UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS:
PSIQUIATRIA

DISSERTAÇÃO DE MESTRADO

GÊMEOS MONOZIGÓTICOS DISCORDANTES PARA TRANSEXUALIDADE: DIFERENÇAS NEUROANATÔMICAS E PSICOLÓGICAS

TAHIANA SIGNORINI ANDREAZZA

Orientador: Prof. Dra.: MARIA INÊS RODRIGUES LOBATO

Porto Alegre, fevereiro de 2012

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS: PSIQUIATRIA

DISSERTAÇÃO DE MESTRADO

GÊMEOS MONOZIGÓTICOS DISCORDANTES PARA TRANSEXUALIDADE: DIFERENÇAS NEUROANATÔMICAS E PSICOLÓGICAS

TAHIANA SIGNORINI ANDREAZZA

Orientador: Prof. Dra. MARIA INÊS RODRIGUES LOBATO

Porto Alegre, Brasil.
2012

CIP - Catalogação na Publicação

Andreazza, Tahiana Signorini
Gêmeos monozigóticos discordantes para transexualidade: diferenças neuroanatômicas e psicológicas. / Tahiana Signorini Andreazza. -- 2012.
61 f.

Orientador: Maria Inês Rodrigues Lobato.

Dissertação (Mestrado) -- Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Ciências Médicas: Psiquiatria, Porto Alegre, BR-RS, 2012.

1. Transexualismo. 2. Transtorno de Identidade de Gênero. 3. Gêmeos monozigóticos. 4. Ressonância Magnética. 5. Testes psicológicos. I. Lobato, Maria Inês Rodrigues, orient. II. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os dados fornecidos pelo(a) autor(a).

SUMÁRIO

ABREVIATURAS E SIGLAS

1- TIG - transtorno de identidade do gênero
2- WAIS - Wechsler Adult Intelligence Scale
3- MpF - masculino-para-feminino
4- FpM - feminino-para-masculino
5- MZ - Monozigóticos
6- HHA - Hipotálamo-hipófise-adrenal
7- HAC- Hiperplasia adrenal congênita
8- SC - Substância cinzenta
9- SB - Substância branca
10- 2D - Duas dimensões
11- 3D - Três dimensões
12- RMf - Ressonância magnética funcional

RESUMO

A presente dissertação trata-se de um estudo de caso exploratório que discorre sobre fatores neuro-estruturais, hormonais, neuropsicológicos e suas possíveis associações, em um par de gêmeos monozigóticos adulto, do sexo masculino, discordantes para o transexualismo. Ambos os gêmeos foram submetidos a entrevistas semi-estruturadas por meio de equipe especializada pertencente ao Programa de Transtorno de Identidade de Gênero do Hospital de Clínicas de Porto Alegre (HCPA). Aplicou-se o intrumento Wechsler Adult Intelligence Scale (WAIS), com o objetivo de avaliar diversas funções cognitivas verbais e não-verbais que contribuem para a inteligência geral e realizou-se Ressonância Magnética do encéfalo, com a finalidade de medir o volume de uma série de estruturas cerebrais. Ainda, a mãe dos sujeitos (o pai alegou não ter disponibilidade em participar) forneceu informações sobre a gestação, parto, condições de nascimento, infância, meio ambiente, alterações clínicas presentes e passadas e eventos incomuns na história de vida dos gêmeos. Em cinco regiões cerebrais foram detectadas diferenças nos volumes de determinadas estruturas, e nas habilidades de linguagem e raciocínio viso-espacial houve divergência entre os gêmeos. Sugere-se que fatores epigenéticos possam estar envolvidos tanto na discordância fenotípica como nos achados deste estudo.

Palavras chave: transexualismo, Transtorno de identidade de gênero, gêmeos, monozigose, Ressonância Magnética, testes psicológicos.

ABSTRACT

The present work is an exploratory study case that discusses about neuroanatomical, hormonal and neuropsychological factors and their possible associations in one monozygotic male twin pair discordant for transsexualism. Both twins answered semi-structural interviews applied by specialized team from Gender Identity Disorder Program of Hospital de Clínicas de Porto Alegre, Brazil; In addition, they were tested with the Wechsler Adult Intelligence Scale (WAIS) battery that evaluate verbal and non verbal cognitive functions that contribute to general intelligence; and underwent magnetic resonance imaging (MRI) to measure the volumes of specific cerebral structures. The mother of the twins gave information (father did not want to participate) about the pregnancy, delivery, conditions of birth, childhood, raising environment, unusual medical or life history events. Both neuroimaging and cognitive function testing detected different outcome between the twins. In six different cerebral regions differences have been found in the volume of specific structures, as well as in language, visuo-spatial abilities. It is suggested that epigenetic factors could be related to the phenotypic discordance and the findings of this study

Keywords: Transsexualism; Gender identity disorder; Twins, monozygotic; Magnetic resonance imaging; Psychological tests.

APRESENTAÇÃO

Este trabalho consiste na dissertação de mestrado intitulada "Gêmeos monozigóticos discordantes para transexualidade: diferenças neuroanatômicas e psicológicas", apresentada ao Programa de Pós-Graduação da Universidade Federal do Rio Grande do Sul em fevereiro de 2012. O trabalho é apresentado em três partes, na ordem que segue:

1. Introdução, Revisão da Literatura e Objetivos
2. Artigo
3. Conclusões e Considerações Finais.
4. Referências

INTRODUÇÃO

Transexualidade é uma condição considerada pela Organização Mundial de Saúde (OMS) como um tipo de transtorno de identidade de gênero (TIG). A Classificação Internacional de Doenças, 10ª versão (CID-10), da OMS, Capítulo V, Transtornos Mentais e do Comportamento, inclui nos chamados Transtornos de Identidade Sexual o transexualismo, o travestismo de duplo papel e os transtornos de identidade sexual na infância, além dos genéricos, outros transtornos de identidade sexual e transtorno de identidade sexual não especificados (OMS, 1993). De acordo com a CID-10, o transexualismo refere-se à condição do indivíduo que possui uma identidade de gênero diferente ao que foi designado no nascimento, tendo o desejo de viver e ser aceito como sendo do sexo oposto, geralmente acompanhado por uma sensação de desconforto ou impropriedade do seu próprio sexo anatômico e um desejo de se submeter a tratamento hormonal e cirurgia para tornar seu corpo congruente quanto possível com o sexo preferido. Para que esse diagnóstico seja feito, esta condição deve ter estado presente persistentemente por pelo menos dois anos e não deve ser um sintoma de outro transtorno mental, tal como esquizofrenia, nem estar associada a qualquer anormalidade intersexual, genética ou do cromossomo sexual. Transexuais freqüentemente relatam sentirem-se “presos no corpo errado", referem vontade de mudar sua aparência física e assemelharem-se ao sexo oposto o quanto for possível (Cohen-Kettenis e Gooren, 1999).

Segundo o DSM-IV-TR, para realizar o diagnóstico de TIG, pelo menos dois critérios devem estar presentes:

(A) Forte e persistente identificação com o gênero oposto, que consiste no desejo de ser, ou a insistência do indivíduo de que ele é do sexo oposto - essa identificação como gênero oposto não deve refletir um mero desejo de quaisquer vantagens culturais percebidas por ser do outro sexo.

(B) Evidências de um desconforto persistente com o próprio sexo atribuído ou uma sensação de inadequação no papel de gênero deste sexo.

(C) O diagnóstico não deve ser feito se o indivíduo tem uma condição intersexual física concomitante (p. ex., síndrome de insensibilidade aos andrógenos ou hiperplasia adrenal congênita)

(D) Evidência de sofrimento clinicamente significativo ou prejuízo no funcionamento social ou ocupacional ou entre outras áreas importantes da vida do indivíduo.

A prevalência estimada do transexualismo varia de 1 em 10.000 até 1 em 100.000 em transexuais masculino-para-feminino (MpF) e de 1 em 30.000 até 1 em 400.000 nos transexuais feminino-para-masculino (FpM) (Cohen-Kettenis & Gooren, 1999). O transexualismo pode ter início precoce ou tardio, o que facilita a divisão em subgrupos. Transexualismo de início precoce é aplicado ao indivíduo que tem o desejo de se tornar do sexo oposto já na infância, enquanto que de início tardio se aplica ao indivíduo em que a identificação com o gênero oposto surge na puberdade ou mais tarde. A idade de 12 anos marca a divisão entre entre esses dois períodos (Doorn, Poortinga, & Verschoor, 1994)

Na busca de evidências de fatores biológicos como determinantes na gênese do transexualismo, historicamente têm-se duas linhas de pesquisa: a que envolve fatores hormonais, que vem se desenvolvendo desde a década de 70 e evoluiu desde a busca por alterações quantitativas de hormônios até a influência dos hormônios masculinos na diferenciação cerebral; e a que busca alterações genéticas e/ou cromossômicas (Saadeh, 2004).

Alguns achados indiretos, têm sido propostos como marcadores biológicos do transexualismo: uso preferencial da mão esquerda (refletindo lateralidade cerebral organizada antes do nascimento); padrões de assimetria em impressões digitais, que se desenvolvem antes do nascimento e provavelmente são influenciados por hormônios esteródes, tanto em transexuais masculinos quanto femininos, diferindo dos controles, homens e mulheres (Green &Young, 2001); ordem de nascimento, sendo os transexuais masculinos os irmãos mais novos, (Green, 2000) e, por fim, os transexuais masculinos tendo mais tias maternas do que tios maternos, achado similar aos dos homossexuais masculinos não transexuais (Green & Kervene, 2000).

Até o presente momento, o entendimento etiológico da transexualidade segue inconclusivo. Um grande volume de evidências aponta o envolvimento de alterações de aspecto genético, hormonal e nas diferentes exposições ambientais, tanto na fase pré-natal como ao longo do desenvolvimento (Coates, 1990; Zucker & Bradley, 1995; Cohen-Kettenis & Gooren, 1999;), a seguir examinadas.

Fatores genéticos:

Até o presente momento, há um número pequeno de relatos publicados de pares de gêmeos monozigóticos (MZ) concordantes ou discordantes para o transexualismo. Delineamentos ancorados em gêmeos são importantes por proporcionarem uma estimativa da contribuição relativa de fatores genéticos e não genéticos para um específico fenótipo. A dicotomia “ambiente versus herdabilidade” proposta por Francis Galton em 1865, tem estimulado estudos com gêmeos com o propósito de analisar duas hipóteses centrais: o papel da influência genética na suscetibilidade da doença (Bailey, et al, 2000; Coolidge, et al, 2002) e o papel dos fatores ambientais na gênese da discordância entre gêmeos MZ (Zucker & Bradley, 1995; Braun-Sharm, 2004; Kato et al., 2005). Eventos genéticos pós-zigóticos de variados tipos e gravidade não apenas precedem a gemelaridade, mas também são responsáveis por disparar este evento. Enquanto é verdadeiro que a maioria dos gêmeos MZ são fenotipicamente semelhantes, existem um significativo número de pares MZ que não são genotipicamente nem fenotipicamente “idênticos”. Recentemente, um expressivo número de relatos de casos revelou que a discordância fenotípica entre gêmeos MZ pode ser explicada por diversos tipos de diferenças genéticas ou epigenéticas, inter-relacionadas entre si (Machin, 1996), sendo o último fenômeno definido como “o estudo das variações hereditárias mitóticas ou meióticas na função gênica que não podem ser explicadas por alterações na sequência de DNA” (Petronis et al., 2006). Destes mecanismos, metilação de resíduo de citosina na molécula de DNA, acetilação e outras modificações de histonas já foram descritos. Sendo assim, a comparação entre gêmeos idênticos se torna um delineamento ideal para testar epigenética ambiental, já que as diferenças na seqüência de DNA teoricamente não seriam fatores de confusão.

