""Differential Brain Activation in Exclusively Homosexual and Heterosexual Men Produced by an SSRI

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Abstract

Two recent studies have shown a relationship between “sexual orientation” and size of anterior hypothalamic nuclei; others that hypothalamic serotonin is involved in male sexual arousal and behavior. We hypothesized that serotonergic differences might parallel sexual orientation differences in the hypothalamus. Accordingly, we administered 40 mg of fluoxetine (in a counterbalanced design with placebo) as a challenge to the serotonergic systems of homosexual and heterosexual men who differed maximally in their sexual orientation, and measured cerebral metabolic changes with FDG-PET.

In accord with our hypothesis, differential effects were observed in the hypothalamus, as well as in other brain areas. In the hypothalamus, the homosexual group exhibited a significantly smaller reduction in glucose metabolism in response to fluoxetine than the heterosexual group. The fact that metabolic differences were produced

by a pharmacologic challenge to the serotonergic system, might be reflective of underlying neurochemical differences between homosexual and heterosexual men.

Introduction

It has been known for some time that the brains of males and females differ anatomically, but only recently has a relationship been shown between sexual orientation and brain anatomy. LeVay (1991), for example, reported that the third interstitial nucleus of the anterior hypothalamus, or INAH3--a nucleus in the medial preoptic area (MPOA) critical for the expression of sexual behavior in male animals--was significantly smaller in the postmortem brains of heterosexual women and homosexual men than in those of heterosexual men. In another study (Byne et al., 2001), this same area in postmortem brains of homosexual men was found to be intermediate in volume between postmortem brains of heterosexual men and heterosexual women. Likewise in rams, a sexually dimorphic MPOA nucleus was reported to be smaller in rams that chose to copulate with other rams than in the majority that chose to copulate only with ewes (K. Larkin, K., Resko, J. A., Stormshak, F., Stellflug, J. N. and Roselli, C. E., unpublished observations presented at the 32nd Annual Meeting of the Society for Neuroscience, Orlando, FL, November 2002).

Studies in rats have shown that hypothalamic serotonin (5-HT) is involved in sexual arousal and sexual expression in males (Mas et al., 1995), and that sex differences exist as well in levels of serotonin and serotonin metabolites (Carlsson and Carlsson, 1988).

Materials and Methods

These findings suggested to us that differences in serotonin activity, particularly in the INAH3, might parallel differences in sexual orientation. Accordingly, we administered the selective serotonin reuptake inhibitor (SSRI), fluoxetine, as a pharmacologic challenge to the serotonergic systems of homosexual and heterosexual men, and measured the resulting cerebral metabolic changes with fluorodeoxyglucose positron emission tomography (FDG-PET). The use of acutely administered SSRIs as challenge agents to study cerebral serotonin pharmacology was proposed by Cook, et al. (1994). The method measures the effect of a given neurotransmitter on the brain, independently of the behavioral and cognitive effects of the drug administered. Specifically, a visual monitoring task (VMT) was used during the period of FDG uptake to minimize the effects of behavior, cognition and ideation on the resulting brain images. Subjects were instructed to press a button in response to the random presentation of a dim light (50% of the trials) and to refrain from pressing when a bright light is shown. In this way subjects were kept in essentially the same cognitive and behavioral condition during both drug and placebo conditions so that in a cognitive subtraction paradigm, image differences could essentially be taken to reflect drug effects alone.

Subjects were scanned approximately 90 minutes after oral administration of 40 mg. of fluoxetine or placebo in a double-blind counterbalanced design. Scanning sessions were separated by at least 7 days. Images were acquired on a PETT-IV scanner (FWHM approximately 8 mm in each plane), and realigned and spatially normalized using MEDx-

SPM96 (Sensor Systems, Inc., Sterling, VA). Spatial smoothing, gray-matter masking to remove non-brain and white matter, z-score normalization and subsequent statistical analyses (voxel-by-voxel two-tailed paired and unpaired t-tests comparing drug and placebo conditions within and between groups) were performed using the MIICRO Statistical Analysis (MSA) software package (MIICRO, Inc., Chicago, IL). Areas of significant effect were overlaid on a structural MRI in standard anatomical space.

