UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS: PSIQUIATRIA

TESE DE DOUTORADO

ANÁLISE DOS EFEITOS METABÓLICOS E DAS ALTERAÇÕES NEUROQUÍMICAS EM PACIENTES BIPOLARES RECÉM DIAGNOSTICADOS COM O PRIMEIRO EPISÓDIO DE MANIA

Leonardo Evangelista da Silveira

Orientadora: Profa. Dra. Adriane Ribeiro Rosa

Co-orientador: Prof. Dr. Flávio Pereira Kapczinski

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APRESENTAÇÃO

A presente tese de doutorado está organizada em três partes:

Parte I: resumo, *abstract*, Introdução e Objetivos;

Parte II: resultados apresentados na forma de dois artigos científicos;

Parte III: Considerações finais e Referências bibliográficas.

Os trabalhos que compõem esta tese foram desenvolvidos entre os anos de 2012 e 2014 em duas localidades: no Laboratório de Psiquiatria Molecular, localizado no Centro de Pesquisas Experimentais do Hospital de Clínicas de Porto Alegre, UFRGS, sob a orientação da Profa. Dra. Adriane Ribeiro Rosa e do Prof. Flávio Pereira Kapczinski e no Centro de Transtornos do Humor localizado no Hospital da Universidade da Columbia Britânica (Vancouver/British Columbia, Canadá), sob a orientação do Prof. Lakshmi Yatham (Doutorado Sanduíche). A população analisada nos trabalhos incluiu pacientes recrutados em, no máximo, 03 meses após o diagnóstico do primeiro episódio de mania. A avaliação e o seguimento destes pacientes ocorreram em Vancouver, Canadá.

Além dos dois artigos científicos principais que compõem os dois primeiros capítulos desta tese, são discutidos na seção de considerações finais outros trabalhos científicos produzidos em coautoria durante o período de desenvolvimento do doutorado. Estes artigos encontram-se na seção de referências, mas são introduzidos nesta seção:

- Bond DJ, da Silveira LE, MacMillan EL, et al. Relationship between body mass index and hippocampal glutamate/glutamine in bipolar disorder (em processo de submissão).
- Bücker J, Kozicky J, Torres IJ, et al. The impact of childhood trauma on cognitive functioning in patients recently recovered from a first manic episode: data from the Systematic Treatment Optimization Program for Early Mania (STOP-EM). J Affect Disord. 2013; 148(2-3):424–30.
- Kozicky J-M, Torres IJ, Silveira LE, Bond DJ, Lam RW, Yatham LN. Cognitive change in the year after a first manic episode: association between clinical outcome and cognitive performance early in the course of bipolar I disorder. J Clin Psychiatry. 2014; 75(6):e587–93.
- Kozicky J-M, Bond DJ, Golzalez M, et al. Opposing grey matter changes associated with sustained remission and episode recurrence in the year following a first manic episode Data from the Systematic Treatment Optimization Program for Early Mania (STOP-EM) (em processo de submissão).

SUMÁRIO

Lista de abreviaturas e siglas

BD Transtorno do Humor Bipolar (do inglês *Bipolar Disorder)*

BDNF Fator Neurotrófico Derivado do Cérebro (do inglês *brain-derived neurotrophic fator*)

BMI Índice de Massa Corporal (do inglês *body mass index*)

BRPS Escala Breve de Avaliação Psiquiátrica (do inglês *Brief Psychiatric Rating Scale*)

CANMAT Rede Canadense para o Tratamento de Transtornos de Humor e Ansiedade (do inglês *Canadian Network for Mood and Anxiety Treatments*)

Cho Choline

CVLT-II Teste de Aprendizagem Verbal California (do inglês *California Verbal Learning Test—2nd Edition*)

Cr Creatina

CSF Líquido Cerebroespinhal (do inglês *Cerebrospinal Fluid*)

DSM Manual Diagnóstico e Estatístico de Transtornos Mentais (do inglês *Diagnostic Statistical Manual of Mental Disorders*)

GAF Escala de Avaliação Funcional Global (do inglês *Global Assessment of Functioning Scale*)

GLM Modelo Linear Generalizado (do inglês *General Linear Model*)

Gln Glutamina

GLU Glutamato

Glx Glutamato+Glutamina

HRSD-29 Escala de Depressão de Hamilton (do inglês *Hamilton Rating Scale for Depression, 29 items*)

IL Interleucina

MI Mioinositol

MINI Mini Entrevista Neuropsiquiátrica Internacional (do inglês *Mini International Neuropsychiatric Interview*)

NAA N-Acetil-Aspartato

PANSS Escala das Síndromes Positiva e Negativa (do inglês *Positive and Negative Syndrome Scale*)

PCR Proteína C Reativa

PRESS Sequência de Espectroscopia Resolvida no Ponto (do inglês *Point Resolved Spectroscopy Sequence*)

REC/NREC Recorrência/não recorrência (do inglês *Recurrence/no recurrence*)

RMN Ressonância Magnética Nuclear

RVIP Processamento Rapido de Informacao Visual (do inglês *Rapid Visual Information Processing*)

STOP-EM Programa de Otimização Sistemática de Tratamento para o Primeiro Episódio de Mania (do inglês *Mania Systematic Treatment Optimization Program for Early Mania*)

TNF Fator de Necrose Tumoral (do inglês *Tumoral Necrosis Factor*)

YMRS Escala Young para Avaliação de Mania (do inglês *Young Mania Rating Scale*)

1H-MRS Espectroscopia de Ressonância Magnética Nuclear de Próton (do inglês *Proton Magnetic Resonance Spectroscopy*)

RESUMO

O conjunto das evidências atuais sobre o Transtorno do Humor Bipolar (THB) aponta para um curso progressivo modulado por fatores clínicos e ambientais, sendo possível observar este fenômeno em áreas como neurocognição, funcionalidade, neuroimagem e bioquímica. Neste contexto, ressalta-se a importância de se avaliar indivíduos bipolares precocemente na evolução da doença, reduzindo a potencial influência dos fatores já consagrados e dos fatores ainda a serem estudados no curso do THB. Os trabalhos apresentados nesta tese tiveram como objetivo principal avaliar a influência da comorbidade com obesidade na função neurocognitiva e explorar longitudinalmente a neuroquímica cerebral. O primeiro capítulo se propôs a avaliar o efeito da obesidade na função cognitiva de pacientes bipolares avaliados em no máximo 03 meses do primeiro episódio de mania e a comparação foi feita com indivíduos saudáveis. Os pacientes, embora tenham apresentado as alterações neurocognitivas esperadas para o estágio da doença, não apresentaram déficit adicional em função da comorbidade. Portanto, embora a obesidade imponha déficit adicional em pacientes bipolares com doença estabelecida, em estágios precoces do transtorno, este déficit adicional não ocorre. Considerando o impacto que a função neurocongitiva tem na evolução do THB, este achado é altamente relevante na medida em que informa sobre a oportunidade de se intervir precocemente. O segundo capítulo se propôs a investigar a evolução dos níveis de N-Acetil-Aspartato (NAA) e da combinação de Glutamato e Glutamina (Glx) no hipocampo de pacientes bipolares em primeiro episódio de mania ao longo de um ano de seguimento em comparação a indivíduos saudáveis. Não houve diferença entre os pacientes e os indivíduos saudáveis ao longo de um ano nas concentrações absolutas dos metabólitos hipocampais. Além disso, embora os pacientes tenham melhorado o desempenho funcional medido através da escala de avaliação funcional, os pacientes que se mantiveram eutímicos durante o seguimento apresentaram melhora mais robusta na

funcionalidade. Considerando que pacientes bipolares com doença estabelecida apresentam concentrações cerebrais reduzidas de NAA e aumentadas de Glutamato ou de Glx, em especial no hipocampo, nossos resultados apontam para outro achado associado à neuroprogressão do THB. Os resultados apresentados nesta tese informam sobre os achados de fatores associados à progressão do THB em pacientes recém diagnosticados com o transtorno, ressaltando a importância da adoção de intervenções neuroprotetoras precocemente na evolução do THB no sentido de manter a integridade neuronal e, com isso, preservar ou melhorar o funcionamento neurocognitivo e psicossocial.

ABSTRACT

The current body of evidence about Bipolar Disorder (BD) points to a progressive course of the illness modulated by clinical and environmental factors, which is possible to be observed in areas such as neurocognition, functionality, neuroimaging, and biochemistry. In this context, it is highlighted the importance of evaluating bipolar patients in the early stages of the illness progression, reducing the potential influence of well-known factors and still to be studied aspects of the course of BD. The studies included in this thesis had the main objective of evaluating the influence of obesity as a comorbidity in the neurocognitive functioning of BD patients as well as exploring the brain's neurochemistry longitudinally. The first chapter evaluates the effect of obesity in the cognitive functioning of BD patients recruited within 03 months of their first manic episode, and the comparison group included healthy subjects. Even though BD patients presented the expected neurocognitive deficits for the stage of the illness, no additional deficit was found as a result of the comorbidity. Therefore, although obesity imposes additional deficits on cognition of BD patients with established illness, in the early stages of the illness this additional deficit does not occur. Considering the impact of the neurocognitive functioning in the progress of BD, our findings informs about the opportunity of early interventions. The second chapter investigates the evolution of the N-Acetyl-Aspartate (NAA) and the combination of Glutamate and Glutamine (Glx) in the hippocampus of BD patients right after their first manic episode over one year of follow-up in comparison to healthy subjects. There was no difference between patients and healthy subjects over the follow-up period in the absolute concentration of brain metabolites. Furthermore, although patients improved their functional performance, patients who remained euthymic over the follow-up period presented more robust functional recoveries. Considering the fact that BD patients with established illness present increased concentrations of Glutamate or Glx, and reduced

concentrations of NAA, especially within the hippocampus, our results point to findings associated with the neuroprogression of BD. The results presented in this thesis inform about factors associated with the progression of BD in patients recently diagnosed, highlighting the relevance of early neuroprotective interventions in the course of the disorder, thus maintaining neuronal integrity and, consequently, preserving or improving the neurocognitive and psychosocial functioning.

1.INTRODUÇÃO

1.1. Transtorno de Humor Bipolar

O Transtorno de Humor Bipolar (THB) é um transtorno psiquiátrico crônico, potencialmente grave e incapacitante, que representa uma importante questão de saúde pública. Caracteriza-se por episódios recorrentes de mania ou de hipomania e de depressão (não atribuíveis a substâncias ou a condições médicas), podendo ser subdividido em sete entidades diagnósticas segundo o Manual Diagnóstico e Estatístico de Transtornos Mentais 5ª edição(1) (DSM-V) (tabela 1). Os pacientes apresentam sintomas envolvendo alterações no humor, cognição e comportamento. Tem prevalência estimada de 0,6 a 1% para o THB tipo I e de 0,4 a 1,1 para o THB tipo II, dependendo da população estudada e a intensidade dos sintomas é variável, acarretando prejuízos no desempenho das atividades diárias e em sofrimento pessoal(2,3). O THB é uma das maiores causas de incapacidade por doença, representando a sexta causa de anos perdidos por doença entre adultos jovens(2,4).

Transtorno Bipolar tipo I
Transtorno Bipolar tipo II
Transtorno Ciclotímico
Transtorno Bipolar induzido por substância/medicação
Transtorno Bipolar induzido por outra condição médica
Outros Transtornos Bipolares específicos
Transtorno Bipolar não-especificado

Tabela 1 – Subtipos de THB segundo a classificação do DSM-V(1)

Os episódios de mania são caracterizados por humor anormalmente elevado, expansivo ou irritável e aumento de atividade e de energia associado a três ou mais dos

seguintes sintomas: autoestima aumentada ou grandiosidade, redução da necessidade de sono, aumento da quantidade de fala ou pressão para falar, fuga de ideias ou sensação de pensamentos acelerados, distratibilidade, aumento de atividades direcionadas a objetivos ou agitação psicomotora ou envolvimento excessivo em atividades potencialmente danosas. Os sintomas devem ter duração mínima de 7 dias (ou menos se necessária internação), causar significativo impacto no funcionamento social ou ocupacional, ou incluir sintomas psicóticos. Para o diagnóstico de hipomania, são necessários apenas 4 dias de duração e os sintomas não podem ser graves a ponto de motivar hospitalização ou incluir sintomas psicóticos.

Os episódios de depressão são caracterizados pela presença de ao menos cinco dos seguintes sintomas por um período de, no mínimo, duas semanas e representa marcada mudança em relação ao funcionamento prévio: humor deprimido, redução do interesse ou prazer, perda ou ganho significativo de peso (variação de ao menos 5%) ou aumento ou diminuição de apetite, insônia ou hipersonia, agitação ou retardo psicomotor, fadiga ou sensação de perda de energia, sentimentos de desvalia ou culpa excessiva ou inapropriada, diminuição da capacidade de pensar ou se concentrar ou indecisão, pensamentos recorrentes em morte ou ideação suicida ou plano suicida ou tentativa de suicídio. Os sintomas devem causar marcado sofrimento ou impacto no funcionamento psicossocial.

O tratamento do THB envolve abordagem psicofarmacológica para a resolução de episódios agudos, tanto depressivos quanto maníacos/hipomaníacos, e para a manutenção da eutimia. O tratamento de manutenção visa a reduzir a recorrência dos episódios de humor e a estabelecer níveis ótimos de funcionalidade, tendo a psicoeducação um papel altamente relevante. A principal classe de fármacos utilizada no tratamento do THB é a dos estabilizadores de humor, em monoterapia ou em combinação. São também utilizados no tratamento antipsicóticos, benzodiazepínicos e, em casos selecionados, antidepressivos.

Casos reservados podem necessitar estabilização dos sintomas com o uso de terapias de estimulação cerebral, sendo a mais estabelecida a eletroconvulsoterapia(3).

1.2. THB e Comorbidades

O THB está associado a elevadas taxas de comorbidades, psiquiátricas e clínicas gerais(5,6). Os pacientes apresentam também mais fatores de risco (sedentarismo, tabagismo, dieta) para doenças clínicas(7) (metabólicas, cardiovasculares e neurológicas). Em particular, a obesidade é frequente em pacientes com THB e representa importante fator associado ao curso da doença(8). Outros fatores associados ao aumento de risco são a polifarmacoterapia, idade avançada, menor escolaridade e maior tempo de doença(9,10). Em função do alto índice de comorbidades, acaba sendo elevado o número de consultas ambulatoriais, internações, uso de psicofármacos e intervenções psicossociais(11,12).

As comorbidades psiquiátricas mais comumente diagnosticadas em pacientes bipolares são: transtornos de ansiedade, transtornos por uso de substâncias e transtornos alimentares(13–16). Em termos de comorbidades médicas, os indivíduos com diagnóstico de THB apresentam prevalências aumentadas de doenças metabólicas, cardiovasculares, respiratórias e neurológicas(14,16–19). Obesidade em especial está associada a patologias metabólicas e cardio e neurovasculares, sendo frequentemente diagnosticada em pacientes com THB(8,14).