Fatores hormonais:

Em relação à contribuição hormonal, pode-se afirmar que distúrbios endócrinos pré-natais, como hiperplasia adrenal congênita (HAC), condição caracterizada por produção excessiva de andrógenos no período pré-natal, resistência a andrógenos ou impregnação por hormônios exógenos foram, por muito tempo, aventadas como principais alterações clínicas responsáveis pelo desenvolvimento do transexualismo. Porém, essa teoria tornou-se insuficiente para explicar a transexualidade, uma vez que a maioria dos sujeitos acometidos por estes distúrbios endócrinos não desenvolveram esta condição (Kester P, Green R, Finch SJ & Williams K, 1980). Meninas com HAC foram estudadas quanto ao comportamento. A maioria das afetadas demonstrou uma maior agressividade e um interesse em atividades tipicamente masculinas, quando comparadas aos controles (Berenbaum, 1999; Berenbaum, Korman, Duck, &

Resnick, 2004). Poucos casos de troca de gênero foram documentados (Cohen-Kettenis & Gooren, 1999). Ainda, a maioria dos indivíduos afetados que foram criadas pelos pais como meninas desenvolveram uma identidade de gênero feminina. Não obstante, alterações indeterminadas na secreção das gonadotrofinas (déficits androgênicos ou hiperandrogenismo) durante a diferenciação cerebral, ainda são apontadas como ponto chave no mecanismo causal.

Fatores ambientais:

Exposição a altos níveis de estresse durante a gestação tem o potencial de impactar negativamente o desenvolvimento fetal, desfechos do parto e, consequentemente, a saúde na infância e fase adulta (Van den Bergh 2005; Wadhwa 2005; Entringer 2008; Weinstock 2008; O'Donnell et al. 2009). Desta forma, o estresse vivenciado pela mãe durante o período pré-natal também foi proposto como possível fator etiológico implicado no transexualismo. Esta hipótese estaria baseada em um experimento com modelo animal que evidenciou o papel feminilizante do estresse materno no comportamento sexual da prole de ratos do sexo masculino (Ward, Denning, Hendricks & French, 2002) por meio do atraso da liberação de testosterona em um estágio crítico da diferenciação sexual do cérebro (Ward & Weisz, 1980). Descrições detalhadas de modificações neuroanatômicas e comportamentais induzidas pelo estresse pré-natal em humanos foram abordadas em algumas revisões (Weinstock, 1997, 2001), que ressaltam o papel da atividade autonômica do sistema nervoso central e sua influência no fluxo sanguíneo placentário. Entretanto, em 2002, Hines et al, publicaram uma análise prospectiva que evidenciou um efeito discreto do estresse pré-natal no comportamento ligado ao gênero no sexo feminino e nenhum efeito no sexo masculino.

Influências parentais também foram apontadas como fatores implicados no desenvolvimento do transexualismo (Springer, 1981; Kuchenhoff, 1988). Todavia, nenhum suporte empírico sólido foi encontrado ao testar algumas destas hipóteses posteriormente (Green, 1987; Zucker, 1994).

Fatores neuroanatômicos:

Sugere-se que a neuroanatomia desempenhe um papel crítico na determinação da identidade de gênero. A diferenciação sexual cerebral durante o desenvolvimento embrionário parece ocorrer em momentos diferentes em relação à diferenciação sexual do restante do corpo (Zhou et al., 1995). Nos últimos anos, investigaram-se evidências de diferenças sexuais morfológicas no sistema nervoso central, em particular, no núcleo intersticial do hipotálamo anterior. Com o objetivo de explorar essa hipótese, vários estudos examinando estruturas cerebrais em transexuais MpF foram realizados. Análises cerebrais *pós-mortem* demonstraram que transexuais MpF apresentavam uma subdivisão central do núcleo do leito da *estria terminalis* semelhante ao padrão encontrado no sexo feminino, em relação ao tamanho e número de neurônios (Zhou et al., 1995). Do mesmo modo, outro estudo encontrou volume e densidade neuronais do núcleo intersticial do hipotálamo anterior (INAH3) semelhante ao sexo do feminino (Garcia-Falgueras & Swaab, 2008). Em estudos de neuroimagem, Emory, Williams, Cole, Amparo & Meyer (1991), não detectaram associações entre o transexualismo e a anatomia do corpo caloso. Em uma recente análise morfológica exploratória, encontrou-se que o volume da massa cinzenta do putâmen foi maior em transexuais MpF que em controles masculinos e femininos (Luders, Sanchez, et al., 2009). Em contraste a estudos prévios, Savik & Arver (2011) observaram uma redução significativa no volume do tálamo e do putâmen quando comparados a controles femininos ou masculinos, indicando que o transexualismo pode estar associado com alterações anatômicas em regiões cerebrais localizadas fora do hipotálamo. Esse estudo também sugeriu que indivíduos com transexualismo apresentam um volume de substância cinzenta (SC) maior na região insular direita, no córtex frontal inferior e no giro angular direito, assim como no cerebelo e giro lingual, e há diminuição de SC e substância branca (SB) no giro pré-central.

Fatores cognitivos:

Existem evidências de diferenças entre os sexos nas funções cognitivas, como linguagem e percepção espacial, embora isso não seja um consenso. A inteligência parece refletir algumas demandas que têm sido atribuídas a várias regiões cerebrais, ex.: tarefas verbais demandam do lobo frontal inferior e temporal posterior; visuo-espaciais demandam do parietal; codificação e recuperação de informações exigem do hipocampo, tarefas executivas como resolução de problemas, planejamento, raciocínio, são realizadas pelo córtex frontal (Andreasen et al., 1993 Flashman et al.,1997). Diferenças individuais na inteligência geral são avaliadas através do Wechsler Adult Intelligence Scale (WAIS), um instrumento validado no Brasil (Nascimento, 2004) que consiste em 11 diversos subtestes que avaliam uma variedade de habilidades mentais verbais e não-verbais que contribuem para a inteligência geral. A espessura de SC e SB estão ligadas à inteligência (Gignac,Vernon, & Wickett, 2003; Haier et al., 2004; Haier, Jung, Yeo, Head, & Alkire, 2005). Alguns estudos confirmam diferença entre os sexos nestas estruturas: a razão SC/SB é discretamente maior em mulheres do que em homens (Gur et al., 1999; Goldstein et al., 2001; Allen et al., 2003). Análises regionais específicas demonstraram que mulheres apresentam maior volume de SC no giro pré-central, córtex órbito-frontal, frontal superior e giro lingual. Enquanto homens apresentam volumes maiores no córtex fronto-medial, hipotálamo, amígdala e giro angular (Goldstein et al., 2001). Tanto SB como SC parecem estar sob forte influência genética (Baare, van Oel, Hulshoff Pol, Schnack, & Durston, 2001; Thompson et al., 2001). Apesar de ser altamente herdável, (Thompson et al., 2001; Posthuma et al., 2002;), existem evidências que o volume de SC em humanos pode aumentar com o aprendizado motor (Draganski et al., 2004) ou com o aprendizado de uma segunda língua (Mechelli et al., 2004).

A inteligência geral avaliada através do WAIS não demonstrou nenhuma diferença entre homens e mulheres (Jensen, 1998). Contudo, em relação a habilidades específicas, sugere-se que os homens se destacam nas tarefas de rotação mental e percepção espacial, enquanto que as mulheres apresentam melhor desempenho em tarefas de memória verbal, fluência verbal e velocidade da articulação (Zaidi, 2010). Testes de rotação mental em três dimensões (3D) produzem a mais consistente diferença entre os sexos, a favor dos homens (Voyer et al., 1995; Kara ´di et al., 2003; Peters, 2005).

Estudos com Ressonância magnética funcional (RMf) vem sendo desenvolvidos a fim de investigar as bases cerebrais nas diferenças sexuais em tarefas espaciais. Gur et al. (2000), ao analisar uma tarefa de rotação mental em duas dimensões (2D), demonstrou que homens e mulheres ativam preferencialmente áreas cerebrais diferentes para a mesma tarefa. Ao estudar sujeitos com desempenho semelhante em tarefas de rotação mental, Jordan et al. (2002), observou um aumento significativo da ativação no córtex motor esquerdo em homens, e uma maior ativação na região temporal e parietal em mulheres.

Fatores hormonais:

Estudos sugerem que as diversas funções neuropsicológicas e as regiões cerebrais são afetadas por hormônios sexuais específicos. Embora alguns argumentem que o tratamento com estrógenos não é capaz de alterar certas estruturas cerebrais (Garcia-Falgueras and Swaab, 2008), outro estudo demonstrou que o tratamento com drogas anti-androgênicas e estrógenos diminui o volume cerebral dos transexuais MpF para padrões semelhantes aos do sexo femininos (Hulshoff Pol et al. 2006). Altos níveis salivares de testosterona demonstraram estar associados com baixo erro e respostas mais rápidas em testes de rotação mental (Hooven et al., 2004). Ainda, uma única dose de testosterona aumentou o desempenho nas habilidades de rotação mental 3D em mulheres jovens (Aleman et al. 2004). Em contraste, sujeitos tratados com bloqueador androgênico para câncer de próstata demonstraram queda no desempenho das habilidades espaciais, porém melhora no desempenho de memória verbal (Cherrier et al., 2001). Há evidências de que o estradiol exerça um efeito negativo nas habilidades espaciais em mulheres durante o ciclo menstrual (Hausmann et al., 2000) e em homens (Kozaki & Yasukouchi, 2008).

Em transexuais, Slabbekoorn et al.(1999) evidenciou que MpF não tratados com hormônios tinham melhor desempenho nas tarefas de rotação mental em 3D do que transexuais FpM também não tratados, porém, após dez meses de tratamento ocorria reversão desta diferença. Outro estudo de pacientes transexuais não tratados, evidenciou que o modelo de rotação mental era consistente com o sexo biológico dos pacientes e não com a identidade de gênero (Haraldsen et al., 2003). Dois anos após, o mesmo grupo demonstrou que o tratamento hormonal não modifica a habilidade de rotação mental, já que os resultados dos pacientes tratados foram idênticos àqueles encontrados nos controles (Haraldsen et al., 2005). Da mesma forma, Miles et al (2006) evidenciaram que o estrógeno não tem influência na rotação mental em transexuais MpF.