In order to maximize the likelihood of finding between-group differences, we tested only individuals who differed maximally in their sexual orientation. Accordingly, through questionnaire and oral report, we selected a total of 16 men without physical illness or psychiatric history: a) eight of whom self-identified as "exclusively homosexual" and eight as "exclusively heterosexual" on the Kinsey Scale (Kinsey, 1948); and b) who attested that their past and present sexual behavior, desires and fantasies were directed entirely toward men or women, respectively. Because of technical problems associated with one of his scans, one heterosexual subject was dropped from the final analysis, leaving15 subjects. The mean age of the homosexual subjects was 29 (range 27 - 36), while that of the remaining heterosexual subjects was 28 (range 23 – 35). All but one heterosexual subject were consistently right handed.

Results

In accord with our hypothesis, differential effects were observed in the hypothalamus, with the homosexual group exhibiting a significantly ($p \leq .01$) smaller reduction in hypothalamic glucose metabolism in response to fluoxetine as compared

with the heterosexual group. Interestingly, areas not known to play a role in sexual behavior were activated differentially as well (Fig. 1). Both groups, however, did exhibit similar widespread lateralized metabolic responses to fluoxetine relative to placebo, with most areas of the brain responding in the same direction in both groups (Fig. 2).

Discussion

This study is the first to report evidence of a sexual-orientation-related metabolic difference produced by a pharmacologic challenge to a neurochemical system, possibly reflecting underlying between-group differences in neurochemical activity. Our results also suggest the possibility that homosexual and heterosexual individuals may respond differently to SSRIs, particularly with regard to side effects. It need be said, however, that the differential activation observed may have been produced not only by the effect of fluoxetine on serotonergic neurotransmission, but on noradrenergic and dopaminergic neurotransmission as well, given that fluoxetine, while highly specific, does act on catecholaminergic receptors (Tatsumi et al., 1997). In addition, the limited spatial resolution of PET and partial volume effects prevent us from determining whether the reported hypothalamic activation was restricted to the INAH3 or even to the larger medial preoptic area, nor can we determine whether the activation confined to the right hypothalamus was artifactual or a reflection of true laterality. Finally, we cannot rule out the possibility that some other factor or factors that covary with sexual orientation, and not sexual orientation itself, may have affected the SSRI response, producing the differential activation we observed.

In conclusion, it should be mentioned that the failure of previous studies to report physiological, and in some cases neuroanatomical, differences between homosexual and heterosexual men might be related to within-group heterogeneity. Specifically, individuals of diverse sexual orientations have been included routinely under the rubric of either "homosexual" or "heterosexual," based solely on their declared sexual preference. But to assert simply that an individual is homosexual or heterosexual does not, for example, distinguish homosexual men who have never been aroused by female sexual stimuli from those who have been aroused by such stimuli, but who have come to prefer same-gender sexual partners. Accordingly, we would suggest that future studies concerned with the biology of sexual orientation acknowledge the diversity that exists among both homosexuals and heterosexuals. Perhaps additional neurochemical and neuroanatomical differences might be revealed once stringent criteria for subject selection are used.

Footnotes

We thank MIICRO, Inc. for support, and Terry Brown and Declan Cooper for assistance in data collection and analysis. Special thanks go to Charles Pelizzari of the University of Chicago for assistance in data analysis. This paper is dedicated to the memory of Malcolm Cooper, M.D. who passed away prior to its publication.