Embora os mecanismos envolvidos ainda não estejam completamente esclarecidos, as comorbidades mais comuns em THB parecem impor pior prognóstico aos pacientes. Assim, indivíduos bipolares com comorbidade psiquiátrica apresentam pior curso de doença, tendo início mais precoce do transtorno, menos tempo em eutimia, mais episódios de humor, pior resposta ao tratamento e mais tentativas de suicídio(15,16,20). As comorbidades

clínicas impõem também significativa morbidade aos pacientes bipolares na medida em que determinam curso mais adverso, com mais episódios de humor e menos tempo em eutimia(14,16,17,19,21). Interessantemente, fatores clínicos da doença bipolar estão associados a maior prevalência de comorbidades. Por exemplo, história de trauma emocional na infância, início do THB mais precoce e diagnóstico de transtorno de ansiedade estão associados a ocorrência de maior ocorrência de comorbidades clínicas nos pacientes adultos(16). Por outro lado, significativas comorbidades clínicas parecem estar significativamente associadas a mais elevada taxa de comorbidades psiquiátricas nos pacientes bipolares(14). Parece, portanto, haver estreita interação entre o curso das doenças psiquiátricas, em especial do THB, com as patologias clínicas comórbidas.

De particular interesse é a comorbidade do THB com obesidade e sobrepeso, problema físico que parece permear grande parte da associação do THB com as comorbidades clínicas. O tecido adiposo é entendido como um órgão endócrino, que regula metabolismo e inflamação(22). A obesidade provoca alterações no tecido adiposo, de modo que os adipócitos, ao se expandirem, tornam-se infiltrados por macrófagos ativados. Este infiltrado gera um desequilíbrio, criando um estado pró-inflamatório associado a redução dos mecanismos anti-inflamatórios(22,23). Evidências recentes na área de neuroimagem têm demostrado redução nos volumes de substância cinzenta e cerebral total em população de portadores de obesidade sem outras patologias(24–26). Indivíduos obesos estão em risco aumentado para o desenvolvimento de transtornos psiquiátricos, em particular depressão(27). A obesidade é altamente prevalente na população de paciente com THB, tendo importante impacto negativo no curso da doença(8,28,29). Pacientes bipolares com obesidade comórbida apresentam taxas aumentadas de episódios maníacos e depressivos(29,30) e de tentativas de suicídio(31). Além disso, esta comorbidade altera de modo marcado o curso do THB, na medida em que os pacientes apresentam períodos menos

longos de eutimia e maior recorrência de episódios(29). Uma variável importante neste contexto é o tratamento do THB, que envolve medicamentos associados com potencial risco para aumento de peso, em particular antipsicóticos e estabilizadores de humor(32–34). A obesidade ou sobrepeso acaba por ter significativo impacto no THB. Neste contexto, pacientes recrutados logo após o primeiro episódio de mania que experimentaram aumento de peso no seguimento de um ano evidenciaram piora adicional na funcionalidade global em comparação com os pacientes em geral(35). Nesta população, foi demonstrado também que os pacientes bipolares apresentam reduções volumétricas significativas no volume de substância branca e no volume do lobo temporal, áreas cerebrais reconhecidamente envolvidas na regulação do humor(36).

1.3. Cognição e funcionalidade

Os pacientes bipolares apresentam disfunção em múltiplos domínios do funcionamento neurocognitivo, tanto durante os episódios de humor quanto nos períodos de eutimia. Mais especificamente, os pacientes exibem alterações nos domínios cognitivos da velocidade de processamento, atenção, memória verbal e não-verbal e função executiva (37–40). Estas disfunções parecem atuar sob a modulação de fatores como: tipo de medicação usada, principalmente antipsicóticos e estabilizadores de humor(37,41–43), comorbidade com abuso ou dependência de substâncias(44), tempo de doença, número de hospitalizações e de episódios(37,41,45,46), em particular maníacos, sintomas depressivos subclínicos(47), trauma emocional na infância(48) e potencialmente obesidade(49). Estudos em populações de pacientes bipolares recrutados logo após o primeiro episódio de mania mostram que os déficits cognitivos estão presentes mesmo em fases precoces da doença. Nestes estudos, os pacientes apresentam prejuízos nos domínios da atenção, memória ou aprendizado e função

executiva(50–52). Estudos longitudinais em amostras de primeiro episódio de mania mostram recuperação dos déficits neurocognitivos apresentados em fases iniciais da doença nos domínios da velocidade de processamento e na função executiva(53). O único trabalho que avaliou o papel da obesidade na cognição de pacientes bipolares encontrou menor escore no teste de fluência verbal (que avalia a função executiva) dos pacientes em comparação a indivíduos saudáveis(49). Além disso, foi encontrada significativa correlação negativa entre o IMC dos pacientes e os escores no teste de substituição do símbolo do dígito (que avalia atenção e velocidade de processamento psicomotor). No entanto, este trabalho avaliou pacientes com maior tempo de doença. Embora não seja citado o tempo de duração da doença na descrição demográfica dos indivíduos incluídos no estudo, pode-se inferir que os pacientes apresentavam THB estabelecido, já que apresentavam no mínimo 6,23 (8,10) episódios depressivos, média (desvio-padrão), e 6,46 (9,56) episódios maníacos, média (desvio-padrão), ao longo da vida. Sendo assim, variáveis clinicas potencialmente confundidoras podem ter influenciado este resultado. O estudo de população de pacientes de primeiro episódio de mania oferece a oportunidade de avaliar o papel individual da obesidade ou sobrepeso sobre a função cognitiva dos pacientes, já que existe menor exposição aos fatores que potencialmente influenciam a cognição.

Além disto, tem-se discutido na literatura se as disfunções cognitivas dos pacientes poderiam caracterizar estado ou traço do THB. Neste contexto, disfunções nos domínios da atenção e da memória verbal parecem estar presentes tanto nos pacientes sintomáticos quanto nos em remissão. Em contrapartida, função executiva e memória visual parecem estar alterados em pacientes durante os episódios de humor, normalizando-se na medida em que há remissão(54). Ainda, aspectos da memória verbal e da função executiva são sugeridos como endofenótipos do THB na medida em que são altamente herdáveis, estão associados com o transtorno, as alterações ocorrem independente do quadro clínico e são detectados em

familiares de primeiro grau não afetados pelo THB(39,53,55). Sendo assim, existem alguns aspectos da função neurocognitiva que parecem refletir aspectos da herança genética do THB.

O THB está também associado a significativa alteração na funcionalidade psicossocial, na medida em que afeta a capacidade de viver de maneira autônoma e a habilidade de manter atividades laborais e sociais(56,57). Estudos têm demonstrado que pacientes eutímicos apresentam dificuldades para atingir plena recuperação funcional(58–60) e apresentam disfunções em áreas importantes como funcionamento ocupacional, gerenciamento financeiro, relacionamento interpessoal e autonomia(61–63). Os fatores clínicos do THB associados a pior desempenho funcional são: idade mais avançada, sintomas depressivos, número de episódios mistos e número de hospitalizações(61). Estas disfunções parecem estar presentes nas fases iniciais da doença(52,64,65) e evoluem para piora com a progressão da doença(66,67).

Inúmeros estudos têm mostrado uma estreita relação entre o déficits cognitivos e funcionalidade. Um estudo transversal(67) avaliou os pacientes funcional e cognitivamente levando em consideração o modelo de estadiamento de Kapczinski (2009) (68). Embora não tenha avaliado diretamente a relação entre cognição e funcionalidade, o estudo mostrou que os pacientes em estágio mais avançado da doença apresentavam maiores déficits cognitivo e funcional(67). Em outro estudo, com seguimento longitudinal de 04 anos, déficits de memória e disfunção executiva foram preditores do funcionamento psicossocial de pacientes com THB(69). Neste mesmo estudo, fatores preditores do funcionamento ocupacional, um dos aspectos avaliados na funcionalidade, foram: sintomas depressivos subclínicos e uma medida da função executiva. Adicionalmente, um estudo conduzido por Torres (2010) (70) mostrou que a memória/aprendizado verbal nos pacientes recém diagnosticados após o primeiro episódio de mania é forte preditor da funcionalidade a longo prazo. O

funcionamento psicossocial dos pacientes com THB, tanto em medidas globais quanto em medidas específicas, parece correlacionar-se com a função cognitiva, em especial, os domínios de memória, atenção e função executiva. Os pacientes apresentam déficits funcionais quando sintomáticos, mas existe literatura robusta evidenciando os déficits mesmo quando as análises são controladas para intensidade dos sintomas(71,72). Em particular, sintomas depressivos subclínicos estão associados significativamente a pior habilidade funcional(61). Uma revisão sistemática recente concluiu que os fatores mais associados a menor funcionalidade nos pacientes foram sintomas de humor subclínicos e déficits cognitivos(73). Embora as associações entre variáveis cognitivas e funcionais estejam bem estabelecidas, ainda não são claros os mecanismos através dos quais estas relações se estabelecem.

1.4. Alterações de neuroimagem

Na pesquisa em THB, a neuroimagem é um campo de intensa investigação, tendo achados robustos que forneceram dados altamente relevantes sobre a fisiopatologia envolvida no desenvolvimento do transtorno. Em especial, alterações nos circuitos límbico-talâmico-cortical e límbico-estriado-pálido-talâmico têm sido documentadas em um grande número de estudos, contribuindo para um melhor entendimento acerca do modelo neuroanatômico envolvendo o córtex pré-frontal, amigdala, hipocampo, tálamo, núcleos da base e cerebelo no THB(74).

Embora não específicos do THB, os estudos usando Ressonância Magnética Nuclear (RMN) mostram que as alterações estruturais mais encontradas em pacientes bipolares são o aumento de volume dos ventrículos laterais e o aumento das hiperintensidades de substância branca cerebrais(75,76). Além disso, reduções nas substâncias cinzentas de áreas

corticais como córtex pré-frontal, estriado ventral e córtex mesotemporal foram encontradas em pacientes com THB. Apesar de resultados conflitantes na literatura atual, uma metanálise recente evidenciou o achado de redução volumétrica no hipocampo de pacientes bipolares(77). Outra estrutura do sistema límbico que está alterada no THB é a amigdala, apresentando volumes reduzidos na população de pacientes adultos(78). Interessantemente, pacientes tratados com Lítio apresentam volumes cerebrais aumentados (do hipocampo e amigdala) em relação aos que faziam uso de outros fármacos(75).

A Espectroscopia de Ressonância Magnética de Próton (1H-MRS) é um protocolo de neuroimagem que avalia *in vivo*, de modo não-invasivo, potenciais alterações na bioquímica cerebral, mesmo quando a anatomia cerebral é normal. Com este protocolo, podem ser detectados metabólitos cerebrais como: Mioinositol (MI: envolvido no sistema de segundo mensageiro do ciclo fofatidilinositol celular), N-Acetil-Aspartato (NAA: considerado marcador de integridade neuronal e de função metabólica), Glutamato (GLU: principal neurotransmissor excitatório do sistema nervoso central) e Glutamina (Gln: precursor glial de GLU). A maioria das anormalidades encontradas em neurometabólitos em pacientes bipolares estão concentradas no circuito límbico-talâmico-cortical dos pacientes. O NAA está reduzido no hipocampo de pacientes bipolares eutímicos(79), maníacos(80) e deprimidos(81,82). Em outras regiões, diferentes alterações foram encontradas, levando à consideração de que diferentes regiões cerebrais podem apresentar deferentes mudanças mesmo quando os pacientes são avaliados durante o mesmo episódio(83). Um achado bastante consistente, reportado em duas metanálises independentes é o aumento de GLU, Gln ou de Glx em pacientes bipolares em estágios mais avançados da doença(84,85). Aumentos de NAA foram reportados em pacientes bipolares em episódio depressivo tratados com Lítio ou Lamotrigina(86). Associadas a reduções nos escores de depressão avaliados por escalas, concentrações cerebrais de GLU/Gln parecem também responder ao tratamento

com medicamentos, especificamente com Lítio ou Riluzole(87,88) (medicamento que tem efeito inibitório sobre a secreção de GLU). Além disso, concentrações reduzidas de glutamina pós tratamento com Riluzole estão associadas a remissão dos sintomas(88).

Considerando-se que o volume de estruturas e a concentração de neurometabólitos cerebrais alteram-se em função de variáveis associadas ao curso do THB - como tempo de doença, número e polaridade dos episódios de humor, gravidade de sintomas, uso de medicações - estudos com amostras de pacientes em risco de desenvolver THB ou em fases precoces da doença são altamente relevantes na avaliação dos mecanismos envolvidos na neuroprogressão do transtorno.

1.5. Neuroprogressão do THB

I) Modelo de estadiamento clínico

Recentes avanços sobre a fisiopatologia do THB têm sugerido que a doença segue um curso progressivo desde fases consideradas latentes até estágios mais avançados ou refratários a tratamento. Estas alterações podem ser percebidas na mudança dos padrões de ocorrência dos episódios e também nos padrões de resposta ao tratamento. Desta forma, os episódios de humor são preditores importantes de recorrência de novos episódios(89), sendo que a duração dos períodos entre os episódios se torna mais curto(90). Com relação ao tratamento, verificam-se alterações de resposta tanto a psicofármacos como também a psicoterapia. Assim, indivíduos com mais de 10 episódios de humor tendem a responder pior a Lítio quando comparado a Ácido Valpróico(91). Além disso, após 10 episódios de humor a resposta de episódios maníacos a Olanzapina parece estar diminuída(92). Indivíduos com menos de 12 episódios de humor apresentaram melhor resposta a psicoterapia do tipo Terapia Cognitivo-Comportamental em comparação a pacientes bipolares com mais de 12 episódios(93). Além disso, psicoeducação

oferecida a familiares de pacientes com THB foi benéfica apenas para indivíduos em estágios precoces da doença, não oferecendo benefício aos pacientes em estágios mais avançados(94).

A literatura recente tem proposto critérios clínicos para caracterizar o curso progressivo da doença através de modelos de estadiamento. O modelo de estadiamento proposto por Kapczinski (2009) (68), por exemplo, utiliza parâmetros clínicos, cognitivos e de funcionalidade. Tal modelo classifica os pacientes em: estágio latente (história familiar positiva para THB, mas ainda sem critérios para episódios de humor no passado); estágio I (houve ao menos um episódio de mania/hipomania e os períodos inter-episódios são marcados por ausência de sintomas); estágio II (sintomas durante períodos inter-episódios são relacionados a comorbidades); estágio III (o paciente apresenta marcada dificuldade nas habilidades cognitiva ou funcional); estágio IV (inabilidade de viver de maneira autônoma em função das dificuldades cognitivas ou funcionais). Os modelos de estadiamento propostos para o THB, assim como em outras áreas da medicina, são de extrema relevância clínica já que ajudariam a avaliar a gravidade do transtorno assim como delinear estratégias terapêuticas específicas para cada estágio da doença(68).