Existem apenas dois estudos de RMf e rotação mental com transexuais. O primeiro, não obteve resultados significativos, provavelmente pelo pequeno tamanho da amostra (Sommer et al., 2008). Mais recente, Schöning et al. (2009) estudou uma amostra de transexuais MpF e evidenciou que tanto os tratados com hormônios quanto os não tratados tiveram maior ativação na região têmporal e menor ativação no lobo parietal esquerdo durante a tarefa, quando comparados aos controles masculinos.

Considerando os fatores revisados, o presente trabalho tem como objetivo estudar as diferenças em relação à exposição ambiental no período de desenvolvimento, o desempenho cognitivo e neuroanatomia em um par de gêmeos MZ discordantes para o transexualismo.

REFERÊNCIAS BIBLIOGRÁFICAS

Aleman A, Bronk E, Kessels RP, Koppeschaar HP, van Honk J. A single administration of testosterone improves visuospatial ability in young women. Psychoneuroendocrinology**.** 2004; 29:612-617.

Allen JS, Damasio H, Grabowski TJ, Bruss J, Zhang W. Sexual dimorphism and asymmetries in the gray-white composition of the human cerebrum. NeuroImage. 2003; 18:880-894.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders (4th ed., text rev.). 2000; Washington, DC: Author.

Andreasen NC, Flaum M, Swayze V, O'Leary DS, Alliger R, Cohen G, et al. Intelligence and brain structure in normal individuals. American Journal of Psychiatry. 1993; 150:130−134.

Baare WFC, van Oel CJ, Hulshoff Pol HE, Schnack HG, & Durston SEE. Volumes of brain structures in twins discordant for schizophrenia. Archives of General Psychiatry. 2001; 58:33−40.

Bailey, JM, Dunne, MP, & Martin, NG. Genetic and environmental Influences on sexual orientation and its correlates in an Australian twin sample. Journal of Personality and Social Psychology. 2000; 78:524–536.

Berenbaum, SA. Effects of early androgens on sex –type activities and interests in adolescents with congenital adrenal hyperplasia. Hormones and Behavior. 1999; 35:102-110.

Berenbaum SA, Korman Bryk K, Duck SC, Resnick SM. Psychological adjustment in children and adults with congenital adrenal hyperplasia. J Pediatr. 2004; 144:741-746

Blanchard, R. Varieties of autogynephilia and their relationship to gender dysphoria. Archives of Sexual Behavior. 1993; 22:2412–2451.

Cherrier, MM, Rose, AL, Higano, C. The effects of combined androgen blockade on cognitive function during the first cycle of intermittent androgen suppression in patients with prostate cancer. Journal of Urology. 2003; 170:1808–1811.

Coates S. Ontogenesis of boyhood gender identity disorder. Journal of The American Academy of Psychoanalysis. 1990; 18:414–438.

Cohen-Kettenis PT, Gooren LJ. Transsexualism: A review of etiology, diagnosis and treatment. Journal of Psychosomatic Research. 1999; 46:315–333.

Coolidge FL, Thede LL, & Young SE. The heritability of gender identity disorder in a child and adolescent twin sample. Behavior Genetics. 2002; 32:251–257.

Démonet, JF, Chollet,F, Ramsay, S, Cardebat, D, Nespoulous, JL, Wise, R, Rascol, A, Frackowiak, R. Theanatomy of phonological and semantic processing in normal subjects. Brain. 1992; 115:1753–1768.

Desikan, RS, Ségonne, F, Fischl, B, Quinn, BT., Dickerson, BC., Blacker, D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage. 2006; 31:968–80.

Doorn, CD, Poortinga, J, & Verschoor, AM. Cross-gender identity intransvestites and male transsexuals. Archives of Sexual Behavior. 1994; 23:185-201.

Draganski B, Gaser C, Busch V, Schuierer G, Bogdahn U, May A. Neuroplasticity: changes in grey matter induced by training. Nature. 2004; 427:311–312.

Emory, LE, Williams, DH, Cole, CM, Amparo, EG, Meyer, WJ.Anatomic variation of the corpus callosum in persons with gender dysphoria. Archives of Sex and Behaviour. 1991; 20:409–417.

Entringer S, Wust S, Kumsta R, Layes IM, Nelson EL, Hellhammer DH, Wadhwa PD. Prenatal psychosocial stress exposure is associated with insulin resistance in young adults. Am J Obstet Gynecol. 2008; 199:491–497.

Filipek PA, Richelme C, Kennedy, DN, Caviness VS. The young adult human brain: An MRI-based morphometric analysis. Cerebral Cortex. 1994; 4:344–360.

Fischl B, Salat DH, Busa E, Albert M, Dieterich, M, Haselgrove, C, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron. 2002; 3:341–355.

Flashman, LA, Andreasen, NC, Flaum M, & Swayze VW. Intelligence and regional brain volumes in normal controls. Intelligence. 1997; 25:149−160.

Galton F. The history of twins, as a criterion of the relative powers of nature and nurture. Journal of Anthropology Institute. 1875;12:566 –576.

Garcia-Falgueras A, Swaab DF. A sex difference in the hypothalamic uncinate nucleus: Relationship to gender identity. Brain. 2008; 131:3132–3146.

Giedd JN, Castellanos FX, Rajapakse JC, Vaituzis AC, Rapoport JL. Sexual dimorphism of the developing human brain. Progress in Neuro-Psychopharmacology & Biological Psychiatry. 1997; 21:1185–1201.

Giedd JN, Clasen LS, Lenroot R, Greenstein D, Wallace GL, Ordaz S, et al. Puberty-related influences on brain development. Molecular and Cellular Endocrinology. 2006; 254:154–162.

Gignac GE , Vernon PA, & Wickett, JC. Factors influencing the relationship between brain size and intelligence. In H. Nyborg (Ed.), The Scientific Study of General Intelligence: Tribute to Arthur R. Jensen Oxford: Pergamon. 2003.

Goldstein JM, Seidman LJ, Horton NJ, Makris N, Kennedy DN, Caviness VS Jr, Faraone SV, Tsuang MT. Normal sexual dimorphism of the adult human brain assessed by in vivo magnetic resonance imaging. Cereb Cortex. 2001; 11:490–497

Green R. The “sissy boy syndrome” and the development of homosexuality. New Haven, CT: Yale University Press; 1987.

Green R. Family cooccurrence of ‘gender dysphoria’: Ten sibling or parent–child pairs. Archives of Sexual Behavior. 2000; 29:499–507.

Green R, Kaverne EB. The disparate maternal aunt-uncle ratio in male transsexuals: an explanation invoking genomic imprinting. J Theor Biol.2000; 202:55-63.

Green R, Young R. Hand preference, sexual preference and transsexualism. Arch Sex Behav. 2001;30:565-75.

Gur RC, Turetsky BI, Matsui M, Yan M, Bilker W, Hughett P, et al. Sex differences in brain gray and white matter in healthy young adults: correlations with cognitive performance. Journal of Neuroscience. 1999; 19:4065−4072.

Haraldsen IR, Opjordsmoen S, Egeland T, Finset A. Sex-sensitive cognitive performance in untreated patients with early onset gender identity disorder. Psychoneuroendocrinology**.** 2003; 28:906–915.

Haraldsen IR, Egeland T, Haug E, Finset A, Opjordsmoen S. Cross-sex hormone treatment does not change sex-sensitive cognitive performance in gender identity disorder patients. Psychiatry Res. 2005; 137:161–174.

Hausmann M, Slabbekoorn D, Van Goozen SHM, Cohen-Kettenis PT, Güntürkün, O. Sex hormones affect spatial abilities during the menstrual cycle. Behavioral Neuroscience. 2000; 114:1245–1250.

Hepp U, Milos G, Braun-Sharm, H. Gender identity disorder and anorexia nervosa in male monozygotic twins. International Journal of Eating Disorders. 2004; 35:239–243.

Hines M, Golombok S, Rust J, Johnston KJ, Golding J**.** Testosterone during pregnancy and gender role behavior of preschool children: a longitudinal, population study. Child Dev. 2002; 73:1678-1687.

Hooven, CK, Chabris, CF, Ellison, PT, Kosslyn, SM. The relationship of male testosterone to components of mental rotation. Neuropsychologia. 2004; 42:782–790.

Hulshoff Pol HE, Cohen-Kettenis PT, Van Haren NEM, Peper JS, Brans RGH, Cahn W, Schnack HG, Gooren LJG, Kahn RS. Changing your sex changes your brain: influences of testosterone and estrogen on adult human brain structure. European Journal of Endocrinology. 2006; 155:107–114.

Jensen A. The g factor. Westport, CN: Praeger. 1998.

Jordan K, Wüstenberg T, Heinze HJ, Peters M, Jäncke L. Women and men exhibit different cortical activation patterns during mentalrotation tasks. Neuropsychologia. 2002; 40:2397-2408.

Karádi K, Csathó A, Kovács, B., Kosztolányi, P. Subgroup analysis of sex difference on the Vandenberg-Kuse mental rotation test. Percept. Mot. Skills. 2003; 96:197—200.

Kato T, Iwamoto K, Kakiuchi C, Kuratomi G, & Okazaki Y. Genetic or epigenetic difference causing discordance between monozygotic twins as a clue to molecular basis of mental disorders. Molecular Psychiatry. 2005; 10:622–630.

Kester P, Green R, Finch SJ, & Williams K. Prenatal female hormone administration and psychosexual development in human males. Psychoneuroendocrinology. 1980; 5:269–285. .

Kozaki T, & Yasukouchi A. Relationships between salivary estradiol and components of mental rotation in young men. Journal of Physiological Anthropology. 2008. 27:19–24.

Kuchenhoff B. Transsexualism as a symptom of a personality disorder and its treatment. Der Nervenarzt. 1988; 59:734–738.

Luders E, Sánchez F, Gaser C, Toga AW, Narr KL, Hamilton SL, Vilain E. Regional gray matter variation in male-to-female transsexualism. Neuroimage. 2009; 46: 904–907.

Mechelli A, Crinion JT, Noppeney U, O'Doherty J, Ashburner J, Frackowiak RS, Price CJ. Neurolinguistics: structural plasticity in the bilingual brain. Nature. 2004; 431(7010):757.

Murphy DG, DeCarli C, McIntosh AR, Daly E, Mentis MJ, Pietrin P, Szczepani J, Schapiro MB, Grady CL, Horwitz B. Sex differences in human brain morphometry and metabolism: an in vivo quantitative magnetic resonance imaging and positronemission tomography study on the effect of aging. Archives of General Psychiatry. 1996; 53:585–59

Nascimento E. WAIS–III: Escala de Inteligência Wechsler para Adultos Manual/David Wechsler; Adaptação e padronização de uma amostra brasileira [WAIS-III: Wechsler Intelligence Scale for Adults – Manual/David Wechsler; Adaptation and Standardization of a Brazilian sample]. São Paulo, Brazil: Casa do Psicólogo. 2004.