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Figures

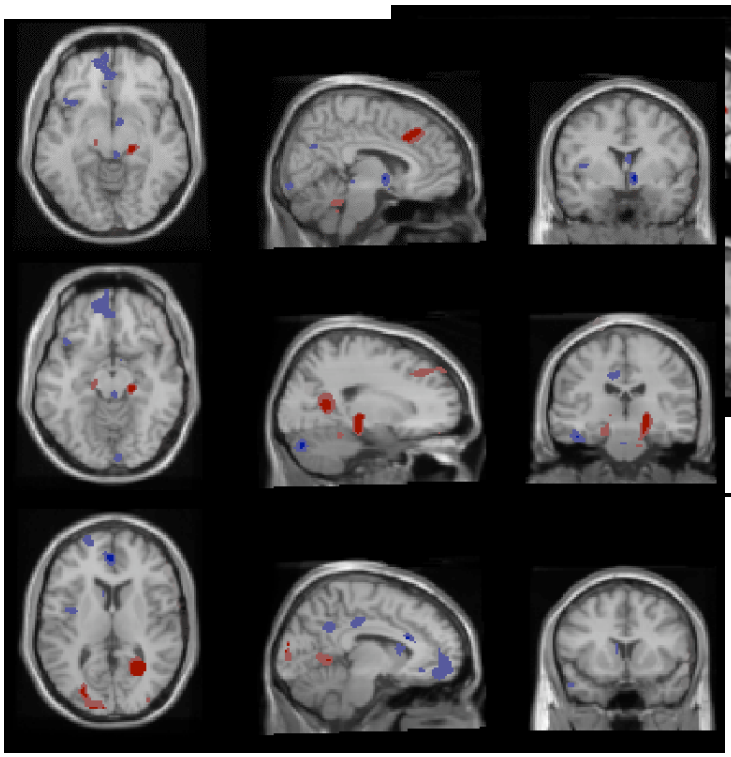

Fig 1. Between-Group Differential Activation. Areas in which the heterosexual group, relative to the homosexual group, exhibited a significantly greater increase (or significantly smaller decrease) in cerebral glucose in response to fluoxetine (relative to placebo) are shown in RED. Areas in which the homosexual group, relative to the heterosexual group, exhibited a significantly greater increase (or significantly smaller decrease) in CMRglu are shown in BLUE. Relative to the heterosexual group, the homosexual group exhibited a significantly smaller reduction in glucose metabolism in the right hypothalamus. The homosexual group also exhibited significant increases in a portion of the prefrontal association cortex in which the heterosexual group exhibited no change, and in portions of the cingulate cortex in which the heterosexual group exhibited decreases. In contrast, the heterosexual group showed a significantly larger relative increase in lateral anterior cingulate, bilateral hippocampus/parahippocampal gyrus, and cuneate gyrus.

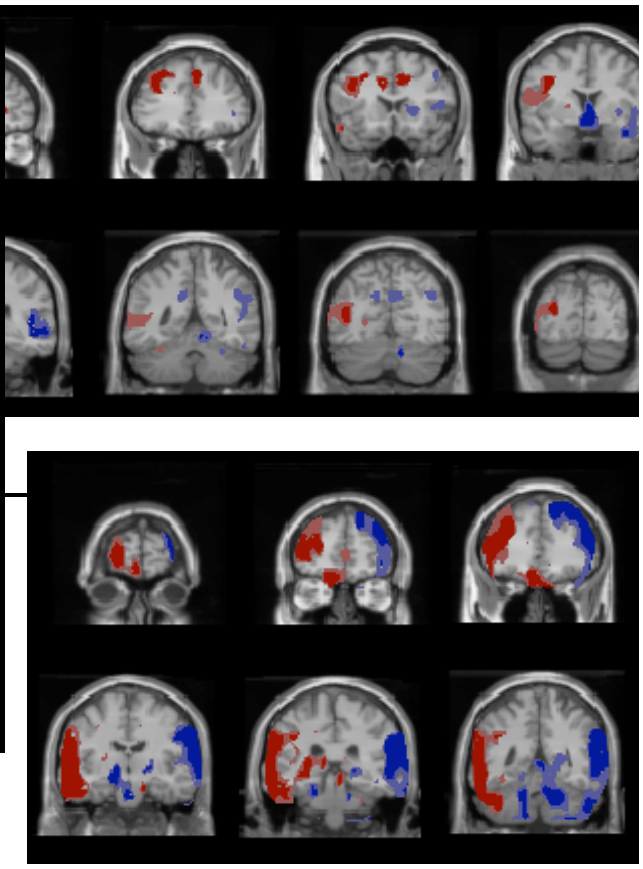

Fig 2. Within-Group Activations. Heterosexual group shown in bottom panel. In each group, increases were seen mainly on the l Although most areas of the brain responded in the same direction homosexual group appeared larger in spatial extent than that of th CMRglu was not significantly different between the fluoxetine (7 heterosexual group, 7.79 ± 1.19 mg/100g/min in the homosexual (7.64 ± 0.74 mg/100g/min in the heterosexual group, 7.92 ± 1.54 group) either within or between groups.

Fig 1. Areas of significant increase or decrease in regional cerebral glucose metabolism (CMRglu) in response to fluoxetin are shown in RED, decreases in BLUE. Darker colors are significant at $p < 0.01$, lighter colors at $p < 0.05$. All images are in neu