II) Aspectos bioquímicos

O conjunto dos achados bioquímicos parece apontar para um padrão de toxicidade sistêmica aumentada durante os episódios de humor, com consequente alteração na medida em que se acumulam novos episódios ao longo do tempo. Neste sentido, moléculas como neurotrofinas (envolvidas na proliferação e sobrevida neuronal) e citocinas inflamatórias (mediadoras da resposta inflamatória) estão alterados com a progressão da doença. Ilustrando este aspecto, pode-se citar o aumento de Proteína-C-Reativa (PCR), marcador sensível de inflamação, que encontra-se aumentado principalmente durante a fase maníaca(95). Citocinas

proinflamatórias estão aumentadas durante episódios de mania e de depressão. Por exemplo, a interleucina-6 (IL-6) foi correlacionada positivamente com gravidade dos sintomas durante episódios de mania e de depressão medidos por escalas de graduação de sintomas(96). O Fator de Necrose Tumoral alfa (TNF-alfa) também tem sido avaliado no THB e tem sido proposto como molécula-chave na orquestração do processo de apoptose associado ao THB(97). Estas citocinas também estão associadas à progressão do THB na medida em que os níveis de IL-6, IL-10 e TNF-alfa estão aumentados nos pacientes em fase inicial do THB. Nas fases mais tardias do transtorno, os níveis de TNF-alfa e IL-6 mantém-se aumentados(98). O Fator Neurotrófico Derivado do Cérebro (BDNF) é uma das principais neurotrofinas e tem sido intensamente estudado no THB. Os níveis séricos estão negativamente correlacionados com a gravidade dos sintomas maníacos avaliada por escalas de graduação de sintomas(99). Além disso, relevante é o achado de redução dos níveis de BDNF com a progressão do THB, tendo sido encontrada correlação significativa negativa entre os níveis séricos e a duração do transtorno(98). Associado a estas alterações, robusta literatura tem sugerido alterações importantes no metabolismo energético nos pacientes portadores de THB; esta disfunção, em última análise, gera espécies reativas de oxigênio levando a dano celular. O processo leva o nome de estresse oxidativo e tem sido foco de interesse de pesquisa em THB(100). Interessantemente, assim como ocorre com neurotrofinas e citocinas inflamatórias, alguns achados de estresse oxidativo têm sido associados a um padrão estágio-dependente nos pacientes. Assim, a atividade de enzimas antioxidantes (como, por exemplo, a Superóxido Dismutase) tem níveis aumentados durante episódios de humor(101). Além disso, a atividade de outra enzima, a Glutationa Redutase, tem seus níveis aumentados em pacientes nos estágios mais tardios do THB(102). Em conjunto, estas alterações nos parâmetros oxidativos podem contribuir para a progressiva falha nos mecanismos compensatórios associada à progressão do THB(103). Do ponto de vista do funcionamento celular, a progressão do THB pode ser

observada na falha dos mecanismos de resiliência celular. Com isso, parece válido inferir que pacientes em estágio avançado do THB apresentam disfunção na resposta ao estresse em função de falhas nos mecanismos de resiliência. Recentemente, achados do nosso grupo de pesquisa têm ilustrado estes mecanismos celulares. Indivíduos em estágio avançado do THB apresentam alterada resposta do retículo endoplasmático ao estresse(104). Além disso, sinais precoces de apoptose podem ser observados em células mononucleares no sangue periférico de pacientes bipolares(105). Os episódios de humor são, portanto, tóxicos, e mais especificamente, neurotóxicos(106) e as alterações neuroquímicas impostas parecem acumular-se na medida em que a recorrência ocorre(103,107).

III) Aspectos de neuroimagem

A maioria dos estudos avaliando neuroimagem tem avaliado pacientes de maneira transversal em diversos estágios do transtorno, o que torna a inferência causal problemática. Além disso, diversos achados parecem ser comuns a outras condições médicas e psiquiátricas, tornando as alterações algo inespecíficas e a necessidade de estudos longitudinais imperiosa. Há também evidências de que o cérebro tem sua anatomia alterada em função da progressão do THB. Strakowski e col. (2002) (108) mostraram que pacientes com múltiplos episódios apresentam alargamento dos ventrículos comparado com aqueles com apenas um primeiro episódio ou controles saudáveis. Com o avanço do THB, há progressiva redução na espessura da substância cinzenta, e esta associação está correlacionada de maneira inversa ao tempo de doença(109). Sendo assim, alterações anatômicas no sistema nervoso central observadas em pacientes portadores de THB devem ser uma consequência da progressão do transtorno.

1.6. Justificativa

Apesar dos avanços recentes sobre a fisiopatologia do THB, os mecanismos neuroquímicos pelos quais o transtorno se desenvolve não estão suficientemente esclarecidos. Considerando que o THB é uma patologia crônica, potencialmente grave e altamente incapacitante, um maior conhecimento acerca dos aspectos neurobiológicos envolvidos, e mais especificamente sobre a neuroprogressão associada ao THB, é fundamental. Isto poderia contribuir de forma significativa para o desenvolvimento de novas estratégias terapêuticas assim como ajudar na implementação de terapias mais individualizadas.

Uma das principais dificuldades encontradas nos estudos envolvendo pacientes com THB é a presença de inúmeros potenciais confundidores relacionados ao caráter crônico da doença, como por exemplo: múltiplos episódios, tempo de doença e a presença de sintomas subclínicos. Além destes, fatores ambientais, genéticos e o próprio tratamento psicofarmacológico interagem e devem contribuir para desfechos clínicos variáveis. Portanto, o desenvolvimento de estudos com pacientes nos estágios iniciais da doença (i.e., durante o primeiro episódio de humor) é fundamental para o melhor entendimento da patofisiologia da mesma sem a interferência de fatores associados à progressão da doença. Sendo assim, esta tese engloba estudos conduzidos em população de pacientes com diagnóstico de THB recente (primeiro episódio maníaco) com o objetivo principal de investigar possíveis alterações nos metabólitos cerebrais assim como o papel dos fatores clínicos/metabólicos e neurocognitivos sobre a patofisiologia do THB.

2.OBJETIVOS

2.1.Objetivo geral:

O objetivo geral desta tese foi avaliar aspectos neuroquímicos, clínicos/metabólicos e cognitivos em uma amostra de pacientes com um primeiro episódio de mania.

2.2.Objetivos específicos:

- Avaliar o efeito da obesidade e/ou sobrepeso na função cognitiva de pacientes recém diagnosticados com o primeiro episódio de mania;

- Avaliar a evolução de parâmetros neuroquímicos no hipocampo de pacientes com THB recém diagnosticados com o primeiro episódio de mania através de exame de espectroscopia em um ano de seguimento longitudinal.

3. ARTIGOS CIENTÍFICOS

3.1. Capítulo 1

Carta de aceite:

Re: CJP-2014-039-OR.R1 Neurocognitive functioning in overweight/obese patients with Bipolar Disorder: Data from the Systematic Treatment Optimization Program for Early Mania (STOP-EM)

15-Jul-2014

Dear Dr. Yatham:

I am pleased to advise you that the above-noted manuscript has been accepted for publication in The Canadian Journal of Psychiatry. You will receive further correspondence when the manuscript is scheduled for a specific issue.

However, there is one minor conformity issue that still needs to be addressed. Please email Virginia, who is copied on this email, the titles/positions of each coauthor at their various institutions.

I have attached a copyright release form for the above-noted manuscript. Please print, sign, and return it to me. In doing so, you give the Canadian Psychiatric Association all of your copyright throughout the world. Please note that if we do not receive copyright release forms from each of the coauthors, publication of your manuscript might be delayed. When your manuscript is copy edited and laid out, you will be asked to verify and specify changes and confirm that the manuscript is complete and correct.

I have also attached an open access form. Authors who would like to have their articles freely accessible to everybody immediately upon publication can pay Can$3000, with Canadian Psychiatric Association members/affiliates getting a 50% discount. The fee is payable anytime after a manuscript has been accepted (it does not affect the editorial decision) and before the publication date.

If you have any questions, comments, or concerns, or if you have any difficulty opening and printing the attached file, please do not hesitate to contact me.

Thank you for publishing in The Canadian Journal of Psychiatry.

Sincerely,

Joel Paris, MD

Editor-in-Chief / Rédacteur en chef

The Canadian Journal of Psychiatry

La Revue canadienne de psychiatrie

Artigo:

Neurocognitive Functioning in Overweight and Obese Patients With Bipolar Disorder: Data From the Systematic Treatment Optimization Program for Early Mania (STOP-EM)

Leonardo E Silveira, MD[1]; Jan-Marie Kozicky, PhD[2]; Kesavan Muralidharan, MD[3]; Joana Bücker, PhD[4]; Ivan J Torres, PhD[5]; David J Bond, MD, PhD[6] Flavio Kapczinski, MD, PhD[7]; Marcia Kauer-Sant'Anna, MD, PhD[8]; Raymond W Lam, MD, FRCPC[9]; Lakshmi N Yatham, MBBS, FRCPC, MRCPsych (UK), MBA (Exec)[10]

[1] Mood Disorders Centre, Department of Psychiatry, University of British Columbia, Vancouver, British Columbia; Laboratory of Molecular Psychiatry, Centro de Pesquisas Experimentais, Hospital de Clínicas de Porto Alegre, and INCT for Translational Medicine, Porto Alegre, RS, Brazil; Postgraduate Program in Medicine: Psychiatry, Universidade Federal do Rio Grande do Sul, UFRGS, Porto Alegre, RS, Brazil.

[2] Mood Disorders Centre, Department of Psychiatry, University of British Columbia, Vancouver, British Columbia.

[3] Mood Disorders Centre, Department of Psychiatry, University of British Columbia, Vancouver, British Columbia; Department of Psychiatry, National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore, India.

[4] Mood Disorders Centre, Department of Psychiatry, University of British Columbia, Vancouver, British Columbia; Laboratory of Molecular Psychiatry, Centro de Pesquisas Experimentais, Hospital de Clínicas de Porto Alegre, and INCT for Translational Medicine,

Porto Alegre, RS, Brazil; Postgraduate Program in Medicine: Psychiatry, Universidade Federal do Rio Grande do Sul, UFRGS, Porto Alegre, RS, Brazil.

[5] Mood Disorders Centre, Department of Psychiatry, University of British Columbia, Vancouver, British Columbia; British Columbia Mental Health and Addictions Services, Vancouver, British Columbia.

[6] Mood Disorders Centre, Department of Psychiatry, University of British Columbia, Vancouver, British Columbia; Department of Psychiatry, University of Minnesota, Minneapolis, Minnesota.

[7] Laboratory of Molecular Psychiatry, Centro de Pesquisas Experimentais, Hospital de Clínicas de Porto Alegre, and INCT for Translational Medicine, Porto Alegre, RS, Brazil.

[8] Laboratory of Molecular Psychiatry, Centro de Pesquisas Experimentais, Hospital de Clínicas de Porto Alegre, and INCT for Translational Medicine, Porto Alegre, RS, Brazil.

[9] Mood Disorders Centre, Department of Psychiatry, University of British Columbia, Vancouver, British Columbia.

[10] Professor of Psychiatry, Mood Disorders Centre, Department of Psychiatry, University of British Columbia, Vancouver, British Columbia.

Correspondence:

Room 2C7–2255 Wesbrook Mall, Vancouver, BC V6T 2A1; yatham@mail.ubc.ca.

Objective: Obesity is frequent in people with bipolar I disorder (BD I) and has a major impact on the course of the illness. Though obesity negatively influences cognitive function in patients with BD, its' impact in the early phase of the disorder is unknown. We investigated the

impact of overweight and obesity on cognitive functioning in clinically stable patients with BD recently recovered from their first manic episode.

Method: Sixty-five patients with BD (25 overweight or obese and 40 normal weight) recently remitted from a first-episode of mania and 37 age and sex-matched healthy control subjects (9 overweight or obese and 28 normal weight) were included in this analysis from the STOP-EM Program. All subjects had their cognitive function assessed using a standard neurocognitive battery. We compared cognitive function between normal weight patients, overweight–obese patients, and normal weight healthy control subjects.

Results: There was a negative effect of BD diagnosis on the domains of attention, verbal memory, nonverbal memory, working memory, and executive function, but we were unable to find an additional effect of weight on cognitive functioning in patients. There was a trend for a negative correlation between body mass index and nonverbal memory in the patient group.

Conclusions: These data suggest that overweight–obesity does not negatively influence cognitive function early in the course of BD. Given that there is evidence for a negative impact of obesity later in the course of illness, there may be an opportunity to address obesity early in the course of BD.

Clinical Implications

- Overweight–obesity does not negatively influence cognitive function early in the course of BD.
- Adequate management of overweight–obesity early in the course of BD may help reducing the burden associated with the disorder.

Limitations

- The sample size, particularly in the group of overweight–obese patients, was relatively modest.

- The availability of information about the course of overweight–obesity in the subjects was limited.

Key Words: bipolar disorder, mania, obesity, overweight, body mass index, cognitive function

Abbreviations

BD	bipolar disorder
BDNF	brain-derived neurotrophic factor
BMI	body mass index
BRPS	Brief Psychiatric Rating Scale
CVLT-II	California Verbal Learning Test—2nd Edition
GAF	Global Assessment of Functioning Scale
HRSD-29	Hamilton Rating Scale for Depression, 29 items
PANSS	Positive and Negative Syndrome Scale
RVIP	Rapid Visual Information Processing
STOP-EM	Systematic Treatment Optimization Program for Early Mania
YMRS	Young Mania Rating Scale

Introduction

Patients with BD exhibit impairments in multiple domains of neurocognitive functioning. Patients with euthymic BD show deficits in processing speed, attention, verbal and visual memory, and executive function at different stages of illness.[1–4] These deficits are robustly associated with poor psychosocial outcomes,[5] and identifying predictors of cognitive impairment, particularly modifiable ones, is therefore a priority. To date, such predictors include medications, namely, mood stabilizers and atypical antipsychotics,[1,6–9] substance abuse or dependence,[10] duration of illness and number of episodes,[1,6,11] childhood trauma,[12] and possibly obesity.[13] The deficits in the broad domains of attention, learning–memory, and executive function are also present even in patients with first episode of mania, where the variables associated with the progression of BD are fewer.[14–16]

Overweight and (or) obesity have been reported to have a significant impact on the clinical course of BD, and potentially on cognitive functioning. BD is associated with an increased burden of obesity-related conditions, including higher risk for metabolic syndrome, diabetes, hypertension, cardiovascular disease, and dyslipidemia.[17–19] Obesity is highly prevalent in this population[20–23] and has been shown to have a negative impact on the course of the illness.[20,22,24] Moreover, patients with BD who experience significant weight gain during the course of 1 year show impairments in their functioning.[25] As well, overweight patients with BD have been shown to have reduced brain volumes in important brain regions involved in mood regulation.[26] Thus obesity appears to negatively impact brain functioning in people with BD.

An extensive literature has identified an important relation between obesity and cognition. Otherwise healthy obese people show poorer performance on cognitive tests when compared with normal weight–matched control subjects, in particular, on memory and

executive function–related tasks.[27–29] This effect of obesity may be expected to be even more pronounced in patients with BD, given their intrinsic vulnerability to cognitive impairment. However, to date, only one study has shown that overweight patients with BD performed poorly on tasks assessing processing speed and attention when compared with normal weight patients with BD.[13] Participants in our study had an average duration of illness of 15 years and a mean of 7 episodes of both depression and mania, which indicates that obesity may negatively impact cognition in patients with established illness. However, the impact of overweight and obesity on cognitive functioning in patients early in the course of BD is unknown.