Neufang S, Specht K., Hausmann, M., Gunturkun, O., Herpertz-Dahlmann, B., Fink, G. R., Konrad, K. (2009). Sex differences and the impact of steroid hormones on the developing human brain. Cerebral Cortex, 19, 464–473.

Paus T, Tomaiuolo F, Otaky N, MacDonald D, Petrides M, Atlas J, Morris R, Evans AC. (1996). Human cingulate and paracingulate sulci: pattern, variability, asymmetry, and probabilistic map. Cerebral Cortex. 1996; 6:207–214.

Peters M. Sex differences and the factor of time in solving Vandenberg and Kuse mental rotation problems. Brain and Cognition. 2005; 57, 176–184

Posthuma D, Geus, EJC, Baare WFC, Pol HEH, Kahn RS, Boomsma DI. The association between brain volume and intelligence is of genetic origin. Nature Neuroscience. 2002; 5:83−84.

Raz N, Torres IJ, Acker JD. Age, gender, and hemispheric differences in human striatum: a quantitative review and new data from in vivo MRI morphometry. Neurobiology of Learning and Memory. 1995; 63:133–142.

Saadeh A. Transtorno de identidade sexual: um estudo psicopatológico de transexualismo masculino e feminino [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2004. 266p.

Savik I, & Arver S. Sex dimorphism of the brain in male-to-female transsexuals. Cerebral Cortex. 2011; 21:2525–2533.

Schöning S, Engelien A, Bauer C, Kugel H, Kersting A, Roestel C, Zwitserlood P, Pyka M, Dannlowski U, Lehmann W, Heindel W, Arolt V, Konrad C. Neuroimaging differences in spatial cognition between men and male-to-femaletranssexuals before and during hormone therapy. J Sex Med. 2009; 7:1858-67.

Simon O, Mangin JF, Cohen L, Bihan D, Dehaene S. (2002). Topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe. Neuron; 2002: 33:475–487,

Slabbekoorn D, van Goozen SH, Megens J, Gooren LJ, Cohen-Kettenis PT. Activating effects of cross-sex hormones on cognitive functioning: a study of short-term and long-term hormone effects in transsexuals. Psychoneuroendocrinology. 1999; 24:423-447.

Sommer IE, Cohen-Kettenis PT, van Raalten T, Vd Veer AJ, Ramsey LE, Gooren LJ, Kahn RS, Ramsey NF. Effects of cross-sex hormones on cerebral activation during language and mental rotation: An fMRI study in transsexuals. Eur Neuropsychopharmacol. 2008; 18:215-221.

Springer A. (1981). Pathology of sexual identity, transsexualism, and homosexuality: Theory clinical aspects, therapy. Wien, Germany: Springer.

Thompson PM, Cannon TD, Narr KL, van Erp T, Poutanen VP, Huttunen, M, et al. Genetic influences on brain structure. Nature Neuroscience. 2001; 4:1−6.

Van den Bergh BR, Mulder EJ, Mennes M, Glover V. Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: Links and possible mechanisms. A review. Neurosci Biobehav Rev 2005; 29:237–258.

Voyer D. Effect of practice on laterality in a mental rotation task. Brain and cognition. 1995; 29:326–335.

Wadhwa PD. Psychoneuroendocrine processes in human pregnancy influence fetal development and health. Psychoneuroendocrinology. 2005;30:724–743

Ward IL. The prenatal stress syndrome: Current status. Psychoneuroendocrinology. 1984; 9:3–11.

Ward IL, & Weisz J. Maternal stress alters plasma testosterone in fetal males. Science. 1980; 207:328–329.

Ward OB, Ward IL, Denning, JH, Hendricks SE, & French, JA. Hormonal mechanisms underlying aberrant sexual differentiation in male rats prenatally exposed to alcohol, stress, or both. Archives of Sexual Behavior. 2002; 319–16.

Wechsler D. Wechsler Adult Intelligence Scale — Revised. San Antonio, TX: Psychologica Corporation. 1981

Weinstock M. The long-term behavioural consequences of prenatal stress. Neurosci Biobehav Rev. 2008; 32:1073–1086.

Zaidi ZF. Gender differences in human brain: a review. The Open Anatomy Journal. 2010; 2:37-55.

Zhou JN, Hofman MA, Gooren LJ, & Swaab DF. A sex difference in the human brain and its relation to transsexuality. Nature. 1995; 378;68–70.

Zucker KJ, & Bradley SJ. Gender identity disorder and psychosexual problems in children and adolescents. New York, NY: Guilford Press. 1995.

Zucker KJ, Green R, Garofano C, Bradley SJ, Williams K, Rebach HM, & Lowry Sullivan CB. (1994). Prenatal gender preference of mothers of feminine and masculine boys: Relation to sibling sex composition and birth order. Journal of Abnormal Child Psychology. 1994; 22:1–13.

OBJETIVOS

Objetivo Geral

Investigar diferenças neuroanatômicas, cognitivas e ambientais em um par de gêmeos monozigóticos masculino discordante para o transexualismo.

Objetivos Específicos

Comparar os resultados individuais do WAIS e da Ressonância Magnética do encéfalo (um gêmeo contra o outro).

Correlacionar os resultados do WAIS com o volume das estruturas cerebrais e fatores ambientais

Discordant Transsexualism in Male Monozygotic Twins: Neuroanatomical and Psychological Differences

Abstract

One monozygotic male twin pair discordant for transsexualism is described. Both twins were interviewed, tested with the Wechsler Adult Intelligence Scale (WAIS) battery for cognitive functions and underwent magnetic resonance imaging (MRI) to measure the volumes of specific cerebral structures. Interviews with the twins and their mother indicated no unusual medical or life history events that could have a causal role in the emergence of the disorder. Both cognitive function testing and neuroimaging detected different outcome between the twins. In six different cerebral regions differences have been found in the volume of specific structures, as well as in language and spatial abilities. It is suggested that epigenetic factors could be related to the phenotypic discordance and the results found in this study

Introduction

Transsexuality is defined as a gender-identity disorder (GID), characterized by a firm conviction that one belongs to the opposite sex, which often leads to a request of sex reassignment surgery (SRS) (Blanchard, 1993; Cohen-Kettenis & Gooren, 1999). The etiology of transsexualism remains uncertain, and explanations ranging from biological to psychosocial causes have been suggested (Coates, 1990; Cohen-Kettenis & Gooren, 1999; Zucker & Bradley, 1995).

The "nature (heredity) versus nurture (environment)" dichotomy (Galton, 1865) stimulated two central types of twin studies: studies aimed at determining the magnitude of the genetic influence on disease susceptibility (Bailey, Dunne, & Martin, 2000; Coolidge, Thede, & Young, 2002) and studies aimed at identifying environmental risk factors causing discordance between monozygotic (MZ) twins (Hepp, Milos & Braun-Scharm, 2004; Kato, Iwamoto, Kakiuchi, Kuratomi, & Okazaki, 2005; Zucker & Bradley, 1995). Recently, a number of case reports have revealed that phenotypic discordance between MZ twins can arise from several types of interrelated genetic and epigenetic differences (Machin, 1996), being the last phenomena defined as "the study of mitotically or meiotically heritable variations in gene function"(Petronis et al., 2006).

Regarding the "nurture" factor, resistance to androgens, the presence of exogenous hormones during fetal development and prenatal endocrine disorders, such as congenital adrenal hyperplasia, were among the earliest proposed origins of transsexualism. However, this explanation was weakened since the majority of individuals with these conditions were not transsexual despite the phenotypic difference (Kester, Green, Finch, & Williams, 1980). Nevertheless, undetermined alterations in gonadotrophin secretion (androgenic deficits or hyperandrogenia) during brain differentiation are still considered as a key causal mechanism of the emergence of the disorder.

Stressful events such as trauma, illness, and maternal use of alcohol, nicotine and other substances during pregnancy have also been proposed as causes of transsexualism. Prenatal stress has been shown in animal studies to be associated with neurodevelopmental and behavioral disturbances and with long-lasting structural and functional changes in the brain (I. L. Ward, 1984). Additionally, an animal model demonstrated a feminizing role of maternal stress on the sexual behavior of male rat progeny (O. B. Ward, I. L. Ward, Denning, Hendricks, &French, 2002) via a delay in the release of testosterone during the stage of sexual differentiation of the brain (I. L. Ward & Weisz, 1980).

Parental influences, such as extreme closeness to the mother ("blissful symbiosis"), atypical psychosexual development of the parents, father absence, or parental dynamics (such as a maternal wish for a daughter) have also been held responsible for the development of GID (Kuchenhoff, 1988; Springer, 1981). However, no solid empirical support was found in subsequent studies testing these hypotheses (Green, 1987; Zucker et al., 1994).

A number of studies have examined brain structures in male-to-female (MtF) transsexuals. Sexual morphological differences in the hypothalamic nuclei have been found from some postmortem brain analyses which revealed that the central subdivision of the bed nucleus of the stria terminalis in MtF transsexuals is similar to females in terms of its size and number of neurons (Zhou, Hofman, Gooren, & Swab, 1995). Recently, Garcia-Falgueras & Swaab (2008) also found female-like volume and neuronal density of the interstitial nucleus of the anterior hypothalamus (INAH3). In terms of neuroimaging studies, Emory, Williams, Cole, Amparo & Meyer, (1991), did not detect any associations between transsexualism and the anatomy of the corpus callosum. In a recent explorative voxel-based morphological (VBM) analysis, gray matter (GM) volume in the putamen was more pronounced in MtF transsexuals than in male and female controls (Luders, et al., 2009). In opposition to previous studies, Savik and Arver (2011) observed a significant reduction in thalamus and putamen volume in MtF transsexuals compared to male and female controls.

There is some evidence of sexual differences in cognitive functions, although researchers continue to debate this issue. Individual differences in general intelligence as assessed with the Wechsler Adult Intelligence Scale (WAIS), one measure of IQ, are strongly related to differences in GM and white matter (WM) volumes in a number of specific areas distributed mostly in frontal, temporal, and parietal regions (Haier, Jung, Yeo, Head, & Alkire, 2004). Evidence has demonstrated that men excel in mental rotation and spatial perception, whereas women perform better in verbal memory tasks and verbal fluency tasks and demonstrate a faster speed of articulation (Zaidi, 2010). Moreover, It has been found that three-dimensional (3D) mental rotation tests produce the most consistent sex differences in favor of males (Karádi, Csathó, Kovács, Kosztolányi , 2003; Peters, 2005; Voyer, 1995).

