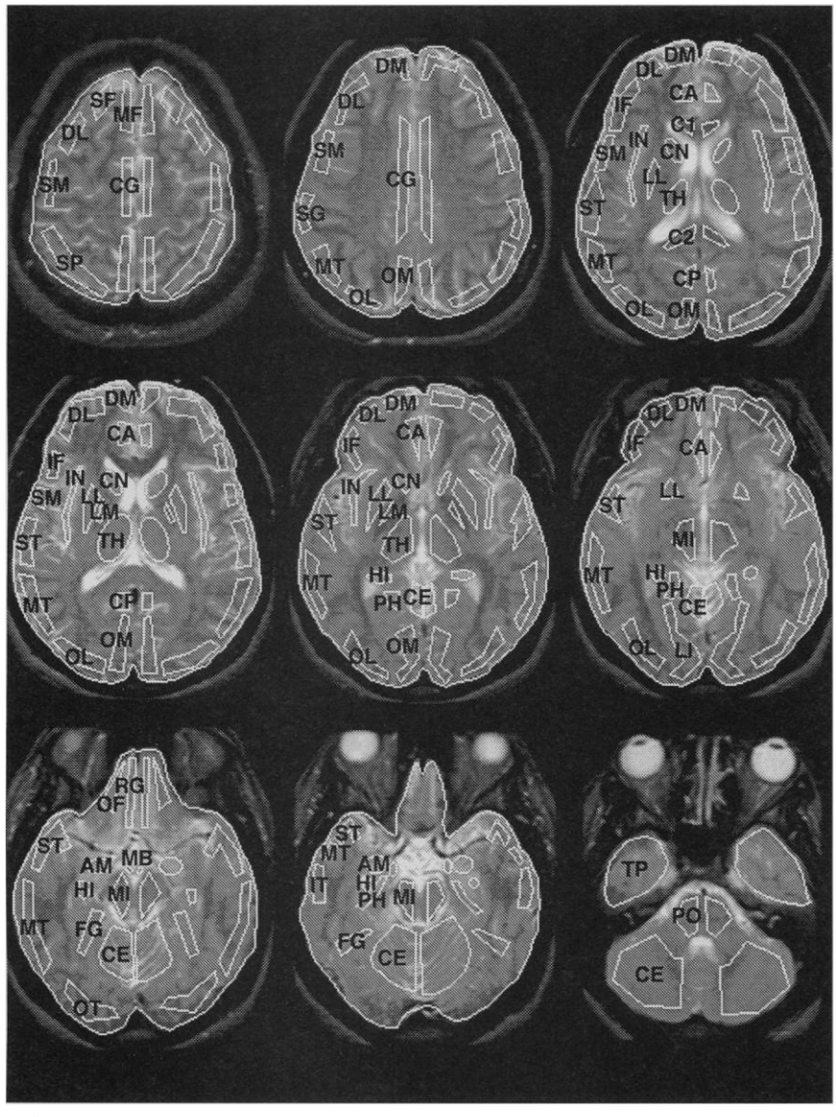

Fig. 1. Placement of ROIs. AM, amygdala; C1, corpus callosum, anterior; C2, corpus callosum, posterior; CA, cingulate gyrus, anterior; CE, cerebellum; CG, cingulate gyrus; CN, caudate nucleus; CP, cingulate gyrus, posterior; DL, dorsal prefrontal, lateral; DM, dorsal prefrontal, medial; FG, fusiform gyrus; HI, hippocampus; IF, inferior frontal; IN, insula; IT, inferior temporal; LI, lingual gyrus; LL, lenticular, lateral (putamen); LM, lenticular, medial (globus pallidus); MB, mammillary body; MF, mid-frontal; MI, midbrain; MT, mid-temporal; OF, orbital frontal; OL, occipital cortex, lateral; OM, occipital cortex, medial; OT, occipital temporal; PH, parahippocampal gyrus; PO, pons; RG, rectal gyrus; SF, superior frontal; SG, supramarginal gyrus; SM, sensorimotor; SP, superior parietal; ST, superior temporal; TH, thalamus; and TP, temporal pole.