The study of patients with first-episode mania has the potential to provide important information about the effect of elevated BMI on cognitive functioning in the early stages of the illness, without the bias introduced by the numerous confounding factors that accrue during the course of BD (for example, duration of illness, number of previous mood episodes, and use of medication). It also has the potential to provide information about the vulnerabilities imposed by the overweight or obesity in the BD population. Establishing the nature of the potentially harmful association between obesity and BD could provide important insights into development of management strategies focusing on weight loss to help prevent an additional negative influence on the burden of BD.

We have previously reported that patients with recently remitted first-episode of mania have significant impairments in various domains of neurocognitive functioning (see Torres et al[14]). In our present analysis, we evaluated the effect of overweight–obesity on cognitive functioning in patients with recently diagnosed BD. We hypothesized that patients would show impaired cognition, compared with a healthy comparison group, and that the presence of elevated BMI would have an additional negative effect on cognitive functioning.

Methods

Subjects

Sixty-five patients meeting criteria for BD I according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision,[30] were recruited from the STOP-EM at Vancouver Hospital Health Sciences Centre and affiliated sites. Patients were enrolled in STOP-EM via the inpatient Mood Disorders Clinical Research Unit at University of British Columbia Hospital, as well as through community and hospital referrals from physicians and psychiatrists. To be included in the study, patients were required to be aged between 16 to 35 years old, and to have experienced their first manic and (or) mixed episode, with or without psychosis, and with or without comorbid conditions, within 3 months of enrolment into the study and to be clinically stable to undergo cognitive testing. Patients were excluded if they could not provide informed consent or if they had a previous undetected manic episode. A description of the full longitudinal study protocol can be found elsewhere.[14,31] Thirty-seven healthy control subjects, matched for age and sex, were recruited for comparison purposes. The study protocol was approved by the University of British Columbia ethics committee. Written informed consent was obtained from all patients and control subjects before any study procedures were conducted.

Diagnosis of BD was based on a clinical interview by a trained psychiatrist and a standardized psychiatric examination using the Mini-International Neuropsychiatric Interview[32] at baseline. We collected sociodemographic data and information about the course of the illness using a standardized protocol. The clinical status of the patients was assessed by clinical interview and clinical rating scales: GAF,[33] PANSS,[34] BPRS,[35] YMRS,[36] and HRSD-29).[37] Subjects presenting with a history of major medical illness underlying their manic symptoms were excluded. Healthy control subjects were assessed with a standardized interview, and they were enrolled if they had no personal history of psychiatric illness or major medical illness and no family history of psychiatric illness in their first-degree relatives.

Body Mass Index

Patients and healthy control subjects underwent a physical examination at enrolment and follow-up. Participants were weighted in a nonfasting state in light clothing, with footwear removed. BMI was calculated using the following formula: BMI = weight (kg)/height (m).[2] Normal weight was defined as BMI of 18.50 to 24.99, overweight–obesity as BMI greater than or equal to 25.00 and underweight as BMI less than 18.50[33]. Within the patient group, 25 were overweight or obese and 40 had normal weight; within the healthy control subject group, 9 were considered overweight or obese and 28 had normal weight.

Cognitive Assessment

Subjects were tested at baseline. The neurocognitive testing was administered by research assistants or PhD-level graduate students trained and supervised by a registered senior clinical neuropsychologist. To assure consistency across testers, the training included in-vivo observation of testing by the senior neuropsychologist. Testers administered the battery when the subjects were clinically stable (see mean mood ratings in Table 1). On average, the testing took 2 to 3 hours to administer. Subjects were allowed smoking breaks during testing sessions.

Premorbid IQ and current IQ were assessed using the North American Adult Reading Test full scale IQ, and Kaufman Brief Intelligence Test, respectively. The cognitive battery was selected to assess 6 domains, which have been demonstrated to be relevant to BD.[34] The categorization of tasks was modelled closely after the MATRICS Consensus Cognitive Battery, which has been validated in BD.[35] The 6 domains assessed, and the respective measures within each domain, have been used in our previous work,[12,36] and were as follows:

1) Processing Speed: Trail-Making Test time to complete part A; Stroop Test Word and Colour Naming trials number correct; Letter Fluency number correct;

2) Attention: CANTAB RVIP discriminability score, RVIP latency score;

3) Verbal Memory: CVLT-II recall trials 1–5; CVLT-II delayed free recall trial;

4) Nonverbal Memory: CANTAB Spatial Recognition Memory per cent correct; CANTAB Pattern Recognition Memory per cent correct; CANTAB Paired Associate Learning total errors adjusted score;

5) Working Memory: Wechsler Memory Scale 3rd Edition Letter and Number Sequencing; CANTAB Spatial Working Memory between errors; and

6) Executive Function: Trail-Making Test B time; Stroop Colour and Word trial number correct; CANTAB Intra Extra Dimensional set shifting task number of extra-dimensional shifting errors, CANTAB Stockings problems solved in the minimum number of moves.

The raw scores obtained for each primary cognitive measure were converted into *z* scores (ranging from –4 to 4) based on demographics-adjusted normative data from test manuals. Domain scores for each subject were calculated as the average of *z* scores of the primary measures within each cognitive domain.

Data Analysis and Statistics

Patients and healthy control subjects were divided according to their BMI into overweight–obese or normal weight groups. To assess demographic and clinical group differences, we used Student *t* test, ANOVA, or chi-square statistics as appropriate. In our primary analyses, to compare groups on cognitive domain scores, we used factorial MANOVA with BMI (overweight–obese, compared with normal weight) and diagnosis (patients, compared with control subjects) as between-subject factors. Because one of the groups (overweight–obese control subjects) had a small sample size of only 9 subjects, we performed further direct comparisons exclusively between the 2 groups of patients. For these analyses, we

used MANOVA, with and without controlling for current IQ. As secondary analyses, we performed Pearson correlation analysis between BMI and individual cognitive domain scores in control subjects and partial correlations controlling for mood scores (HRSD and YMRS) in patients. All statistical tests were 2-tailed and had a significance threshold of $\alpha = 0.05$. Data are presented as means with standard deviations. Analyses were conducted using the IBM SPSS Statistics software for windows, Version 20.0 (IBM SPSS Inc, Armonk, NY).

Results

Demographics

Overweight–obese and normal weight patients and healthy control subjects were well matched in age ($P = 0.20$), sex ($P = 0.98$), years of education ($P = 0.18$), premorbid IQ ($P = 0.66$), and ethnicity ($P = 0.10$) (Table 1). Overweight–obese patients had lower current IQ, compared with normal weight control subjects ($P = 0.03$). Patients and control subjects had the same proportion of people who were overweight–obese and normal weight ($\chi^2 = 2.121$, $df = 1$, $P = 0.14$). Additionally, no differences were found among the 2 groups of patients regarding their GAF ($P = 0.84$), BPRS ($P = 0.36$), PANSS ($P = 0.53$), YMRS ($P = 0.95$), and HRSD-29 ($P = 0.82$) scores, medication use, and other relevant clinical measures, such as age of onset of mania ($P = 0.14$), number of previous depressive episodes ($P = 0.92$), overall age of onset of BD ($P = 0.56$), medical comorbidity ($P = 0.19$), and alcohol and (or) substance abuse or dependence history ($P = 0.098$) (Table 1).

Between-Group Analysis of Cognitive Functioning

Table 2 presents the mean *z* scores for each domain and the results of the factorial MANOVA. The multivariate tests revealed a significant diagnosis effect (Wilks $\lambda = 0.832$, $F = 3.128$, $df = 6/93$, $P = 0.008$). Univariate tests revealed significant diagnosis main effects for the domains of attention ($P = 0.02$), verbal memory ($P < 0.001$), nonverbal memory ($P = 0.005$),

working memory (P = 0.001), and executive function (P = 0.007). Post hoc analyses showed that, in all these domains, patients performed worse than healthy control subjects. The multivariate tests revealed a nonsignificant BMI group effect (Wilks λ = 0.950, F = 0.812, df = 6/93, P = 0.56), and all univariate tests were also nonsignificant (P > 0.05). The multivariate tests for the interaction between the presence of the BD diagnosis and the presence of elevated BMI revealed no significant results (Wilks λ = 0.970, F = 0.473, df = 6/93, P = 0.83). The tests of between-subject effects for this interaction for all 6 domains did not show significant results: processing speed (P = 0.20), attention (P = 0.69), verbal memory (P = 0.90), nonverbal memory (P = 0.77), working memory (P = 0.68), and executive function (P = 0.50). When the groups of patients were compared with each other (excluding healthy control subjects), the multivariate test indicated a nonsignificant BMI group effect Hotelling T = 0.039; F = 0.372 df = 6/58, P = 0.89 (not controlling for current IQ), and Hotelling T = 0.067; F = 0.621, df = 6/56, P = 0.71 (controlling for current IQ).

Correlation Between Body Mass Index and Cognitive Functioning

Table 3 presents the correlations between BMI and the cognitive domains for patients and healthy control subjects. We found a trend for a negative correlation between the BMI and the score of the cognitive domain of nonverbal memory in the patient group (r = –0.246, r^2 = 0.06, P = 0.05), controlling for mood scores (YMRS and HRSD).

Discussion

To our knowledge, this is the first study to explore the relation between overweight–obesity and neurocognitive functioning in a sample of patients with BD who recently recovered from their first episode of mania. The results obtained from the direct comparisons between groups indicate that the cognitive problems early in the course of BD were most likely due to the illness itself and not related to obesity or overweight. The finding of a diagnosis effect is

consistent with results from our prior study (see Torres et al[14]). Moreover, except for a small, statistically nonsignificant, negative correlation between BMI and performance on the domain of nonverbal memory in the patient group, there were no correlations between cognitive domains and BMI within the patient group. Similarly, there were no significant correlations between BMI and neurocognitive domain scores in the healthy control group. Even though some of the participants in the current report were also included in Torres et al,[14] our present study was different from the prior report in the following 2 ways: the sample size has increased by 20 patients in the ongoing longitudinal study; and, the current focus is on the effects of weight status and cognitive function, which was not assessed in the prior report.

Otherwise healthy overweight–obese adults reportedly exhibit impairments mostly in the cognitive domains of memory and executive function.[27] We were unable to show any cognitive impairment in our overweight–obese healthy control group in comparison to their normal weight counterparts. However, our statistical methods likely lacked power to detect those differences owing to the small number of overweight–obese healthy control subjects, and thus our study was unable to sufficiently address whether obesity associates with cognitive impairment in healthy control subjects. Nonetheless, we replicated some findings from previous reports[1,2,35] regarding the impact of BD itself on cognition in the comparison between patients and healthy subjects. Although we replicated the findings from previous literature, we did not detect any differences in the neurocognitive functioning between the overweight–obese and normal weight group of patients. These results were similar when the group of healthy subjects was included or excluded in the analyses. Consequently, given the modest sample size, a type II error cannot be excluded.

As this study was conducted in Vancouver, which has a large Asian population, our study subjects included some subjects of Asian ethnic background. There is a debate about the appropriate BMI cut-offs for categorizing this population into normal weight and overweight

groups.[373] Therefore, one could argue that different BMI cut-offs might have yielded significant effects of BMI on cognition. However, the number of Asian subjects in each group in our study sample was very small, and comparable between the groups, making such an unlikely possibility. Further, correlation analysis is not impacted by different BMI cut-offs, and the assertion that categorization of patients based on BMI into low and high groups did not affect the results also supports the finding of no significant correlation between BMI and cognition in this study.

Although there were no statistically significant differences in comorbidity rates between the various groups in our sample, the rates were numerically higher in the overweight–obese group. There is some evidence that cognitive impairments are more pronounced in the population with BD and alcohol dependence comorbidity,[384] and it is possible that the impact of comorbidity might have biased our findings. However, if there were a negative effect of substance abuse comorbidity in our sample, this would have biased our overweight patient group to have even more cognitive deficits, given that the comorbidity rates were nonsignificantly higher in our overweight group. Even with this potential bias, that we failed to observe a cognitive difference between overweight–obese and normal weight patients suggests that comorbidity did not confound our results.

Study subjects were allowed to take smoking breaks during the neurocognitive testing sessions. There is some evidence that smoking may impact cognitive functioning.[39] We did not systematically collect information about smoking during the cognitive testing sessions in our study, and therefore, we cannot exclude the potential confounding of smoking on our study results.

Another potential explanation for the lack of effect of obesity on cognitive functioning could relate to the limited information available about the course of obesity in the subjects

included in our sample. Our baseline assessment recorded the information about the presence of elevated BMI at the time of recruitment, but the duration of the current obesity was not registered. Therefore, our sample is likely to include subjects who had been obese for only a few weeks to few months at the most. It can be implied from the literature[40–451] that obesity, rather than being a short-term risk factor for cognitive dysfunction, may impose its deleterious effects on cognition over time. Interestingly, several reports point to impairments in cognitive functioning even among young obese subjects[27]. Obese children or adolescents are outperformed by their normal weight comparison group on tests of general intellectual ability,[46] attention,[47,48] and executive function.[47–49] The cross-sectional design of most of these studies limits the conclusions about a definite causative factor. Nonetheless, it is possible that longer duration of obesity leads to a more significant impact on cognitive functioning. Indeed, longitudinal observations concluded that long-term obesity was associated with poor performance on batteries of tests assessing cognition.[43,45,50,51] Additionally, people who had gained more weight during the follow-up period experienced an additional worsening on test scores.[45] Therefore, it is conceivable that the cognitive deficits associated with obesity take place over time and may not be detectable early in the course of BD, particularly if patients have not been obese for a long period of time.

Another possible explanation for our results is the potentially positive influence of the pharmacological treatment received by the subjects enrolled in our study. Obesity has been associated with alterations in circulating proteins associated with neuronal survival. More specifically, obese people have been shown to have lower levels of BDNF, which promotes neuronal cell survival.[52–54] Additionally, plasma levels of BDNF were negatively correlated to BMI.[54] Peripheral levels of BDNF have also been associated with cognitive functioning. Patients from STOP-EM received treatment as per Canadian Network for Mood and Anxiety Treatments (commonly referred to as CANMAT) guidelines for managing BD. These

guidelines recommend as first-line treatment mood stabilizers or antipsychotics in monotherapy or in combination.[55,56] Mood stabilizers and antipsychotics are known to induce increases in the neurotrophic factors, and in particular BDNF, in BD[57–59] and schizophrenia.[606] In line with this, it is possible that the additional negative impact of the elevated BMI may have been overcome by optimal pharmacological treatment provided to the patients, and it could be the reason why we were unable to detect a potentially negative effect of obesity on cognitive functioning in patients in our analyses. However, as we have not collected serum samples for BDNF levels in all our subjects, we are unable to verify this hypothesis.

Atypical antipsychotics and mood stabilizers that are widely used to treat BD are associated with weight gain.[61–63] In this regard, it is possible that some patients who presented elevated BMI at baseline may have experienced a recent weight gain. Patients were recruited within 3 months of their recovery from their first manic episode and most of them were treated with different combinations of atypical antipsychotics and mood stabilizers. Hence the future longitudinal analyses of our full sample may provide important information about the long-term effects of overweight–obesity on cognitive functioning in patients with BD. From our present study and the results obtained in established patients,[13] the implication is that even though elevated BMI does not impose a negative impact on cognitive functioning in BD early in the course of the illness, if unaddressed, it may lead to future deficits.