Besides SRS, the medical treatment of transsexualism involves the administration of exogenous hormones. Although some researchers argue that estrogen treatment does not alter certain brain structures (Garcia-Falgueras & Swaab, 2008), other studies have shown that treatment with anti-androgen and estrogen decreases the brain volumes of MtF transsexual subjects towards female proportions (Hulshoff Pol et al., 2006). Additionally, estradiol has been reported to have a negative effect on spatial abilities in women during the menstrual cycle (Hausmann, Slabbekoorn, Van Goozen, Cohen-Kettenis, & Güntürkün, 2000) and in men (Kozaki & Yasukouchi, 2008). High levels of salivary testosterone are associated with lower error rates and faster responses in mental rotation tests (Hooven, Chabris, Ellison, & Kosslyn, 2004). In contrast, subjects treated with androgen blockade for prostate cancer showed a decrease in spatial abilities but increased performance on verbal memory (Cherrier, Rose, Higano, 2003).

The aim of this study is to investigate differences in environment, neuroanatomy and cognitive functions in a specific pair of male monozygotic twins discordant for transsexualism, . In addition, we investigate if these differences are hormone dependent, since the affected twin is feminilizated by the hormone therapy.

Methods

A MZ male twin pair discordant for gender identity was studied. The material was gathered via unstructured in-person and telephone interviews with the twins and their mother, as well as physical examinations, neuropsychological tests, and neuroimaging studies. This information was supplemented by inspection of medical records for the transsexual twin, who was diagnosed with GID based on DSM-IV-R criteria, received psychological and clinical support, hormone therapy, and sex reassignment surgery in 2010 through the Gender Identity Disorder Program (PROTIG) at Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil. Informed consent was obtained from the twins and their mother to perform the detailed interviews, zygosity examination, and MRI.

To assess general intelligence, both twins were tested with the WAIS battery (Wechsler, 1981), which consists of 11 diverse subtests that tap a variety of verbal and non-verbal mental abilities related to general intelligence. The WAIS full-scale IQ score (FSIQ) is based on performance on all 11 subtests according to age-based norms validated to the Brazilian population (Nascimento, 2004). Six of the WAIS subtests can be summarized as a single verbal IQ score, and the other five subtests can be summarized as performance IQ.

All MRI images were acquired in a 1.5-T Philips MRI scanner, model Achieva, software version 2.6.3, magnetic field gradient model Nova Dual, with an 8-channel head coil. We acquired 1-mm^3 isotropic volumetric MP-RAGE T1-weighted images with the following parameters: repetition time (TR) of 8.7 ms, echo time (TE) of 4.0 ms, flip angle of 8º, inversion time (TI) 1000 ms, acquisition matrix 224 x 221. In total, we acquired 170 slices in 6 min 33 s. Each subject was scanned five times with the same protocol and was removed from the scanner and repositioned between each of the five acquisitions. All images were processed using the automated pipeline of FreeSurfer v5.0 (Fischl et al., 2002). For all 10 image datasets (five from each subject), GM, WM, and subcortical structures were segmented and measured for each hemisphere via the automated segmentation protocol within FreeSurfer (Desikan et al., 2006). Apart from the automated calculations, each dataset was inspected visually to control for gross structural abnormalities, accuracy of registration, and presence of artifacts. All statistical analyses were conducted using SPSS 18.0 for Windows using the volumes of WM and GM for each of the segmented structures calculated within FreeSurfer. The five measures of each twin were treated as independent and analyzed with t-test. Structures with $p < .001$ were considered (table 2).

Results

At the time of assessment, the twins were aged 24 years. P, the affected twin, had begun taking about 2.5mg/day of oral estrogen around three years earlier, and C had never used any type of hormones. P had a very female face, smooth skin, long hair, delicate behavior, and dressed in typical women's clothes, whereas C exhibited typical male conduct and a masculine appearance. Physical examination did not reveal any abnormal external phenotype. Chromosomal analysis revealed a normal male karyotype (46, XY) in both brothers. Molecular genetic analysis using 15 microsatellite markers confirmed monozygosity. The probability of monozygosity was calculated to be 99.9994%. There was no indication of any additional psychiatric disorder in both twins, since there is no positive results in the MINI interview, as well as in their first-degree relatives, according information.

The twins were the second birth to a 23-year-old mother and 27-year-old father. They have one older half-brother from their mother's first marriage, two younger brothers, and one younger sister. They grew up in a very small city in southern Brazil with about ten thousand inhabitants, and were raised in poor economic conditions. Their father worked as a farmer and abused alcohol. He was described as a quiet and indifferent person, except when he consumed alcohol, which made him become verbally aggressive toward his family. He helped his wife to raise the twins and resided with them until they were teenagers The twins' mother was described as nervous and impatient with the children. She held several jobs briefly during the twins' childhood, but most of the time she worked as a housekeeper.

The full-term twin pregnancy was clinically uneventful, although the mother gained only approximately 14 pounds (6 kg), much lower the expected. The pregnancy was neither planned nor wanted. When the mother realized that she was pregnant, she tried to induce miscarriage by drinking a plant tea: *Ruta graveolens*, in which there is "metilnonilcetona" that is responsible to stimulate the uterus. She was feeling distressed and hopeless because she became pregnant just after a traumatic episode: her older son had been kidnapped by her first husband at a bus station and offered for adoption.

During the pregnancy, she smoked five to six cigarettes a day, took Diazepam occasionally, and drank alcohol twice a week in the first two months. The presence of twins was discovered only moments before delivery. There are no formal data concerning the twins' obstetric history because we could not acquire the records from the hospital where they were born. No notable events took place during the cesarean section and the mother does not know why the surgery was chosen The transsexual twin, P, was delivered first and had a birth weight of 6.83 pounds (3100 g); soon after, the unaffected co-twin, C, was delivered at 6.28 pounds (2850 g). Both had slight anemia and jaundice as newborns. Their motor skills and language developed normally according to the mother's. The twins were breastfed until they were one month old. Both twins are right-handed.

P and C were frequently ill during their first years of life, mainly suffering from asthma attacks. Their attacks were treated with β2 agonist (Salbutamol or Fenotherol). P became sick at the same frequency as C, but usually spent more time affected by illness. Nevertheless, the mother reported that the twins weighed the same, contracted the same childhood diseases, and took the same quantity and type of medication. The difference was that whereas C's recovery was typically fast and full, P needed more time to regain his health. C was more sports-minded and played mostly with boys. P enjoyed both playing soccer with the boys in the neighborhood and playing with dolls with the girls. When the twins and their cousins played together, P would touch and kiss the female cousins, whereas C did not display this behavior. P claims to have "felt different" from the other boys since an early age, but he did not understand why.

C was described as not very friendly, quiet and lonely, while P was described as calm, focused and outgoing. They studied in the same class until the end of the primary school, when C left school to dedicate himself to farm work while P attended and graduated high school. At the beginning of adolescence P started to be sexually interested in boys, whereas C was always interested in girls. When P was fifteen years old, he secretly began to experiment with makeup. Gradually, he began to appear in public wearing eyeliner, face powder, and tight clothing. His first sexual experience happened with a man when he was sixteen. He was involved in casual relationships with several married men until he met his husband. C denies any doubt about his gender identity and any homosexual involvement. He married a woman approximately six years before the study and has two young children from this relationship.

In the assessment of cognitive abilities through the WAIS (Table 1), twin C presented average results in the following indexes: Verbal Comprehension Index that assesses acquired verbal knowledge and the ability to understand linguistic information; Processing Speed Index that includes the subtests related to attention and concentration to quickly processes visual information; and Working Memory Index which refers to the ability to pay attention to the information, keep it, process it and then response. In the Perceptual Organization index that gathers the subtests evaluating nonverbal fluid reasoning, attention to detail and visual-motor integration, twin C achieved an above average score.

Twin P presented average results in the Verbal Comprehension Index, Working Memory Index and Perceptual Reasoning Index, and above average results in the subtests grouped in the Processing Speed Index. Although there is no significative difference between the twins in terms of IQ, it is clear that there is a tendency of C performs better in the visual-spatial subtests and P in those in the field of language. As the main objective of this analysis was the comparison between the twins and due the fact that the Brazilian adaptation of the WAIS battery did not include normative tables differentiating genders, we chose to use only raw scores (table 1).

Table 1 WAIS results

	P*	C	Δ	%
Subtests				
Picture Completion	21	18	P>C	15%
Vocabulary	47	32	P>C	28%
Codes	71	50	P>C	30%
Similarities	18	20	P<C	11%
Block Design	34	47	P<C	38%
Arithmetic	11	1	P=C	0%
Matrix Reasoning	15	14	P>C	7%
Digit Span	19	16	P>C	16%
Information	13	6	P>C	54%
Picture Arrangement	6	11	P<C	83%
Comprehension	24	12	P>C	50%
Symbol Search	30	27	P>C	10%
Letter-number Sequencing	9	8	P>C	12%
Object Assembly	37	26	P>C	30%
Indexes				
Verbal Comprehension Index	35	27	P>C	23%
Working Memory Index	34	34	P=C	0%
Perceptual Reasoning Index	35	36	P<C	2%
Processing Speed Index	24	20	P>C	27%
IQs				
Verbal IQ	71	59	P>C	27%
Performance IQ	55	55	P=C	0%
Total IQ	126	114	P>C	10%

*affected twin

highlighted data emphasized differences above 20%

In brain estructural analyses (table 2), the affected twin P presented **smaller** volumes compared to C in the following structures of 5 cerebral regions:

1-Limbic region: (a) posterior cingulate cortex, (b) left isthmus of cingulate gyrus, (c) left rostral cingulate cortex.

2- Intrabrain region: (a) left ventral diencephalon, (b) left inferior lateral ventricle.

3-Parietal lobe; (a) left precuneus cortex, (b) left superior parietal gyrus.

4- Frontal lobe: (a) left caudal middle frontal gyrus, (b) left frontal pole.

5-Temporal lobe: (a) left hippocampus, (b) left fusiform gyrus.

Twin P presented **larger** volumes compared to C in the following structures:

1-Limbic region: (a) left caudal anterior cingulate gyrus.

2-Intrabrain region: (a) right lateral ventricle (b) third ventricle.

3-Parietal lobe: (a) left supramarginal gyrus, (b) right precuneus cortex.

4-Frontal pole: (a) left lateral orbitofrontal cortex, (b) left and right portions of the triangular part of inferior frontal gyrus.

5-Temporal lobe: (a) Left ehtorhinal cortex, (b) right inferior temporal gyrus.

6-Occipital lobe:(a)right cuneus cortex.