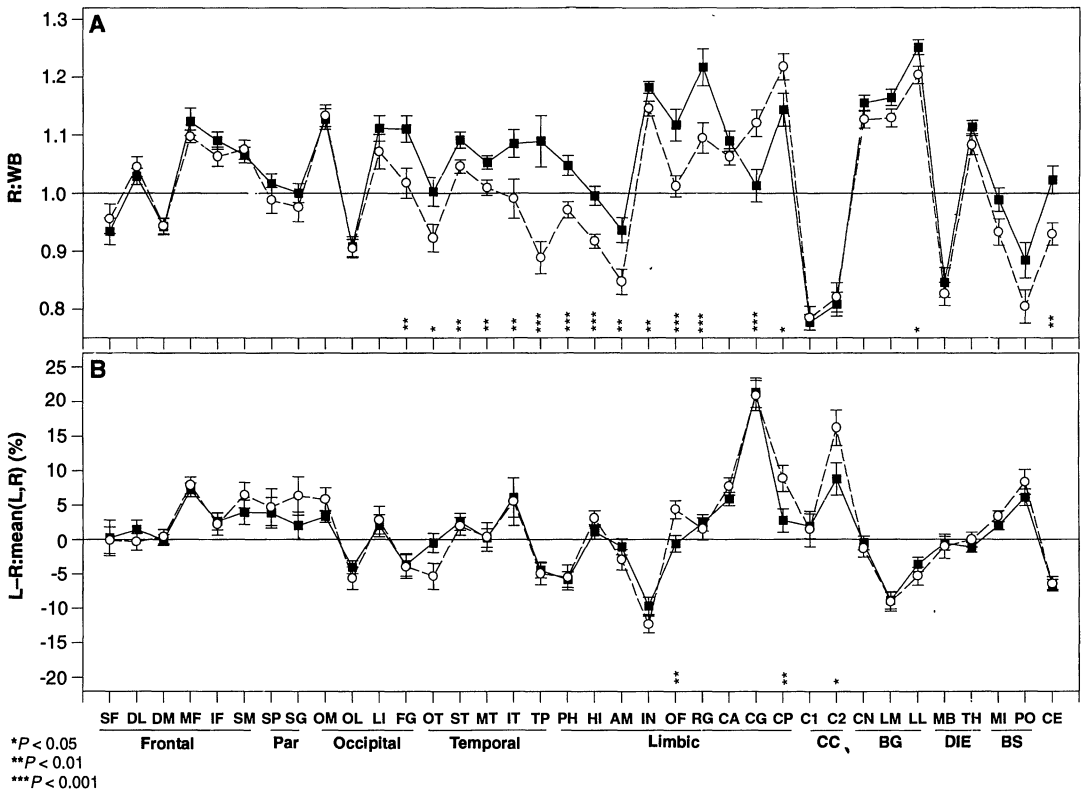

Fig. 2. Topography of metabolic activity in men (filled squares) and women (open circles) for the ROIs delineated in Fig. 1. Cortical regions are grouped by lobe in a rostral to caudal order [frontal, parietal (Par), occipital, temporal, limbic] followed by corpus callosum (CC) and subcortical regions [basal ganglia (BG), diencephalon (DIE), and brainstem (BS)]. Abbreviations are as in Fig. 1. This order heuristically reflects ontogenic and evolutionary development. (**A**) Means ± SEM of R:WB ratios. (**B**) Means ± SEM of laterality differences in percentages. L, left; R, right.

verbal-analytic functions. By contrast, higher right hemispheric metabolism was evident in most ventro-medial temporal lobe components of the limbic system and their projections in lenticular regions of the basal ganglia, consistent with theories of right hemispheric predominance for emotional processing. Men and women were nearly identical in the topographic distribution of lateral asymmetries, with only three regions showing sex differences at the 0.01 level. These regions were the orbital-frontal, posterior cingulate, and posterior corpus callosum, where women had relatively higher left hemispheric metabolism than men.

The findings indicate sex differences in the regional topography of resting cerebral metabolic activity and systematic asymmetries in regional metabolism that are largely shared by men and women. The higher relative metabolism in men in the temporal-limbic system and the reversal of this difference for the middle and posterior cingulate gyrus, where women had higher metabolism, may reflect a different baseline activity. This could relate to emotional processing modes because the cingulate is cytoarchitecturally one of the more complex components of the limbic system.

The observed regional variation in hemispheric asymmetries suggests greater left hemispheric activity in neocortical regions and cingulate cortex and higher right hemispheric metabolism in limbic regions of the ventro-medial temporal lobe, closely associated occipital-temporal cortices, and ventral striatum. Sex differences in these asymmetries were limited and could be chance effects because they appeared in few regions. The predominance of lateral asymmetry in regional cerebral metabolism contrasts with the paucity of lateral asymmetries found in anatomic studies, as well as in physiologic investigations with other methods. The relatively higher left hemispheric activity in premotor, primary motor, and somatosensory regions is consistent with reports of neuroanatomic studies (*28*). However, we found higher right hemispheric metabolism in the medial and lateral lenticular regions, where an anatomic study had reported higher left hemispheric volumes (*29*), and symmetric metabolism in the caudate nucleus, where higher right hemispheric volume had been reported. Possibly, correlations between volume and metabolism differ among regions. The larger number of asymmetric regions relative to earlier neurophysiologic studies may reflect improved resolution and analysis methods and larger samples. The ^{133}Xe clearance studies were sensitive to activity only in superficial layers of cortex, whereas tomographic studies with smaller sample size (particularly of women) did report some asymmetries (*24*).