Our main limitations were a modest sample size, particularly in the overweight–obese group of healthy subjects and the lack of information about the course of obesity prior to intake into the STOP-EM study. Another weakness is our limited ability to address the influence of medications regarding obesity and even cognitive functioning. Nonetheless, our study has several strengths. It is the first attempt to evaluate the impact of obesity on cognitive function in a first-episode mania sample with BD. While cognitive function in long-standing BD is affected by the confounds of age, duration of illness and treatment, multiple mood episodes,

and comorbid conditions, these factors are minimized in a sample of early BD, allowing us to assess the impact of obesity on cognition more directly. Longitudinal assessments of obesity coupled with evaluation of serum markers and cognitive function in BD may be helpful in understanding this further in future studies. The observation that obesity does not seem to worsen cognitive functioning in early BD is potentially clinically relevant, and indicates that adequate management to control obesity along with optimal treatment of BD early in its course has tremendous potential in reducing the disease burden related to BD.

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Table 1 – Demographic variables in patients with BD and healthy controls at baseline

	Patients		**Controls**		**Test**
	Overweight/ Obese (N=25)	Normal weight (N=40)	Overweight/ Obese (N=9)	Normal weight (N=28)	
Demographics	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age	23.80 (4.54)	22.12 (4.10)	25.44 (6.80)	23.14 (4.54)	F(3,98) =01.55
BMI	27.36 (2.22)	22.07 (1.48)	28.34 (2.69)	22.20 (1.58)	F(3,98) =68.30 *
Years of education	14.00 (1.87)	13.45 (2.42)	15.00 (2.95)	14.36 (1.87)	F(3,98) =1.679
Premorbid IQ	105.60 (7.72)	107.50 (7.27)	106.67 (8.80)	108.11 (6.07)	F(3,98) =0.592
IQ (Kbit)	101.96 (9.81)	106.30 (10.07)	105.56 (8.24)	110.21 (8.83)	F(3,97) =3.248 *
CTQ	37.25 (10.06)	36.91 (10.61)	35.66 (12.24)	37.19 (15.15)	F(3,83) =0.031
	% (N)	% (N)	% (N)	% (N)	
Gender (female)	56.00 (14)	52.50 (21)	55.55 (5)	57.14 (16)	X2(3)= 0.164
Ethnicity (Caucasian)	68.00 (17)	77.50 (31)	66.67 (6)	60.71 (17)	X2(9)= 14.578
Clinical Variables	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age of onset of Mania (years)	23.64 (4.48)	22.03 (4.08)			t(63)=-1.494
Overall age of onset of BD (years)	20.40 (5.36)	19.62 (5.02)			t(63)=-0.589
Number of previous depressive episodes	1.16 (1.52)	0.97 (1.56)			t(63)=-0.477
YMRS	1.40 (2.32)	1.35 (3.33)			t(63)=-0.066
HAMD 29	6.72 (7.38)	6.27 (7.61)			t(63)=-0.232
GAF	67.04 (11.64)	67.74 (14.26)			t(62)=0.206
BPRS	21.16 (5.99)	22.60 (6.08)			t(60)=0.912
PANSS	7.48 (1.15)	7.69 (1.39)			t(62)=0.632
	% (N)	% (N)	% (N)	% (N)	
Current or lifetime substance abuse/dependence	58.33 (14)	36.84 (14)			X2(1)= 2.743
Lithium	44.00 (11)	45.00 (18)			X2(1)= 0.006
Valproate	56.00 (14)	40.00 (16)			X2(1)= 1.585
Atypical Antipsychotics	76.00 (19)	80.00 (32)			X2(1)= 0.146

Combination of Mood Stabilizers and Atypical Antypsichotics	76.00 (19)	70.00 (28)			X2(1)= 0.277
Antidepressants	8.00 (2)	7.50 (3)			X2(1)= 0.005

*p<0.05

CTQ: Trauma Questionnaire; YMRS: Young Mania Rating Scale score closest to the time of cognitive testing; HAMD29: Hamilton Depression Rating Scale 29 items score closest to the time of cognitive testing; GAF: Global Assessment of Functioning; BPRS: Brief Psychiatric Rating Scale; PANSS: Positive and Negative Symptom Scale

Table 2 – Mean z score on each cognitive domain in patients with BD and healthy subjects

	Patients		**Controls**				
	Overweight /Obese (N=25)	Normal weight (n=40)	Overweight/Obese (N=9)	Normal weight (N=28)	Main effect of diagnosis	Main effect of elevated BMI	Interaction between diagnosis and elevated BMI
Cognitive Domains	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)			
Processing Speed	-0.49 (0.61)	-0.42 (0.68)	-0.48 (0.76)	0.00 (0.78)	F(1,98)=1.855	F(1,98)=2.959	F(1,98)=1.653
Attention	-0.18 (0.99)	-0.25 (0.78)	0.16 (0.71)	0.24 (0.68	F(1,98)=5.198*	F(1,98)=0.000	F(1,98)=0.161
Verbal Memory	-0.09 (1.09)	-0.26 (1.05)	0.79 (1.04)	0.56 (0.88)	F(1,98)=13.530*	F(1,98)=0.704	F(1,98)=0.016
Non verbal memory	-0.13 (0.87)	-0.03 (0.70)	0.36 (0.43)	0.37 (0.49)	F(1,98)=8.365*	F(1,98)=0.119	F(1,98)=0.085
Working Memory	-0.37 (0.87)	-0.22 (0.99)	0.41 (0.54)	0.39 (0.75)	F(1,98)=12.472*	F(1,98)=0.102	F(1,98)=0.174
Executive function	-0.22 (0.71)	-0.12 (0.79)	0.12 (0.67)	0.45 (0.65)	F(1,98)=7.655*	F(1,98)=1.623	F(1,98)=0.457

*p<0.05

Table 3 – Correlations between BMI and the score on cognitive domains in patients with BD and healthy controls at baseline

	Patients[a]			**Controls**		
Cognitive Domains	N	r	p	N	r	p
Processing Speed	61	-0.035	0.787	37	-0.193	0.253
Attention	61	0.068	0.596	37	-0.006	0.970
Verbal Memory	61	0.081	0.526	37	0.233	0.165
Nonverbal Memory	61	-0.246	0.052	37	0.098	0.565
Working Memory	61	-0.078	0.542	37	0.201	0.233
Executive function	61	0.007	0.975	37	-0.050	0.769

[a] Controlling for mood scores (YMRS and HAMD 29)

3.2.Capítulo 2

Carta de submissão:

03-Mar-2015

Re: SWBP-2015-0046 - "Hippocampal neurochemical markers in bipolar disorder patients following the first-manic episode: a prospective 12-month proton magnetic resonance spectroscopy study"

Dear Mr. Leonardo da Silveira,

Your manuscript entitled "Hippocampal neurochemical markers in bipolar disorder patients following the first-manic episode: a prospective 12-month proton magnetic resonance spectroscopy study" has been successfully submitted online and is presently being given full consideration for publication in The World Journal of Biological Psychiatry.

Your manuscript ID is SWBP-2015-0046.

Please mention the above manuscript ID in all future correspondence or when contacting the Editorial Office with questions. If there are any changes in your postal address or e-mail

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Thank you for submitting your manuscript to The World Journal of Biological Psychiatry.

Best regards

Dr. Andrea King

The World Journal of Biological Psychiatry Editorial Office

wfsbp@meduniwien.ac.at

Artigo:

Hippocampal neurochemical markers in bipolar disorder patients following the first-manic episode: a prospective 12-month proton magnetic resonance spectroscopy study

Leonardo E Silveira, MD[1,2,3], David J Bond, MD, PhD[1,4], Erin Leigh MacMillan[5], Jan-Marie Kozicky, PhD[1], Kesavan Muralidharan, MD[1,6], Joana Bücker, PhD[1,2], Adriane Ribeiro Rosa, PhD[2,7], Flavio Kapczinski MD, PhD[2], Lakshmi N Yatham, FRCPC, MRCPsych[1]

[1] Mood Disorders Centre, Department of Psychiatry, University of British Columbia, 2255 Wesbrook Mall, Vancouver BC Canada V6T2A1.

[2] Laboratory of Molecular Psychiatry, Centro de Pesquisas Experimentais, Hospital de Clínicas de Porto Alegre, and INCT for Translational Medicine, Porto Alegre, RS, Brazil

[3] Postgraduate Program in Medicine: Psychiatry, Universidade Federal do Rio Grande do Sul, UFRGS, Porto Alegre, RS, Brazil

[4] Department of Psychiatry, University of Minnesota, Minneapolis, MN, USA

[5] Division of Neurology, Department of Medicine, Faculty of Medicine, the University of British Columbia

[6] Department of Psychiatry, National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore – 560029, India.

[7] Department of Pharmacology, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

Corresponding Author

Lakshmi N. Yatham MBBS, FRCPC, MRCPsych (UK), MBA (Exec)

Professor of Psychiatry, University of British Columbia

Room 2C7-2255 Wesbrook Mall, Vancouver, BC, Canada V6T 2A1

T: +1 604 822 0562 F: +1 604 822 7922 yatham@mail.ubc.ca

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Abstract

Objectives

Previous studies reported decreased N-acetyl aspartate (NAA) and increased Glx (the sum of glutamate plus glutamine) in chronic bipolar disorder (BD).We evaluated NAA and Glx levels in hippocampi of first episode BD patients and healthy subjects at baseline and at 12 months.

Methods

We used single-voxel proton magnetic resonance spectroscopy (1H-MRS) to compare the hippocampal neurometabolites (NAA and Glx) levels between 41 first episode BD patients and 27 matched healthy subjects at recruitment and 12 months later. We also investigated the effect of new mood episodes in hippocampal neurochemistry.

Results

There was no main effect of either group (diagnosis) or time for hippocampal NAA and Glx levels in BD patients and healthy subjects. We also did not find any group-by-time interaction for the levels of these metabolites. Furthermore, a new mood episode did not influence the hippocampal neurochemistry over 12 month of follow-up.

Conclusions

Our data suggest that NAA and Glx levels are not altered in early stage BD, and that episode recurrence in early stages does not have a significant impact on the levels of these metabolites. These may suggest that there may be an early window for intervention to potentially arrest neuroprogression of the disease.

Key words: bipolar disorder; magnetic resonance; spectroscopy; metabolites; hippocampus

Introduction

Bipolar disorder (BD) is a chronic recurrent illness associated with considerable mortality and morbidity. Patients with BD die 9 years earlier on average, have 2-fold higher all-cause mortality and 8 to 15 fold greater suicide risk compared with the rest of the population(Harris and Barraclough 1997; Crump et al. 2013). BD is one of the leading causes of disability in young adults(Catalá-López et al. 2013) and it is associated with higher direct medical costs compared to the general population(Stender et al. 2002; Simon et al. 2006).

The natural history of illness progression of BD involves relapses, increasing subclinical symptoms, and comorbidity with other psychiatric disorders and medical conditions(Berk et al. 2007; Kapczinski, Dias, et al. 2009; Kapczinski, Videira, et al. 2009). Mood episodes themselves are predictors of recurrence of BD(Kessing et al. 2004) and the duration of the inter-episode recovery tends to be shortened as the illness progresses(Kessing et al. 1998). With accumulating illness episodes, increasing illness severity translates into a higher cognitive and functional impairment(Rosa et al. 2009; Magalhães et al. 2012). Furthermore, a higher number of episodes is associated with poor treatment response to both pharmacological(Swann et al. 1999; Michael Berk et al. 2011) and psychosocial interventions(Scott et al. 2006). Recent literature further suggests that having more mood episodes is also associated with neuroanatomical changes, including ventricular enlargement(Stephen M Strakowski et al. 2002) and progressive loss of grey matter (Ekman et al. 2010).

The hippocampus as part of the limbic-thalamic-cortical system is crucial to emotional regulation. It is also involved in cognitive functioning, in particular, memory tasks(Frey et al. 2007). Reviews of neuroimaging studies in BD suggest volume reductions in the hippocampus(Frey et al. 2007; Phillips and Swartz 2014). In a large meta-analysis, Hallahan et al.(Hallahan et al. 2011), (2011) found a reduction in hippocampal volume in BD patients,

though this seemed to be reversed by lithium therapy. Another study showed no significant difference either in left or right mean hippocampal volumes between euthymic BD patients and healthy controls, but reported that obese bipolar patients had lower left hippocampal volume than non-obese subjects(Vianna-Sulzbach et al. 2013). In aggregate, these data suggest alterations in hippocampal volume, and therefore, it is likely that hippocampus plays a role in the pathophysiology of BD.

Magnetic resonance spectroscopy (1H-MRS) studies have shown abnormalities in neurochemical markers in the limbic-thalamic-cortical circuit of subjects with BD. Specifically, even though there are a few negative studies(Colla et al. 2009), N-acetyl aspartate (NAA), a marker of neuron-myelin coupling(Nordengen et al. 2013 Dec 31), is reduced in the hippocampus of euthymic(Scherk et al. 2008), manic(Atmaca et al. 2006) and depressed patients with BD(Atmaca and Yildirim 2012; Zhong et al. 2014). A study has suggested episode-related differences between mania and depression, depending on the region analyzed(Xu et al. 2013). In addition, increased glutamate + glutamine ("Glx") levels in multiple brain areas is perhaps the most consistent neurochemical finding in patients with BD, as indicated by the findings from two recent meta-analyses(Gigante et al. 2012; Chitty et al. 2013). Thus, there is evidence to support that Glx is elevated and NAA is decreased in BD.

However, most of 1H-MRS studies included in the above meta-analyses have been carried out in samples of patients with BD in advanced stages of the illness, with the bias introduced by the numerous confounding factors such as duration of illness, number of mood episodes and long term use of medications. Hence, prospective cohort studies of early stage BD patients are critical to better understand the relationship between neurochemical markers and pathophysiology of BD, as well as the impact of illness progression on brain metabolites. Here we replicated and expanded our previous cross-sectional research(Gigante et al. 2014) by examining in vivo neuronal metabolites in the hippocampus of patients with BD following their

first manic episode and again within 1-year of follow-up. A secondary aim was to evaluate the potential influence of recurrences on the absolute concentrations of NAA and Glx. We hypothesized that patients would show altered brain chemistry compared to a healthy comparison group, and that the progression of the illness (e.g., presence of new episode over one one-year- follow-up) will result in a greater alteration in brain metabolites.

Methods

Subjects

Patients and healthy subjects in this study were participants of the Systematic Treatment Optimization Program for Early Mania (STOP-EM), which has been described in detail in previous publications(Yatham et al. 2009; Torres et al. 2010).The study protocol was approved by the University of British Columbia ethics committee. Written informed consent was obtained from all patients and healthy subjects before any study procedures took place, in accordance with the Declaration of Helsinki.