T**able 2** Neuroimaging results

Hemisphere	**Region**	**Structure**	**P* - Median volume**	**C - Median volume**	**Δ**	**%¹**
Right	Frontal	Right triangular part of inferior frontal gyrus	4722,2	4197,8	P>C	12%
	Intrabrain	Right lateral ventricle	4618,2	3581,4	P>C	29%
	Intrabrain	Right inferior lateral ventricle	723,4	1108,6	P<C	35%
	Limbic	Right Posterior cingulate cortex	444,4	484,6	P<C	9%
	Occipital	Right cuneus cortex	3647,2	3384,6	P>C	7%
	Parietal	Right precuneus cortex	10373,8	9912,8	P>C	4%
	Temporal	Right inferior temporal gyrus	11740,2	10628,8	P>C	10%
	Intrabrain	Third ventricle	908,2	798,2	P>C	13%
Left	Frontal	Left lateral orbitofrontal cortex	8442,2	7780,6	P>C	8%
	Frontal	Left triangular part of inferior frontal gyrus	3807,6	3737,2	P>C	1%
	Frontal	Left frontal pole	793	896,8	P<C	12%
	Frontal	Left caudal middle frontal gyrus	6802	6837	P<C	1%
	Intrabrain	Left ventral IDC	4127	4270,2	P<C	4%
	Limbic	Left isthmus of cingulate gyrus	2625,8	2682	P<C	3%
	Limbic	Left rostral anterior cingulate cortex	2694,4	2805,2	P<C	4%
	Limbic	Left caudal anterior cingulate cortex	1417	1335,6	P>C	6%
	Parietal	Left precuneus cortex	9522,2	10443,6	P<C	9%
	Parietal	Left superior parietal gyrus	12657,2	12992,8	P<C	3%
	Parietal	Left supramarginal gyrus	10381,2	9988,8	P>C	3%
	Temporal	Left fusiform gyrus	8959,4	9663,8	P<C	8%
	Temporal	Left hippocampus	4063,8	4342	P<C	7%
	Temporal	Left entorhinal cortex	1957	1893,6	P>C	3%

*affected twin

1 $p<.0009$

Highlighted data emphasized differences above 10%

Discussion

The case reported here provides evidences of structural and neuropsychological factors that could be associated for the transsexuality discordance in this twin pair, although it is not possible to determine causality. We can infer that these two brothers were raised in the same environment and exposed to similar external stimuli during childhood. However, the maternal stressful life event during pregnancy and vulnerability of the transsexual brother may be important factors. It is well established that pregnancy dramatically affects the maternal hypothalamic-pituitary-adrenal (HPA) axis, leading to increased basal levels of corticotropin-releasing hormone (Lindsay & Nieman, 2005). The physiological consequences of this increase in cortisol remain a matter of debate, but most discussions have focused on effects on the fetus (Mastorakos & Ilias, 2003). Adverse life situations experienced by the pregnant mother and her reactions to them could alter the fetal environment and have deleterious effects on the child's mental and physical health (Maccari et al., 2003; Wadhwa, Sandman, & Garite, 2001; Weinstock, 2001). Additionally, the intrauterine environment is not necessarily equal for both MZ twin (Machin, 1996), particularly in this pair, since there is no record information if they had the same placenta or membrane. Even though there is not a clear medical history regarding those events it is possible to hypothesize that environment might had a contribution to the discordance outcome between the twins.

The most consistent difference in WAIS battery performance between the two brothers is that the affected twin P, had a better verbal IQ and larger volumes compared to his brother in cerebral regions associated with language: the right inferior temporal gyrus (Démonét, 1992), right triangular part of inferior frontal gyrus (Foundas, Leonard, Gilmore, Fennell, Heilman, 1996), and left supramarginal gyrus (Simon, Mangin, Cohen, Bihan, Dehaene, 2002)

(p<0.01). Otherwise, twin C performed better in spatial and execution tasks and had larger volumes in the MRI in regions associated with this cognitive functions: the left precuneus cortex (Cavanna & Trimble, 2006), left superior parietal gyrus (Hoag, 2008) and left frontal pole (Gur, et al, 2000) (p< 0.01). There is increasing evidence relating psychometric measures of intelligence and reasoning to regional brain structure and function assessed with a variety of neuroimaging techniques (Haier, Jung, Yeo, Head, & Alkire, 2004; Haier, White, & Alkire, 2003; Schmithorst & Holland, 2006; Shaw et al., 2006).

Although a previous study found no evidence of changes in spatial abilities in MtF transsexuals under estrogen treatment (Miles, Green, Hines, 2006), another recent study suggested that exogenous hormone usage could explain hypoactivation in the cerebral regions responsible for spatial abilities in MtF transsexuals (Carrillo et al., 2010), a hypothesis that seems to be in line with the results presented by the transsexual twin in our study.

Brain imaging studies have investigated neuroanatomical differences in transsexual individuals (Garcia-Falgueras & Swaab, 2008; Luders, Sanchez, et al., 2009; Savik & Arver, 2011). Most of them included structures previously reported to be sexually dimorphic, like hippocampus, caudate nucleus (Filipek, Richelme, Kennedy, & Caviness, 1994; Murphy et al. 1996; Giedd, Castellanos Rajapakse, Vaituzis, Rapoport , 1997), anterior cingulate gyrus (Paus et al., 1996), amygdala (Raz, Torres, Acker, 1995 ; Giedd et al., 2006; Neufang et al., 2009). VBM data from MtF transsexuals has previously been published only by Luders, Sanchez, et al. (2009), who did not find any clear signs of cerebral feminization. Despite identifying several structures that show differences specific to transsexual individuals, the results are unreliable. In addition, our study suggests some others structures that may differ in transsexuals, as described above.

The hypothesis of a genetic contribution in transsexualism gained support from case reports of twin and non-twin siblings who are concordant for this condition and from reports of families with more than one member who is a MtF transsexual (Green, 2000). Earlier twin studies were based on the premise that MZ twins are genetically identical, and that phenotypic differences must arise from nonshared environment (Reiss, Plomin, & Hetherington, 1991; Turkheimer & Waldron, 2000) However, knowledge of epigenetic mechanisms provides a new model to understand MZ twin discordance, as explored in this study. Furthermore, many physical and physiological reasons would be expected to lead to discordance in MZ twins — eg, initial differences in the number of cells at the time of separation, differences intravascular flow, differences in attachment to the placenta, type of chorion, and total number of cell divisions (Machin, 1996). Thus, a complex interaction of multiple genetic, epigenetic, developmental, and experiential influences seems to be implicated in the differences found between this MZ twin pair.

Table 3 summarizes the main findings of this study regarding the used techniques: interview with the twins and their mother, the Wais battery and the brain image.

Table 3: Main Finding

Interview	**Information**	**Δ**
	Birth Weigth	P>C
	Sickness Resistence	P<C
	School Years	P>C
Wais Battery[1]	**Test**	**Δ**
	Vocabulary	P>C
	Codes	P>C
	Block Design	P<C
	Information	P>C
	Picture Arrangement	P<C
	Comprehension	P>C
	Object Assembly	P>C
	Verbal Comprehension Index	P>C
	Processing Speed Index	P>C
	Verbal IQ	P>C
Brain Image[2]	**Structure**	**Δ**
	Right triangular part of inferior frontal gyrus	P>C
	Right lateral ventricle	P>C
	Right inferior lateral ventricle	P<C
	Right inferior temporal gyrus	P>C
	Third ventricle	P>C
	Left frontal pole	P<C

1 - differences above 20%

2 – differences above 10%

The present research has some limitations. First limiting factor of this study is the presence of a single twin pair. Clearly larger groups of comparison with others MZ twins, dyzigotic twins, or male and female controls would improve power of the analyses and expand the results. Second, since the affected twin were receiving hormonal treatment, this study cannot establish whether the differences are a direct effect of the hormonal treatment or whether they emerge from underlying differences in the cerebral structure. Third, there is no medical records confirming some obstetrics' information given by the mother Finally, there is no consensus in the field of statistics about the best techniques to use with clustering data. Galbraith, Daniel, & Bryce (2010) suggested that clustering can sometimes be ignored and the data can be treated as if all observations were independent. The resulting data can then be analyzed using standard methods for independent observation, such as t-tests. In these cases, some precautions need to be taken, such as the use of a robust *p*-value (Kirkwood, 2003), to avoid introducing error into the analysis.

The present study showed that a pair of MZ twins discordant for transsexuality unexpectedly presented substantial differences in cognitive and neuropsychological functioning. To our knowledge, it is the first study that investigates the neuroanatomical differences between a twin pair discordant for transexualism. Further studies will need to determine the degree to which genetic variability and environmental factors influence the development of gender identity and its relation to brain structures and cognitive functions. Evidence shows that prenatal hormonal exposure plays a role in early infancy and puberty, critical periods when hormones affect human neurobehavioral organization (Hines, 2011). Although the mechanisms underlying these influences need to be more investigated, they could explain our findings.

References

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC: Author.

Bailey, J. M., Dunne, M. P., & Martin, N. G. (2000). Genetic and environmental influences on sexual orientation and its correlates in an Australian twin sample. *Journal of Personality and Social Psychology*, *78*, 524–536.

Blanchard, R. (1993). Varieties of autogynephilia and their relationship to gender dysphoria. *Archives of Sexual Behavior*, *22*, 2412–2451.

Carrillo, B.**,** Gómez-Gil, E.**,** Rametti, G.**,** Junque C.**,** Gomez, A.**,** Karadi, K.**,** Segovia S.**,** Guillamon, A. (2010). Cortical activation during mental rotation in male-to-female and female-to-male transsexuals under hormonal treatment. *Psychoneuroendocrinology,* *35*, 1213–1222 **.**

Cavanna, A. E., Trimble, M. R. (2006). The precuneus: a review of its functional anatomy and behavioural correlates. *Brain*, *129*, 564–583.

Cherrier, M. M., Rose, A. L., Higano, C. (2003). The effects of combined androgen blockade on cognitive function during the first cycle of intermittent androgen suppression in patients with prostate cancer. *Journal of Urology, 170, 1808—1811*.

Coates, S. (1990). Ontogenesis of boyhood gender identity disorder. *Journal of the American Academy of Psychoanalysis*, *18*, 414–438.

Cohen-Kettenis, P. T., & Gooren, L. J. (1999). Transsexualism: A review of etiology, diagnosis and treatment. *Journal of Psychosomatic Research*, 46, 315–333.

Coolidge, F. L., Thede, L. L., & Young, S. E. (2002). The heritability of gender identity disorder in a child and adolescent twin sample. *Behavior Genetics*, *32*, 251–257.

Démonet, J.F., Chollet, F., Ramsay, S., Cardebat, D., Nespoulous, J. L., Wise, R., Rascol, A., Frackowiak, R. (1992). The anatomy of phonological and semantic processing in normal subjects. *Brain 115*, 1753–1768.

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B.C., Blacker, D., Buckner, R. L., Dale, A. M., Maguire, R. P., Hyman, B. T., Albert, M. S., Killiany, R. J.(2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage, 31*:968–80.

Emory, L. E., Williams, D. H., Cole, C. M., Amparo, E. G., Meyer, W. J. (1991). Anatomic variation of the corpus callosum in persons with gender dysphoria. *Archives of Sex and Behaviour 20,* 409–417.

Filipek, P. A., Richelme, C., Kennedy, D. N., & Caviness, V. S., Jr. (1994). The young adult human brain: An MRI-based morphometric analysis. *Cerebral Cortex*, *4*, 344–360.

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., van der Kouwe A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., Dale, A. M. (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron, 3,* 341–355.