Although we have focused our attention on hemispheric asymmetry and sex differences, these differences in specific regions occur against a background of similarities in the profile of metabolic activity, both between the two hemispheres and between men and women. This similarity attests to the overall reliability of the metabolic parameters and also reminds us that the two cerebral hemispheres and the brains of men and women are fundamentally more similar than different.

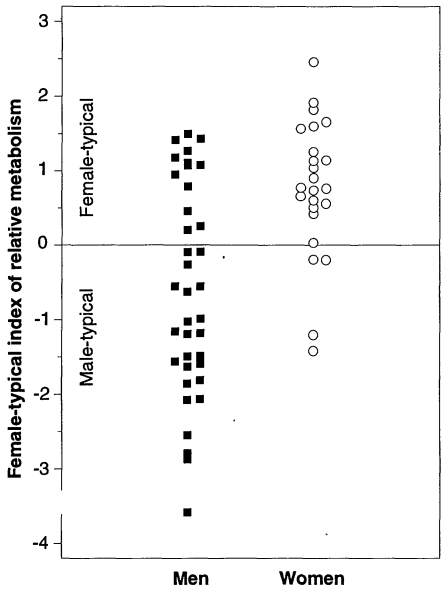

Fig. 3. Scatterplot showing individual differences in the "female-typical" index of relative metabolism with temporal-limbic data subtracted from cingulate averages.

Our study was limited to examining the resting state and did not incorporate activation procedures. Thus, our conclusions concern topography of the human brain while it is "idling" in a semistructured environment, which may itself influence regional brain activity. Further regional and sex differences may become evident when activity is measured during the performance of behavioral tasks or pharmacologic challenges. Nonetheless, the results suggest neural substrates for domains of human behavior related to both cognitive and emotional processing. They support a neurobiologic explanation of some sex differences in these behavioral dimensions and thus may help to explain sex-related differences in behavior. Individual differences within a sex and the overlap between the sexes may reflect "noise" in the measurement but perhaps, as can be tested empirically, can also be related to individual differences in sex-typical behavior.

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Cloning of an Intrinsic Human TFIID Subunit That Interacts with Multiple Transcriptional Activators

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TFIID is a multisubunit protein complex comprised of the TATA-binding protein (TBP) and multiple TBP-associated factors (TAFs). The TAFs in TFIID are essential for activator-dependent transcription. The cloning of a complementary DNA encoding a human TFIID TAF, $TAF_{II}55$, that has no known homolog in *Drosophila* TFIID is now described. $TAF_{II}55$ is shown to interact with the largest subunit ($TAF_{II}230$) of human TFIID through its central region and with multiple activators—including Sp1, YY1, USF, CTF, adenoviral E1A, and human immunodeficiency virus–type 1 Tat proteins—through a distinct amino-terminal domain. The $TAF_{II}55$-interacting region of Sp1 was localized to its DNA-binding domain, which is distinct from the glutamine-rich activation domains previously shown to interact with *Drosophila* $TAF_{II}110$. Thus, this human TFIID TAF may be a co-activator that mediates a response to multiple activators through a distinct mechanism.

The multisubunit protein complex TFIID (*1–5*) is required for transcription by most, if not all, promoters targeted by RNA polymerase II (class II promoters). At TATA-containing class II promoters, TFIID first binds to the TATA box and then recruits other basal factors and RNA polymerase II to the promoter (*6*, *7*). Whereas the TBP subunit is sufficient for basal transcription, activator-dependent transcription requires the TAFs of TFIID as well as upstream stimulatory activity (USA)–derived cofactors (*5*, *6*, *8*). The possibility that individual TAFs may have activator-specific functions is suggested by their multiplicity (up to 8 in *Drosophila* and 13 in human TFIID) (*1–5*) and by the demonstration of *Drosophila* TAF-specific interactions with the mammalian activators Sp1 and Gal4-VP16 (*9*, *10*).

The human TFIID subunit $TAF_{II}55$ was isolated from a cell line that expresses epitope-tagged TBP for the immunopurification of TFIID (*5*). Two peptide sequences derived from thermolysin digestion of $TAF_{II}55$ were used to design degenerate primers for polymerase chain reaction (PCR) amplification (*11*). The PCR product was used as a probe to screen a human placental complementary DNA (cDNA) library. A clone that contained a cDNA insert of a size corresponding to that of the

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