Patients meeting criteria for Bipolar I Disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) were recruited from Vancouver Hospital Health Sciences Centre and affiliated sites, as well as by community and hospital referrals from physicians and psychiatrists. The inclusion criteria required patients to be aged between 14 to 35 years old, and within three months of their first manic or mixed episode, with or without psychosis, and with or without co-morbid conditions. All patients received treatment, according to clinical practice guidelines(Yatham et al. 2013). Patients were

excluded if they had a history of major medical illness underlying their manic symptoms and if they could not provide informed consent.

Healthy subjects matched for age and gender were also recruited for comparison purposes. They were assessed with a standardized interview, and were enrolled if they had no personal history of psychiatric illness or major medical illness and no family history of psychiatric illness in their first-degree relatives.

Demographic and clinical variables

The baseline assessment included a clinical interview by an academic research psychiatrist and a structured clinical interview using the Mini International Neuropsychiatric Interview (MINI), both of which were used to confirm the diagnosis of BD(Sheehan et al. 1998). Sociodemographic and clinical variables were also collected using a standardized protocol. The following clinical rating scales were used: Positive and Negative Syndrome Scale(Kay et al. 1987) (PANSS), Brief Psychiatric Rating Scale(OVERALL and GORHAM 1962) (BPRS), Young Mania Rating Scale(Young et al. 1978) (YMRS) and Hamilton Depression Rating Scale(Hamilton 1960) (HAMD). The functioning was assessed using the Global Assessment of Functioning Scale(Hall 1995) (GAF).

MRI protocol and Hippocampal Volume Extraction

T1-weighted MR images were acquired at enrolment and at 12 months follow-up with a Philips Achieva 3.0 Tesla scanner (Best, the Netherlands), using a three-dimensional axial inversion recovery-weighted spoiled gradient recalled sequence with the following parameters: FOV = 25.6 cm, matrix = 256 × 200 × 180, isotropic voxels (1 × 1 × 1 mm^3), autoshim, TR/TE

= 7.6 / 3.5 ms, transmit-receive head coil, flip angle = 8 degrees. Hippocampal volumes, and the proportions of hippocampal and non-hippocampal GM and WM in the 1H-MRS voxel, were quantified using FSL v. 4.1 (FMRIB Software Library, www.fmrib.ox.ac.uk/fsl/)(Smith et al. 2004; Woolrich et al. 2009).

Acquisition and processing of signals of ^{1}H-MRS

1H-MRS scans were acquired at enrolment and at 12 months with the Philips 3.0 T scanner in addition to T_2-weighted coronal, sagittal, and axial MR images for anatomical parameters.. A point resolved spectroscopy (PRESS) sequence (TR = 2000ms, TE = 35ms) was used to acquire data from 30mm x 15mm x 15 mm voxels encompassing the hippocampus, one scan for each side of the brain. Using the sagittal image, the voxel was placed with the long axis angled along the hippocampus. Its position in the medial/lateral and superior/inferior directions was adjusted based on the coronal and axial images, in order to include the entire hippocampus and avoid CSF (Figure 1a). Projection-based second order shimming was performed, and a single chemical shift selective pulse and crusher gradient were used to suppress the water signal 160 ms prior to the PRESS localization sequence. 128 water suppressed and 16 water-unsuppressed signals were obtained, the latter to allow for eddy current correction and metabolite quantitation referenced to the water peak area.

1H-MRS data were extracted using LCModel v. 6.0(Provencher 1993). Figure 1b presents a sample of the hippocampal 1H-MRS spectra in a patient and a healthy subject. Relative Glx and NAA concentrations, normalized to the unsuppressed water spectrum, were converted to absolute concentrations by multiplying by the tissue-weighted (GM, WM, and CSF) water concentrations in the 1H-MRS voxel and correction factors to account for water and metabolite signal decay during the TE. In each spectrum, metabolites with standard

deviations (Cramer-Rao lower bounds) greater than 25% were excluded from the analysis. We also excluded subjects whose 1H-MRS spectra were not adequate (presence of artifacts) based on the simultaneous visual inspection of two authors (LS and DB). A third author (ELM) was consulted when there was disagreement at the initial evaluation. The levels of NAA, and Glx were quantified in patients and healthy subjects at baseline and after one year of follow-up. The final NAA and/or Glx concentrations consisted of the average of the concentration of these metabolites from right and left hippocampi. If only one side had a valid concentration value, that value was considered the final metabolite concentration for that particular subject.

Statistical Analyses

Statistical analyses were performed using SPSS for Windows 19.0 (SPSS Inc. Chicago, IL). Sociodemographic variables were examined using t-Tests and Chi- Square as appropriate. Pearson correlation was used to evaluate potential associations between clinical variables and biomarkers. General Linear Model (GLM) for repeated measures was used to investigate the longitudinal differences on brain metabolites over the 1-year follow-up period. Effects of diagnosis (BD vs. healthy subjects), time, and group-by-time interactions were analyzed. As a secondary analysis, patients were divided into two groups based on the occurrence of any new mood episode within one year of follow-up: recurrence (REC) and no recurrence (NREC). The GLM for repeated measures was also used to investigate the potential longitudinal influence on brain metabolites between REC and NREC.

Results

Participants

Forty-one patients and 27 matched healthy subjects had baseline and one year 1H-MRS data. Their mean ages were 22.75±4.07 and 22.85±4.92; (p=0.931), respectively. Twenty (48.78%) patients and 15 (55.55%) healthy subjects were women (p=0.627). The groups did not differ in terms of education (p=0.231) and ethnicity (p=0.377). Other characteristics of the whole sample at baseline and 1-year-follow-up are listed in Table 1.

Seventeen patients and four healthy subjects had only baseline 1H-MRS data, and were excluded from the analyses. Using the standard deviation greater than 25% criteria for the metabolite levels, we excluded data from one side of the hippocampus of one patient at one year and one healthy subject at baseline for NAA. For Glx, at baseline, we excluded data from 2 patients and 3 healthy subjects, and at one year we excluded data from 7 patients and 2 healthy subjects.

Hippocampal metabolites measures between patients and healthy subjects

Table 2 presents the mean absolute concentrations of the hippocampal metabolites in the sample. The General Linear Model (GLM) revealed no significant main effect of either group ($F(65,2)=0.291$; $p=0.749$) or time ($F(65,2)=0.665$; $p=0.518$), and no significant group-by-time interaction ($F(65,2)=1.304$; $p=0.278$) on NAA and Glx hippocampal concentrations.

Brain metabolites measures between REC and NREC

At 1-year-follow-up period, 21 (51.21%) were classified as REC and 20 patients (48.78%) were classified as NREC. Ten patients had a hypo/manic episode and 17 patients had a depressive episode. REC and NREC groups had similar years of education (p=0.423), gender (p=0.758), and ethnicity (p=0.097). REC group was older than the NREC group (p=0.033). On clinical variables, REC group had more depressive symptoms at baseline (p=0.020) and at 1-year-follow-up (p=0.047) compared to the NREC group. Analyzing medications, both groups had similar pattern of prescription in terms of lithium (p=0.320), valproate (p=0.527), and a trend towards more use of antipsychotics (p=0.056), combination of mood stabilizer and antipsychotics (p=0.054), and antidepressants (p=0.091) in the REC group at one year visit.

As to the NAA and Glx in REC and NREC groups, we did not find group-by-time interactions within 1-year-follow-up study ($F(36,2)=0.025$; $p=0.976$)). Furthermore, the GLM for repeated measure could not find interaction between the follow-up period and: use of Lithium ($F(35,2)=1.610$; $p=0.214$); use of Valproate ($F(35,2)=2.905$; $p=0.068$), use of antipsychotics ($F(35,2)=0.306$; $p=0.738$), and use of a combination of a mood stabilizer plus an antipsychotic ($F(35,2)=0.146$; $p=0.865$).

Even though both groups improved on their psychosocial functioning within one year, REC group had significantly lower GAF scores compared to the NREC group at baseline (p=0.045) and 1-year-follow-up visit (p=0.014).

Discussion

Here, we expanded the results from our previous cross-sectional study(Gigante et al. 2014) by longitudinally examining hippocampal neurochemistry (e.g., Glx and NAA) in patients with BD recruited within 3 months after recovery from their first manic episode and healthy subjects. Our main findings were that Glx and NAA levels were not different between BD patients and matched healthy subjects at baseline, and that the levels did not change differentially during the one-year follow up period in BD patients compared with controls. Further, Glx and NAA levels were no different between the REC and the NREC BD groups. These results lend support to the report by Gigante(Gigante et al. 2014) showing that there are no abnormalities in Glx and NAA levels in the hippocampus of patients with BD in the early stage of the illness.

The observation that hippocampal Glx and NAA levels did not differ between patients and healthy controls is interesting in light of positive results from other studies(Blasi et al. 2004; Atmaca et al. 2006). Atmaca et al.(Atmaca et al. 2006), (2006) showed that first-episode patients with BD had a significant bilateral reduction of NAA/Cr and of NAA/Cho in the hippocampus compared to control group. Additionally, this study found an association between severity of manic symptoms and NAA levels. Similarly, Blasi et al.(Blasi et al. 2004), (2004) found that first-episode patients with psychotic symptoms exhibit lower NAA/Cr levels than healthy subjects in the hippocampus. These studies evaluated patients during acute mood episode, which might have contributed to alterations in brain metabolites concentrations. Our study included mostly euthymic patients on both end-points. Furthermore, as demonstrated in previous studies, it is plausible that changes in brain metabolites may occur alongside with the progression of the illness(Bertolino et al. 2003; Deicken et al. 2003; Dager et al. 2004; Yildiz-Yesiloglu and Ankerst 2006). Therefore, early in the illness, even though brain chemistry might change during mood episodes, it normalizes as patients improve. Our results report brain

metabolites absolute concentration. Thus, another possible explanation for the discrepancy between our results and other studies could be that the majority of previous studies reported metabolite concentrations as ratios to creatine plus phosphocreatine (Cr) or choline-containing compounds (Cho), both of which may be affected by the pathology and could amplify the differences in the reported ratios.

If Glx and NAA levels are unaltered in early stages of BD, this lends support to the neuroprogression hypothesis of BD, as levels of these metabolites are altered in unselected BD patients which likely included patients in later stages of the illness. Recent literature suggests that having more mood episodes is associated with neuroanatomical changes, which includes ventricular enlargement(Stephen M. Strakowski et al. 2002) and progressive loss of grey matter thickness(Ekman et al. 2010). The Allostatic Load (AL) in BD was proposed as the cumulative effect of the physiologic machinery required for forcing adaptation facing stress, viewed here as mood episodes(Kapczinski et al. 2008), suggesting that mood episodes are neurotoxic. Neurotrophins and inflammatory cytokines are of great interest in BD and widely studied. Proinflammatory cytokines are increased in manic and depressive episodes. In particular, IL-6 is positively correlated with manic and depressive scores on rating scales(Brietzke et al. 2009). TNF-α is thought to have a key role in BD, and serum levels increase during mood episodes. It has been suggested that this cytokine regulates apoptotic cascades(Brietzke and Kapczinski 2008). IL-6, IL- 10 and TNF-α levels are increased in early stages of BD in comparison to healthy subjects. Late stages BD patients show increased levels of TNF-α and reduced levels of IL-6(Kauer-Sant'Anna et al. 2009). Brain Derived Neurotrophic Factor (BDNF) levels were negatively correlated with manic symptoms severity(Cunha et al. 2006). BDNF levels were found to decrease with the progression of BD and were negatively correlated with length of illness(Kauer-Sant'Anna et al. 2009). Moreover, it has been suggested that the process of energy generation in patients with BD is impaired, eventually leading to oxidative stress(Brown

et al. 2014). Antioxidant enzymes (superoxide dismutase) activities are increased during mood episodes(Andreazza et al. 2007). The activity of glutathione reductase is increased in late stages of BD(Andreazza et al. 2009). These changes in oxidative parameters may contribute to a progressive failure of compensatory mechanisms with illness progression(M Berk et al. 2011). From the cellular functioning perspective, the illness progression can be conceived as the failure of the resilience mechanisms. BD patients exhibit impaired endoplasmic reticulum response to stress, and such impairment seems to be more pronounced in patients in the late stages of the illness(Pfaffenseller et al. 2014). Moreover, early apoptosis was detected in the peripheral blood mononuclear cells of BD patients(Fries et al. 2014).

Therefore, mood episodes are toxic and have a progressive and cumulative impact on the severity of BD. Consistent evidence shows that the course of BD is associated with modifications in response to treatment. Not only the duration of BD but also, and more importantly, the number of episodes is associated with progressive lack of efficacy with pharmacological and surprisingly psychotherapy treatment(Swann et al. 1999; Scott et al. 2006; Michael Berk et al. 2011). In line with this, our findings suggest that patients early in the illness and receiving optimal treatment are relatively preserved from the neurobiological perspective. Thus, our study findings provide a compelling rationale for early intervention to arrest disease progression in BD. We also found a significant improvement in global functioning in the whole sample over the 1-year period, as indicated by an increase of overall GAF score from baseline to endpoint. In addition, NREC patients are more likely to present functional recovery than REC group. Evidence that such functional impairment may be a consequence of the severity of the illness (e.g., number of episodes) is supported by several studies on first manic episode of BD(Tohen et al. 2003; Anna et al. 2009; Rosa et al. 2012). Additionally, Lopez-Jaramillo et al(López-Jaramillo et al. 2010)., (2010) showed that BD patients who had just 1 manic episode experience favourable cognitive functioning while those individuals with 3 more mania have

long-term cognitive deficits. Comparing neurocognitive performance between patients with low and high functioning, Martínez-Arán et al.(Martinez-Aran et al.), (2007) showed that those patients with low functioning were significantly more impaired on memory tasks, inhibitory control and working memory. Furthermore, it has recently been shown that a strong linear association exists between functioning and clinical stages of BD, which suggests a progressive functional decline from the early to advanced stages of disorder(Rosa et al. 2014).

The present study has some limitations. First, we assessed only Glx and NAA levels in the hippocampus, which precludes us from drawing conclusions about other metabolites in different areas of the brain. Second, although all patients were on treatment according to internationally recognized clinical guidelines, which provided good clinical response in our sample, some medications (e.g., olanzapine, quetiapine and lithium) might influence brain metabolites levels(DelBello et al. 2006; Yildiz-Yesiloglu and Ankerst 2006; Adler et al. 2013). However, when these medications were introduced as covariates to the analyses in the present study, the results remained the same.

In conclusion, we did not find differences in Glx and NAA levels in the hippocampus either at baseline or at 1-year-follow-up between healthy controls and patients with BD when they are recovered from the first manic episode. These findings may be explained by the fact that our patients were in the early stage of the illness and might not be affected by variables of the progression of the disorder (e.g. mood episodes, duration of illness, medications). Finally, our results highlight the importance of early interventions in order to arrest disease progression in BD.

Statement of interest:

Dr. Bond has received speaking fees or sat on advisory boards for: the Canadian Network for Mood and Anxiety Treatments (CANMAT), the Canadian Psychiatric Association, Pfizer, Sunovion, BMS, Otsuka, Astra-Zeneca, and Janssen-Ortho; and has received research support from: the Canadian Institutes of Health Research (CIHR), the UBC Institute of Mental Health/Coast Capital Depression Research Fund, and Pfizer.