Foundas, A. L., Leonard, C. M., Gilmore, R. L., Fennell, E. B., Heilman, K. M. (1996). *Proceedings of the National Academy of the Sciences of the United States of America*, *23*,719–722

Galbraith, S., Daniel, J., & Bryce, V. (2010). A study of clustered data and approaches to its analysis. *The Journal of Neuroscience, 30*, 10601–10608.

Galton, F. The history of twins, as a criterion of the relative powers of nature and nurture. (1875). *Journal of Anthropology Institute, 12,* 566 –576.

Garcia-Falgueras, A., & Swaab, D. F. (2008). A sex difference in the hypothalamic uncinate nucleus: Relationship to gender identity. *Brain*, *131*, 3132–3146.

Giedd, J. N., Castellanos, F.X., Rajapakse, J.C., Vaituzis, A.C., Rapoport, J.L. (1997). Sexual dimorphism of the developing human brain. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 21, 1185–1201.*

Giedd, J. N, Clasen, L.S, Lenroot, R., Greenstein, D., Wallace, G. L., Ordaz, S., Molloy E.A., Blumenthal, J. D, Tossell, J. W., Stayer, C. (2006). Puberty-related influences on brain development. *Molecular and Cellular Endocrinology, 254,* 154–162.

Green, R. (1987). *The "sissy boy syndrome" and the development of homosexuality*. New Haven, CT: Yale University Press.

Green, R. (2000). Family cooccurrence of 'gender dysphoria': Ten sibling or parent–child pairs. *Archives of Sexual Behavior*, 29, 499–507.

Gur, R. C., Alsop, D., Glahn, D., Petty, R., Swanson, C. L., Maldjian, J. A., Turetsky, B. I., Detre, J. A., Gee, J., Gur, R. E. (2000) An fMRI study of sex differences in regional activation to a verbal and a spatial task. *Brain and Language*, *74*, 157–170.

Haier, R. J., White, N. S., & Alkire, M. T. (2003). Individual differences in general intelligence correlate with brain function during nonreasoning tasks. *Intelligence, 31*, 429−441.

Haier, R. J., Jung, R. E., Yeo, R. A., Head, K., & Alkire, M. T. (2004). Structural brain variation and general intelligence. *Neuroimage*, *23*, 425–433.

Hausmann, M., Slabbekoorn, D., Van Goozen, S. H. M., Cohen-Kettenis, P. T., & Güntürkün, O. (2000). Sex hormones affect spatial abilities during the menstrual cycle. *Behavioral Neuroscience*, *114*, 1245–1250.

Hepp, U., Milos, G., & Braun-Sharm, H. (2004). Gender identity disorder and anorexia nervosa in male monozygotic twins. *International Journal of Eating Disorders*, 35, 239–243.

Hines, M. (2011). Gender development and the human brain. *Annual Review of Neuroscience*, *34*, 69–88.

Hoag, H. (2008). Sex on the brain. *New Science*, *199*, 28–31.

Hooven, C. K., Chabris, C. F., Ellison, P. T., & Kosslyn, S. M. (2004). The relationship of male testosterone to components of mental rotation. *Neuropsychologia*, *42*, 782–790.

Hulshoff Pol, H. E., Cohen-Kettenis, P. T., Van Haren, N. E.M., Peper, J. S., Brans, R. G. H., Cahn, W., Schnack, H .G., Gooren, L. J. G., Kahn, R. S. Changing your sex changes your brain: influences of testosterone and estrogen on adult human brain structure. *European Journal of Endocrinology ,155,* 107–114.

Karádi, K., Csathó, A., Kovács, B., Kosztolányi, P.(2003). Subgroup analysis of sex difference on the Vandenberg-Kuse mental rotation test. *Percept. Mot. Skills 96, 197—200.*

Kato, T., Iwamoto, K., Kakiuchi, C., Kuratomi, G., & Okazaki, Y. (2005). Genetic or epigenetic difference causing discordance between monozygotic twins as a clue to molecular basis of mental disorders. *Molecular Psychiatry*, *10*, 622–630.

Kester, P., Green, R., Finch, S. J., & Williams, K. (1980). Prenatal female hormone administration and psychosexual development in human males. *Psychoneuroendocrinology*, *5*, 269–285. .

Kirkwood, B. R. (2003). *Essentials of medical statistics.* Malden, MA: Blackwell Science.

Kozaki, T., & Yasukouchi, A. (2008). Relationships between salivary estradiol and components of mental rotation in young men. *Journal of Physiological Anthropology*, *27*, 19–24.

Kuchenhoff, B. (1988). Transsexualism as a symptom of a personality disorder and its treatment. *Der Nervenarzt*, *59*, 734–738.

Lindsay, J. R., & Nieman, L. K. (2005). The hypothalamic-pituitary-adrenal axis in pregnancy: Challenges in disease detection and treatment. *Endocrinology Review*, *26*, 775–799.

Luders, E., Sánchez, F. J.; Gaser, C., Toga, A.W., Narr, K. L., Hamilton, S. L., Vilain, E. (2009). Regional gray matter variation in male-to-female transsexualism . *Neuroimage*, *46*, 904–907.

Maccari, S., Darnaudery, M., Morley-Fletcher, S., Zuena, A. R., Cinque, C., & Van-Reeth, O. (2003). Prenatal stress and long-term consequences: Implications of glucocorticoid hormones. *Neuroscience and Biobehavioral Reviews*, *27*, 119–127.

Machin, G. A. (1996). Some causes of genotypic and phenotypic discordance in monozygotic twin pairs. *American Journal of Medical Genetics*, *61*, 216–228.

Mastorakos, G., & Ilias, I. (2003). Maternal and fetal hypothalamic-pituitary-adrenal axes during pregnancy and postpartum. *Annals of the New York Academy of Science*, *997*, 136–149.

Miles, C., Green, R., Hines, M., (2006). Estrogen effects on cognition, memory and mood in male to-female transsexuals. *Hormones and Behaviour*, *50*, 707–708.

Murphy, D. G., DeCarli, C., McIntosh, A. R, Daly, E, Mentis M. J, Pietrin, P., Szczepani, J., Schapiro, M. B, Grady, C. L, Horwitz, B. (1996). Sex differences in human brain morphometry and metabolism: an in vivo quantitative magnetic resonance imaging and positronemission tomography study on the effect of aging. *Archives of General Psychiatry. 53:*585–59

Nascimento, E. (2004). *WAIS–III: Escala de Inteligência Wechsler para Adultos – Manual/David Wechsler;* Adaptação e padronização de uma amostra brasileira [WAIS-III: Wechsler Intelligence Scale for Adults – Manual/David Wechsler; Adaptation and Standardization of a Brazilian sample]. *São Paulo, Brazil: Casa do Psicólogo.*

Neufang, S., Specht, K., Hausmann, M., Gunturkun, O., Herpertz-Dahlmann, B., Fink, G. R., Konrad, K. (2009). Sex differences and the impact of steroid hormones on the developing human brain. *Cerebral Cortex, 19,* 464–473.

Paus, T., Tomaiuolo, F., Otaky, N., MacDonald, D., Petrides, M., Atlas, J., Morris, R., Evans, A. C. (1996). Human cingulate and paracingulate sulci: pattern, variability, asymmetry, and probabilistic map. *Cerebral Cortex, 6,* 207–214.

Peters, M. (2005). Sex differences and the factor of time in solving Vandenberg and Kuse mental rotation problems. *Brain and Cognition, 57,* 176–184

Petronis, A. (2006). Epigenetics and twins: Three variations on the theme. *Trends in Genetics, 22,* 347–350.

Petronis, A., Gottesman, I. I., Peixiang, K., Kennedy, J. L., Basile, V. S., Andrew, D., Popendikyte, V. (2003). Monozygotic twins exhibit numerous epigenetic differences: Clues to twin discordance? *Schizophrenia Bulletin, 29,* 169–178.

Raz, N., Torres, I.J, Acker, J.D. (1995). Age, gender, and hemispheric differences in human striatum: a quantitative review and new data from in vivo MRI morphometry. *Neurobiology of Learning and Memory, 63,* 133–142.

Reiss, D., Plomin, R., & Hetherington, E. M. (1991). Genetics and psychiatry: An unheralded window on the environment. *American Journal of Psychiatry*, *148*, 283–291.

Savik, I., & Arver, S. (2011). Sex dimorphism of the brain in male-to-female transsexuals. *Cerebral Cortex, 21*, 2525–2533.

Schmithorst, V. J., & Holland, S. K. (2006). Functional MRI evidence for disparate developmental processes underlying intelligence in boys and girls. *NeuroImage*, *31*, 1366−1379.

Shaw, P., Greenstein, D., Lerch, J., Clasen, L., Lenroot, R., Gogtay, N. (2006). Intellectual ability and cortical development in children and adolescents. *Nature*, 676−679.

Simon, O., Mangin, J. F., Cohen, L., Bihan, D., Dehaene, S. (2002). Topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe *Neuron,33*, 475–487,

Springer, A. (1981). *Pathology of sexual identity, transsexualism, and homosexuality: Theory,clinical aspects, therapy*. Wien, Germany: Springer.

Turkheimer, E., & Waldron, M. (2000). Nonshared environment: A theoretical, methodological, and quantitative review. *Psychological Bulletin*, *126*, 78–108.

Voyer, D. (1995). Effect of practice on laterality in a mental rotation task. *Brain and cognition, 29,* 326–335.

Wadhwa, P. D., Sandman, C. A., & Garite, T. J. (2001). The neurobiology of stress in human pregnancy: Implications for prematurity and development of the fetal central nervous system. *Program of Brain Research*, *133*, 131–142.

Ward, I. L. (1984). The prenatal stress syndrome: Current status. *Psychoneuroendocrinology*, *9*, 3–11.

Ward, I. L., & Weisz, J. (1980). Maternal stress alters plasma testosterone in fetal males. *Science*, *207*, 328–329.

Ward, O. B., Ward, I. L., Denning, J. H, Hendricks, S. E., & French, J. A. (2002). Hormonal mechanisms underlying aberrant sexual differentiation in male rats prenatally exposed to alcohol, stress, or both. *Archives of Sexual Behavior, 31*, 9–16.

Wechsler, D. (1981). *Wechsler Adult Intelligence Scale — Revised*. San Antonio, TX: Psychologica Corporation.

Weinstock, M. (2001). Alterations induced by gestational stress in brain morphology and behaviour of the offspring. *Program of Neurobiology*, *65*, 427–451.

Zaidi, Z. F. (2010). Gender differences in human brain: a review. *The Open Anatomy Journal, 2,* 37-55.

Zhou, J. N., Hofman, M. A., Gooren, L. J., & Swaab, D. F. (1995). A sex difference in the human brain and its relation to transsexuality. *Nature*, *378*, 68–70.

Zucker, K. J., & Bradley, S. J. (1995). *Gender identity disorder and psychosexual problems in children and adolescents.* New York, NY: Guilford Press.

Zucker, K. J., Green, R., Garofano, C., Bradley, S. J., Williams, K., Rebach, H. M., & Lowry Sullivan, C. B. (1994). Prenatal gender preference of mothers of feminine and masculine boys: Relation to sibling sex composition and birth order. *Journal of Abnormal Child Psychology*, *22*, 1–13.

CONCLUSÕES E CONSIDERAÇÕES FINAIS

Estudos com gêmeos são particularmente úteis na tentativa de elucidar o papel dos fatores ambientais e genéticos na etiologia de várias condições médicas, incluindo transtornos psiquiátricos, visto que a concordância clínica entre os indivíduos costuma ser alta (Petronis, 2003). Em situações em que apenas um dos gêmeos monozigóticos manifesta a doença, a principal hipótese aventada para explicar o fenômeno é a presença dos chamados "fatores ambientais não compartilhados" (Reiss, Plomin, & Hetherington, 1991; Turkheimer & Waldron, 2000). Sugere-se que, precocemente, o ambiente não seja necessariamente idêntico para ambos os gêmeos, mesmo os MZ, já que na fase intra-uterina eles podem não compartilhar da mesma placenta ou membrana, o que contribui para diferenças no desenvolvimento e influi no fenótipo e na vulnerabilidade individual (Machin, 1996).

A partir do relato de caso apresentado, não há evidências claras de fatores que podem ser apontados como responsáveis pela discordância para o transexualismo nesse casal de gêmeos. É possível inferir que esses dois irmãos foram criados no mesmo ambiente e expostos a estímulos externos semelhantes durante a infância. Entretanto, é necessário atentar para duas informações: o evento estressor materno ocorrido durante a gravidez e a saúde vulnerável do irmão transexual. É bem estabelecido que gestações afetam de forma dramática o eixo hipotálamo-hipófise-adrenal (HHA), levando a um aumento nos níveis basais de liberação de corticotrofina (Lindsay & Nieman 2005). As consequências psicológicas maternas do aumento de cortisol ainda permanecem em discussão, porém os efeitos no feto têm sido amplamente estudados (Mastorakos & Ilias 2003). Situações adversas experimentadas na gravidez e as reações decorrentes dela podem induzir alterações no ambiente fetal e resultar em efeitos deletérios na saúde mental ou física do concepto (Maccari et al.,2003; Wadhwa et al., 2001; Weinstock, 2001). Além disso, o ambiente intrauterino não é necessariamente igual para ambos os gêmeos (Machin, 1996) e, neste par de gêmeos especificamente, não há um registro obstétrico que confirme a presença de uma só placenta. Ainda, apesar de não haver uma comprovação clínica dos eventos ocorridos na infância, é possível hipotetizar que o gêmeo transexual era mais suscetível do ponto de vista médico. Este conjunto de inferências aponta para uma possível contribuição ambiental no desfecho discordante do casal em estudo.

Com o objetivo de explorar possíveis diferenças entre os gêmeos, correlacionou-se os resultados do WAIS com a análise estrutural de regiões cerebrais através de Ressonância Magnética. Há evidências crescentes, documentadas por uma variedade de técnicas de neuroimagem, relacionando medidas psicométricas de inteligência e estruturas regionais cerebrais e suas funções, (Haier, Jung, Yeo, Head, & Alkire, 2004; Haier, White, & Alkire, 2003; Schmithorst & Holland, 2006; Shaw et al., 2006). Algumas diferenças consistentes entre os irmãos nesse aspecto merecem ser discutidas. O gêmeo afetado P, apresentou maior QI nas habilidades de linguagem, em associação com aumento de volume de regiões cerebrais apontadas por participarem desta função cognitiva, como o giro temporal inferior direito, pars triangularis (Foundas et al., 1996) e giro supramarginal esquerdo (Gazzaniga, 2009) ($p<0.01$), quando comparado ao irmão gêmeo. Por outro lado, C apresentou um melhor desempenho nas habilidades espaciais e de execução, assim como um maior volume evidenciado no precuneus (Cavanna & Trimble, 2006), giro parietal superior esquerdo (Hoag, 2008) e no pólo frontal esquerdo (Gur, et al, 2000) ($p< 0.01$), regiões cerebrais associadas a estas funções. Apesar de não haver evidências de alterações nas habilidades espaciais em transexuais submetidos a tratamento com estrógenos (Miles et al., 2006), um estudo mais recente sugeriu que uso de hormônios exógenos pode justificar uma hipoativação de regiões cerebrais responsáveis pelas habilidades espaciais em transexuais HpM (Carrillo, et al, 2010).

Algumas limitações deste estudo devem ser citadas. A primeira delas é a presença de apenas um par de gêmeos no estudo. Claramente, um grupo de comparação com outros pares de gêmeos monozigóticos, dizigóticos ou controles femininos e masculinos aumentaria o poder de análise e ampliaria os resultados. Segundo, uma vez que o gêmeo transexual encontra-se em tratamento hormonal, este estudo não pode afirmar se as diferenças encontradas nas estruturas cerebrais são subjacentes ou conseqüências diretas do uso de hormônios. Terceiro, não houve possibilidade de acesso aos registros obstétricos da mãe, o que diminui a confiabilidade das informações. Por último, não há um consenso estatístico sobre o melhor método a ser utilizado para dados agrupados. Galbraith, Daniel, & Bryce (2010) sugerem que, em alguns casos, o agrupamento pode ser ignorado e os dados podem ser tratados como se todas as observações fossem realizadas de modo independente. Os dados resultantes podem ser analisados usando métodos padrão para uma observação independente, tais como teste t. Nestes casos, algumas precauções precisam ser abordadas, como a utilização de um valor p rigoroso (Kirkwood, 2003), para evitar o erro implícito na análise.

O presente trabalho demonstra que gêmeos discordantes para o transexualismo apresentam diferenças substanciais nas funções neuropsicológicas e cognitivas, não esperada em pares monozigóticos. Evidências demonstram que a exposição a hormônios no período pré-natal apresentam um papel importante nos períodos iniciais da infância e puberdade, períodos críticos em que os hormônios afetam a organização neuro-comportamental humana (Hines, 2011). Embora os mecanismos subjacentes a estas influências permaneçam em grande parte não investigadas, esta hipótese poderia justificar nossos achados. Todavia, a razão para a existência de determinadas diferenças deve ser investigada em estudos futuros a fim de identificar a intensidade em que a variabilidade genética e os fatores ambientais influenciam o desenvolvimento da identidade de gênero e afetam estruturas cerebrais e funções cognitivas.

Esse trabalho consiste em um estudo de caso exploratório que, portanto, não pode estabelecer bases objetivas para as diferenças entre os gêmeos e a relação entre neuro-imagem e funções cognitivas, mas, apenas, gerar hipóteses. Para tanto, serão necessárias novas pesquisas comparando neuroimagem e o resultado em tarefas cognitivas em homens e mulheres não afetados com transexuais HpM e MpH, a serem realizadas pelo PROTIG.

REFERÊNCIAS BIBLIOGRÁFICAS

Carrillo, B, Gómez-Gil, E, Rametti, G, Junque C, Gomez, A, Karadi, K, et al. Cortical activation during mental rotation in male-to-female and female-to-male transsexuals under hormonal treatment. Psychoneuroendocrinology. 2010; 35:1213–1222 .

Cavanna, AE, Trimble, MR. The precuneus: a review of its functional anatomy and behavioural correlates. Brain. 2006; 129:564–583.

Foundas AL, Leonard CM, Gilmore RL, Fennell EB, Heilman KM. Proceedings of the National Academy of the Sciences of the United States of America. 1996; 23:719–722

Gur RC, Alsop D, Glahn D, Petty R, Swanson CL, Maldjian JA, et al. An fMRI study of sex differences in regional activation to a verbal and a spatial task. Brain and Language. 2000; 74:157–170.

Haier, RJ, White, NS, Alkire, MT. Individual differences in general intelligence correlate with brain function during nonreasoning tasks. Intelligence. 2003; 31:429−441.

Haier, RJ, Jung, RE, Yeo, RA, Head, K, Alkire, MT. Structural brain variation and general intelligence. Neuroimage. 2004; 23:425–433.

Haier RJ, Jung RE, Yeo RA, Head K & Alkire MT. The neuroanatomy of general intelligence: sex matters. Neuroimage. 2005; 25:320−327.

Hines M. Gender development and the human brain. Annual Review of Neuroscience. 2011; 34:69–88.

Hoag, H. Sex on the brain. New Science. 2008;199:28–31.

Galbraith S, Daniel J, Bryce V. A study of clustered data and approach to its analysis. The Journal of Neuroscience. 2010; 30:10601–10608.

Kirkwood BR. Essentials of medical statistics. Malden, MA: Blackwell Science. 2003

Lindsay, J. R., & Nieman, L. K. (2005). The hypothalamic-pituitary-adrenal axis in pregnancy: Challenges in disease detection and treatment. Endocrinology Review, 26, 775–799.

Maccari S, Darnaudery M, Morley-Fletcher S, Zuena AR, Cinque C, & Van-Reeth O. Prenatal stress and long-term consequences: Implications of glucocorticoid hormones. Neuroscience and Biobehavioral Reviews. 2003; 27:119–127.

Machin, GA. Some causes of genotypic and phenotypic discordance in monozygotic twin pairs. American Journal of Medical Genetics. 1996; 61:216–228.

Mastorakos G, & Ilias I. Maternal and fetal hypothalamic-pituitary-adrenal axes during pregnancy and postpartum. Annals of the New York Academy of Science. 2003; 997:136–149.

Miles C, Green R, Hines M. Estrogen effects on cognition, memory and mood in male to-female transsexuals. Hormones and Behaviour. 2006; 50:707–708.

Petronis A, Gottesman II, Peixiang, K, Kennedy JL, Basile, VS, Andrew D, Popendikyte, V. Monozygotic twins exhibit numerous epigenetic differences: Clues to twin discordance? Schizophrenia Bulletin. 2003; 29;169–178.

Reiss D, Plomin R, & Hetherington, EM. (1991). Genetics and psychiatry: An unheralded window on the environment. American Journal of Psychiatry. 1991; 148:283–291.

Schmithorst VJ, & Holland SK. Functional MRI evidence for disparate developmental processes underlying intelligence in boys and girls. NeuroImage. 2006; 31:1366−1379.

Shaw P, Greenstein D, Lerch J, Clasen L, Lenroot R, Gogtay N. Intellectual ability and cortical development in children and adolescents.

Nature. 2006; 676−679.

Turkheimer E, & Waldron M. (2000). Nonshared environment: A theoretical methodological, and quantitative review. Psychological Bulletin. 2000; 126:78–108.

Wadhwa PD, Sandman CA, & Garite TJ. The neurobiology of stress in human pregnancy: Implications for prematurity and development of the fetal central nervous system. Program of Brain Research; 2001;133:131–142.

Weinstock M. Alterations induced by gestational stress in brain morphology and behaviour of the offspring. Program of Neurobiology. 2001; 65;427–451.