Dr. Lam: Ad Hoc Speaker Honoraria: AstraZeneca, Canadian Psychiatric Association, Canadian Network for Mood and Anxiety Treatments, Lundbeck, Lundbeck Institute, Otsuka, Servier. Ad Hoc Consulting/Advisory Boards: Bristol Myers Squibb, Canadian Network for Mood and Anxiety Treatments, Eli Lilly, Lundbeck, Mochida, Pfizer, Takeda. Research Funds (through UBC): Bristol Myers Squibb, Canadian Institutes of Health Research, Canadian Network for Mood and Anxiety Treatments, Coast Capital Savings, Lundbeck, Pfizer, St. Jude Medical, University Health Network, Vancouver Coastal Health Research Institute. Patents/Copyrights: Lam Employment Absence and Productivity Scale (LEAPS). Book Royalties: Cambridge University Press, Informa Press, Oxford University Press. Stock/Stock Options: None. Gifts/Travel (unrelated to speaker expenses): None.

Dr. Yatham has been a member of advisory board and/or received research grants , and/or been a speaker for Astrazeneca, Janssen, Lilly, GSK, Bristol Myers Squibb, Novartis, Servier, Sunovion, and Pfizer; and has received research grants from CIHR.

Dr. Torres has received funding from CIHR and has consulted with Lundbeck Canada.

Drs. Silveira and Muralidharan as well as Joana Bucker and Jan M Kozicky report no disclaimers.

Dr. Adriane R Rosa has served as speaker for Eli Lilly.

Dr. Kapczinski has received research support from or served as a consultant or speaker for AstraZeneca, CNPq, CAPES, Eli Lilly, Janssen, Janssen-Cilag, NARSAD, Stanley Medical Research Institute, and Servier; has been a member of the board of speakers for Astra-Zeneca, Eli Lilly, Janssen and Servier; and has served as a consultant for Servier.

Dr. MacMillan has served as a consultant for F. Hoffmann-La Roche Ltd.

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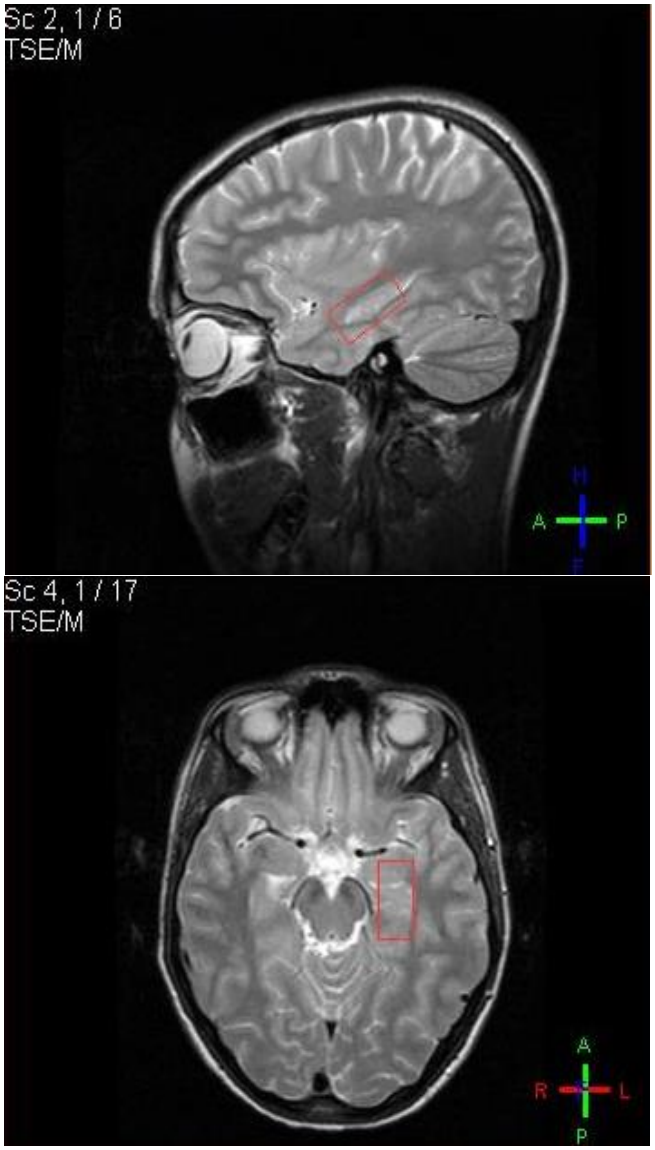
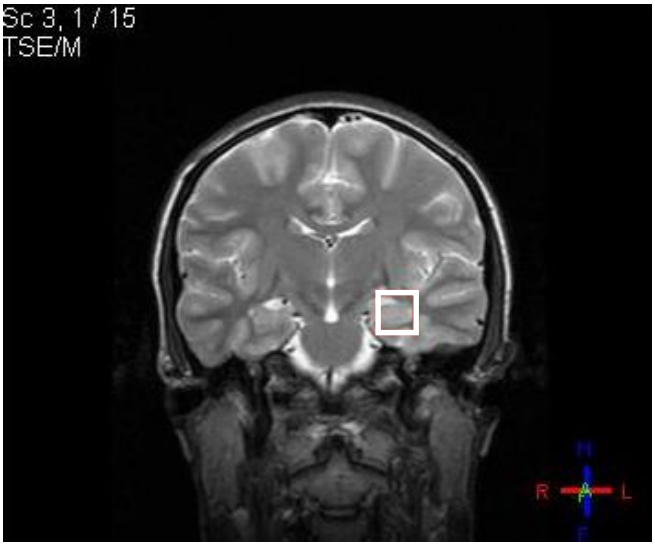
Figure Legends

Figure 1: a) Hippocampal 1H-MRS voxel T2-weighted sagittal, axial, and coronal MR images and b) sample 1H-MRS spectra from a BD patient and a healthy subject;

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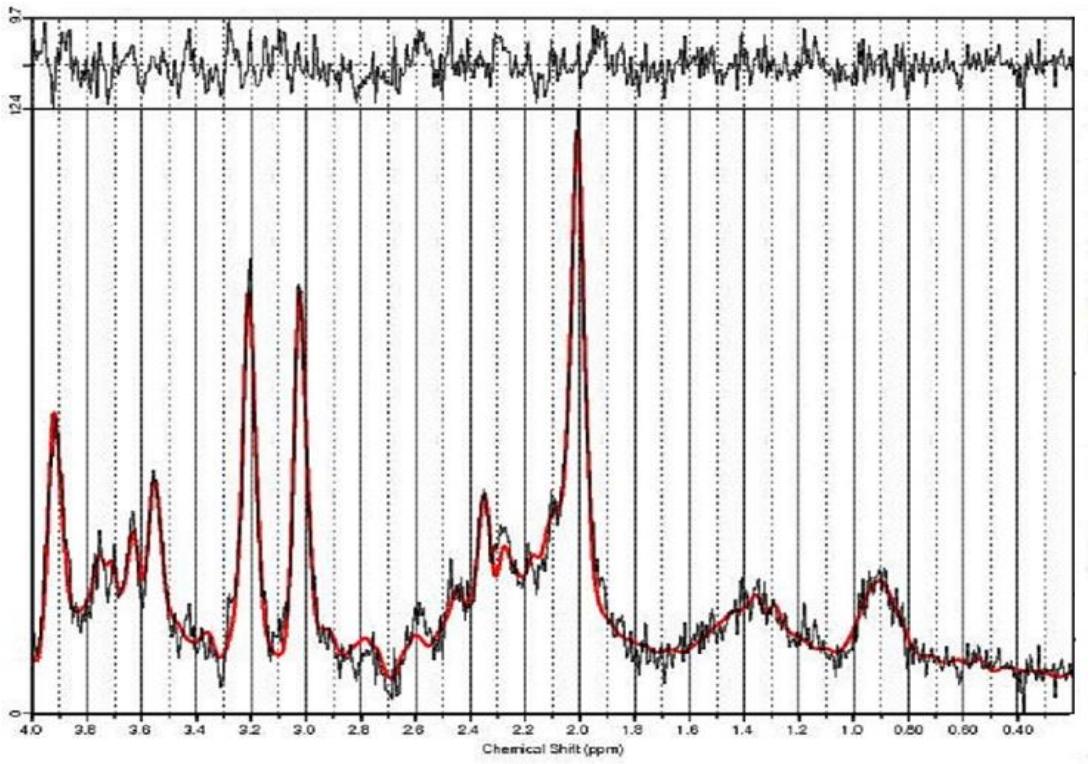
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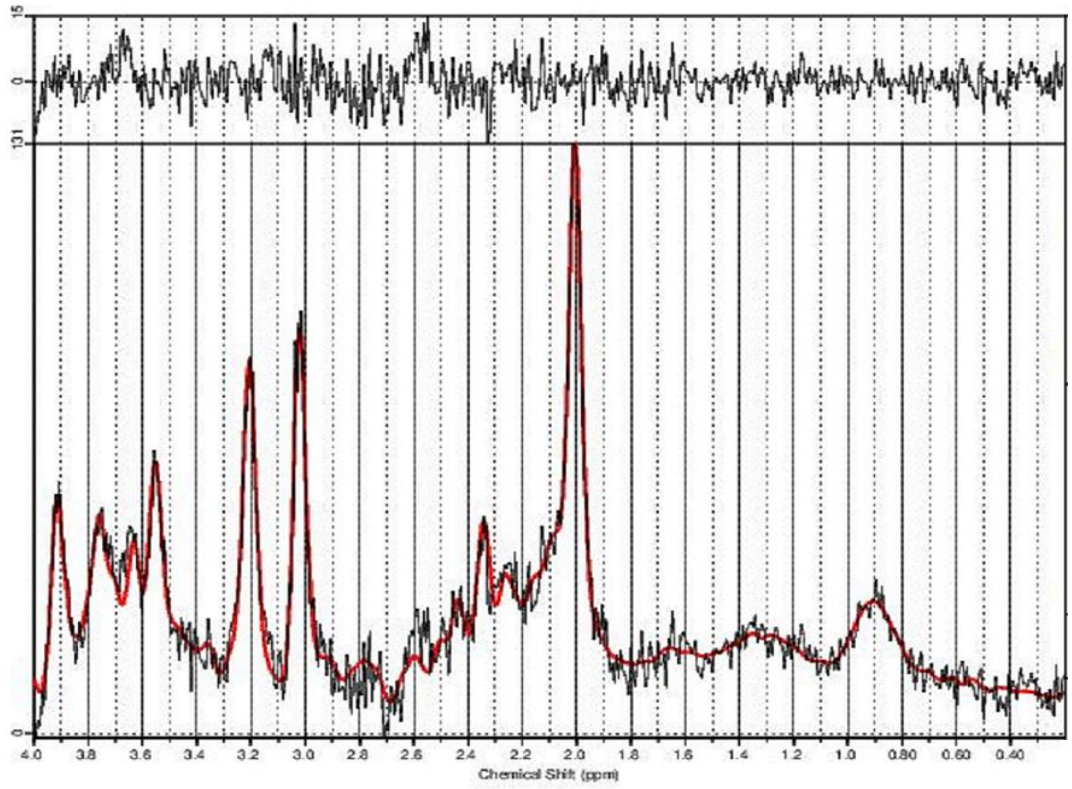
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Chemical Shift (ppm)

b)

Figure 2: Global Assessment of Functioning (GAF) over one year of follow-up period between patients who had a recurrence of BD and patients who remained euthymic

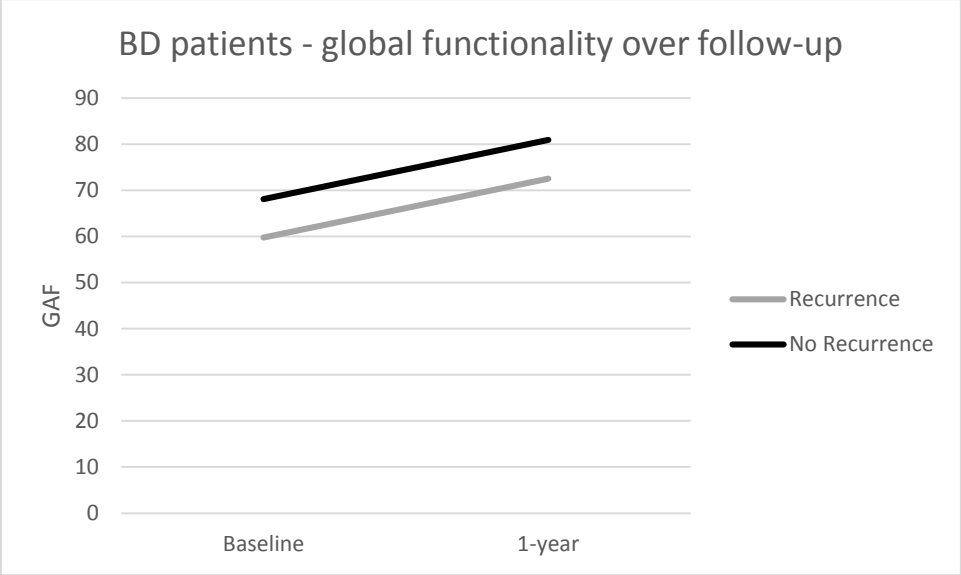

Table 1 – **Demographic and clinical variables for patients and healthy subjects at baseline and at 1-year.** Values are presented as mean (standard deviation) unless indicated otherwise. YMRS: Young Mania Rating Scale score closest to the time of brain scan; HAMD29: Hamilton Depression Rating Scale 29 items score closest to the brain scan; GAF: Global Assessment of Functioning; BPRS: Brief Psychiatric Rating Scale; PANSS: Positive and Negative Symptom Scale

Demographics	Patients (58)	Healthy subjects (31)	
Age	22.67 (4.54)	22.96 (4.62)	p=0.772
Years of education	14.00 (2.27)	15.03 (2.61)	P=0.056
Gender			P=1.000
Female n (%)	31 (53.44)	17 (54.83)	
Male n (%)	27 (46.55)	14 (45.16)	
Ethnicity			P=0.466
Caucasian n (%)	40 (68.96)	20 (64.51)	
Asian n (%)	8 (13.79)	8 (25.80)	
Other n (%)	2 (03.44)	1 (3.22)	
Clinical variables	Patients		
	Baseline	Year 1	
YMRS	3.75 (05.80)	1.00 (03.80)	
HAM-D	6.39 (09.09)	2.85 (04.49)	
BPRS	22.51 (05.46)	19.73 (03.70)	
PANSS	7.73 (01.53)	7.34 (01.87)	
GAF	66.01 (12.76)	76.90 (10.77)	
Mood Stabilizer n (%)	49 (87.50)	32 (78.00)	
Antipsychotic n (%)	45 (80.40)	19 (47.50)	
Antidepressant n (%)	3 (5.80)	4 (9.80)	

Past depressive episode n (%)	1.11 (1.52)		
Psychosis at baseline n (%)	7 (5.40)		
Substance abuse/dependence n (%)	24 (41.37)		

Table 2 – **Patients and healthy subjects Brain Metabolites at baseline and at 1-year.** Values are presented as mean (standard deviation) unless indicated otherwise. NAA: N-acetyl-aspartate; Glx: Glutamate+Glutamine. [a] Repeated measures general linear model. *p<0,05

	Patients (n=41)		Healthy Subjects (n=27)		Main effect of group	Main effect of time	Group-by-time Interaction
METABOLITE	Baseline	Year 1	Baseline	Year 1			
NAA	6.90 (0.81)	6.81 (0.73)	7.01 (0.83)	6.82 (0.90)	F(66,1)=0.151 [a]	F(66,1)=1.309 [a]	F(66,1)=0.182 [a]
Glx	13.25 (2.43)	14.31 (3.04)	13.69 (4.51)	13.08 (2.88)	F(66,1)=0.505 [a]	F(66,1)=0.154 [a]	F(66,1)=2.178 [a]

Supplementary information

Supplementary Methods

To convert the relative water-referenced Glx concentrations generated by LCModel to absolute concentrations in institutional millimolar units, the relative concentrations were multiplied by the mean voxel water concentration (WCONC) and correction factors accounting for water (ATTH2O) and Glx (ATTMET) signal T_1 and T_2 relaxation during the acquisition:

$$\mathbf{WCONC} = 55556\text{mM} \times \left[\mathrm{WC_{wm}} \times \mathrm{F_{wm}} + \mathrm{WC_{gm}} \times \mathrm{F_{gm}} + \mathrm{WC_{csf}} \times \mathrm{F_{csf}}\right]$$

$$\mathbf{ATTH2O} = \mathrm{F_{wm}} \times \left[e^{-\frac{TE}{T2_{wm}}}\left(1 - e^{-\frac{TR}{T1_{wm}}}\right)\right] + \mathrm{F_{gm}} \times \left[e^{-\frac{TE}{T2_{gm}}}\left(1 - e^{-\frac{TR}{T1_{gm}}}\right)\right] + \mathrm{F_{csf}} \times \left[e^{-\frac{TE}{T2_{csf}}}\left(1 - e^{-\frac{TR}{T1_{csf}}}\right)\right]$$

$$\mathbf{ATTMET} = \frac{\mathrm{F_{wm}}}{\left[e^{-\frac{TE}{T2_{wm}}}\left(1 - e^{-\frac{TR}{T1_{wm}}}\right)\right]} + \frac{\mathrm{F_{gm}}}{\left[e^{-\frac{TE}{T2_{gm}}}\left(1 - e^{-\frac{TR}{T1_{gm}}}\right)\right]}$$

For WCONC and ATTH2O:

WC_{type} is the percent concentration wet weight of water in the tissue type (eg. CSF is 99% water so $WC_{csf} = 0.99$)

F_{type} is the volume fraction of each tissue type (eg. if the voxel is composed of 70% WM, $F_{wm} = 0.70$)

TE is the echo time in seconds

$T2_{type}$ is the T_2 relaxation time in seconds of water protons in each tissue type

TR is the repetition time in seconds

$T1_{type}$ is the T_1 relaxation time in seconds of water protons in each tissue type

For ATTMET:

F_{type} is the volume fraction of each tissue type

TE is the echo time in seconds

$T2_{type}$ is the T_2 relaxation time in seconds of Glx in each tissue type

TR is the repetition time in seconds

$T1_{type}$ is the T_1 relaxation time in seconds of Glx in each tissue type

Note: there should not be any metabolites in the CSF so that tissue type is not included.

4. CONSIDERAÇÕES FINAIS

Assim como inicialmente descrito, um dos objetivos específicos desta tese foi avaliar o impacto da obesidade ou sobrepeso na função neurocognitiva de pacientes bipolares após o primeiro episódio de mania. Nossos resultados mostraram que os déficits cognitivos apresentados por pacientes com diagnóstico recente de THB parecem ser independentes de fatores tais como obesidade ou sobrepeso, sugerindo que tais déficits devem-se, mais provavelmente, à doença bipolar *per se*(110). De forma similar, não observamos correlações entre o IMC e a função cognitiva no grupo controle. Alguns estudos, entretanto, têm mostrado o impacto do sobrepeso/obesidade na função cognitiva, em especial, memória e função executiva na população em geral(111–113). Tais discrepâncias poderiam ser justificadas pela falta de poder estatístico e um número relativamente pequeno de sujeitos com sobrepeso ou obesidade incluídos no nosso estudo.

Uma das possíveis explicações para a falta de relação observada entre o sobrepeso/obesidade e cognição no grupo de pacientes poderia ser devido ao efeito dos fármacos usados no tratamento do THB (ex: estabilizadores de humor e antipsicóticos). Todos os nossos pacientes estavam em tratamento conforme as diretrizes CANMAT (Canadian Network for Mood and Anxiety Treatments), internacionalmente reconhecidas, que preconizam o uso de fármacos que parecem estar associados com um aumento ou regularização dos níveis de fatores neurotróficos cerebrais(114–116). A obesidade, por outro lado, tem sido associada com alterações nos fatores neurotróficos, como por exemplo, redução dos níveis de BDNF, importante proteína para a sobrevivência e função neuronal(117–119). Considerando o perfil neuroprotetor dos fármacos usados no tratamento destes pacientes, é plausível considerar que o esperado impacto do IMC sobre a cognição tenha sido suplantado pelo efeito da medicação,

visto que estes indivíduos permaneciam com a função cognitiva preservada. Associado a isto, é possível que o impacto do excesso de peso na função cognitiva dependa do tempo de exposição. Adultos obesos sem outra patologia clínica apresentam déficits nos domínios cognitivos de memória e função executiva. Adicionalmente, pacientes bipolares evidenciam déficits cognitivos tanto logo após o início da doença, quanto após diversos anos de evolução do transtorno. Pacientes bipolares com doença estabelecida e obesos têm menor escore nos testes de fluência verbal, que compõem a função executiva. Portanto, seria esperado que o excesso de peso impusesse déficit adicional na função cognitiva dos pacientes. Pacientes bipolares, obesos ou em sobrepeso, em primeiro episódio de mania apresentam alterações volumétricas nas áreas envolvidas na regulação de humor(36) e nos níveis de metabólitos cerebrais (aumento do Glx - combinação de glutamato e glutamina) do hipocampo(120). Sendo assim, embora a comorbidade com obesidade/sobrepeso imponha disfunções neurocognitivas nos pacientes com THB crônico, no início da doença este déficit ainda não é detectado. No entanto, há evidências de que alterações cerebrais, em termos de anatomia e neuroquímica, estão sendo moduladas por esta comorbidade já nas primeiras manifestações do THB.

Outro potencial fator de modulação da função neurocognitiva na população de pacientes bipolares em primeiro episódio é a presença de trauma infantil. Estudos anteriores têm mostrado que pacientes bipolares com história de trauma na infância, ainda que em estágios iniciais da doença, são mais predispostos a terem disfunções cognitivas evidenciadas por um pior rendimento nos testes de atenção, memória verbal, memória de trabalho e no quoeficiente de inteligência(48).

Além de fatores citados acima, a grande maioria dos estudos tem mostrado uma forte relação entre déficits cognitivos e variáveis relacionadas com a progressão do THB, tais como: tempo de doença e número de episódios(37,41,45,46), sintomas depressivos subclínicos(47), comorbidades(49), entre outros. Nesta linha, um recente estudo longitudinal envolvendo uma

amostra de pacientes bipolares em primeiros episódios, também mostrou um empobrecimento da função cognitiva à medida que aumentam o número de episódios(121). Além disso, em outro estudo, os mesmos autores mostraram uma associação negativa entre o número de episódios e o volume de substância cinzenta em diversas áreas cerebrais (córtex pré-frontal, o cingulado anterior, áreas parietais e temporais)(122). Lopez-Jaramillo et al., (2012)(123) mostraram previamente que a presença de pelo menos dois episódios maníacos contribui de forma substancial para um pior funcionamento cognitivo quando comparados a indivíduos com um primeiro episódio ou controles. Claramente, esses achados sugerem que a progressão da doença bipolar (i.e., número de episódios, tempo de doença) leva a alterações neuroanatômicas e cognitivas que, provavelmente, contribuem para um pior desfecho clínico (Figura 1).

Ainda como objetivos específicos desta tese, investigou-se a relação entre alguns marcadores neuroquímicos (Glx, NAA) e a fisiopatologia do THB, através de um estudo longitudinal de um ano de duração em uma amostra de pacientes bipolares recentemente diagnosticados com o primeiro episódio de mania (124). Assim como demonstrado previamente por Gigante e col., (2014)(125), nosso estudo mostrou que os níveis de Glx e NAA no hipocampo de pacientes bipolares foram similares em comparação a controles saudáveis. Adicionalmente, a evolução dos níveis cerebrais destes metabólitos não foi diferente entre pacientes e indivíduos saudáveis ao longo de um ano de seguimento. Estes dados são relevantes na medida em que informam sobre o status da neuroquímica cerebral dos pacientes nos estágios iniciais da doença sem a interferência de fatores relacionados com a progressão da mesma.

O fato de não termos observado diferenças nos níveis hipocampais de GLx e NAA entre pacientes e controles é interessante quando olhamos para os dados da literatura(80,126). Atmaca e col., por exemplo, (2006)(80) mostrou que pacientes com primeiro episódio maníaco apresentavam uma redução bilateral das taxas de NAA/Cr e NAA/Cho no hipocampo quando comparados aos controles. Ainda, neste estudo observou-se uma associação entre os níveis de

NAA e os sintomas de mania. De forma similar, Blasi et al., (2004)(126) mostrou uma diminuição hipocampal dos níveis de NAA/Cr em pacientes maníacos com sintomas psicóticos comparados aos controles. A divergência entre os dados da literatura e nossos resultados deve ser justificada pelas diferenças entre as amostras estudadas, em especial, em relação aos marcadores de gravidade. Em suma, estes dados sugerem que pacientes em estágios iniciais da doença parecem manter a integridade neuronal no hipocampo e que mudanças nos níveis dos metabólitos cerebrais devam ocorrer com a progressão da doença.

5. CONCLUSÕES

Concluindo, cabe ressaltar que o estudo de populações de pacientes bipolares recentemente diagnosticados oferece a oportunidade de se avaliar o fator em estudo em indivíduos com menor exposição a variáveis já conhecidas e associadas à progressão da doença, tais como número de episódios, tempo de doença, persistência de sintomas subclínicos, comorbidades, entre outros. Em uma amostra de pacientes bipolares recentemente diagnosticada, mostramos que as alterações cognitivas observadas foram independentes de fatores metabólicos tais como sobrepeso/obesidade e mais relacionadas com o próprio transtorno. Além disso, não encontramos alterações nas concentrações de metabólitos cerebrais no hipocampo destes pacientes. Finalmente, nossos dados apontam para a importância do diagnóstico e intervenção precoce no THB com o objetivo central de manter a integridade neuronal e, consequentemente, um melhor funcionamento cognitivo e psicossocial.

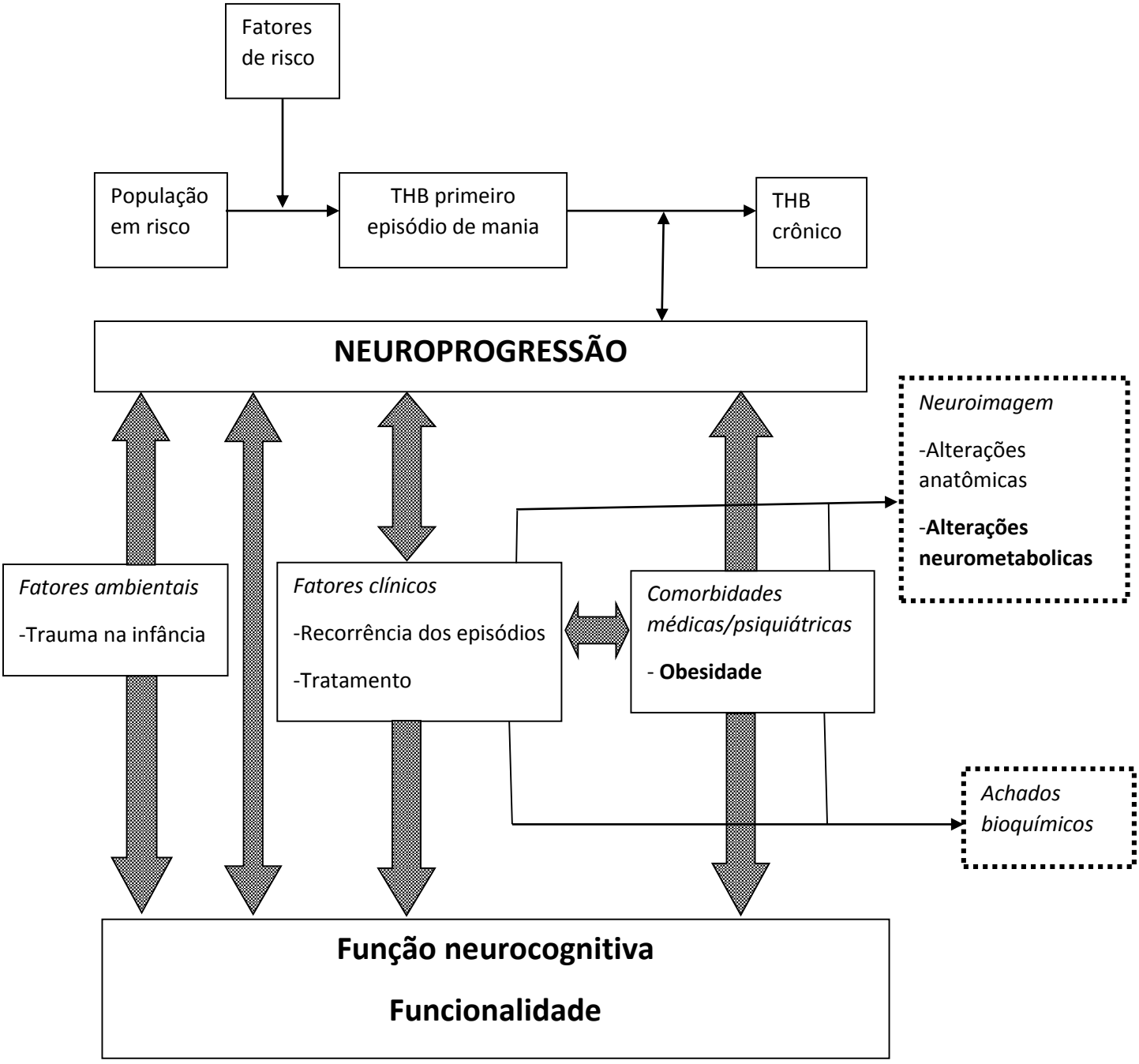

Figura 1. Fatores associados à neuroprogressão do THB. A população em risco de desenvolver THB, quando exposta aos fatores de risco, apresenta o primeiro episódio de mania. A doença cronifica na medida em que novos episódios de humor ocorrem. A neuroprogressão modula o curso do THB, sendo influenciada por fatores clínicos, ambientais e comorbidades médicas gerais e psiquiátricas. A função neurocognitiva e a funcionalidade dos pacientes é influenciada por fatores clínicos e ambientais, bem como pelas comorbidades. A neuroprogressão pode ser evidenciada através de achados bioquímicos e por exames de neuroimagem.

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