PONTIFÍCIA UNIVERSIDADE CATÓLICA DO RIO GRANDE DO SUL

FACULDADE DE BIOCIÊNCIAS

PROGRAMA DE PÓS-GRADUAÇÃO EM BIOLOGIA CELULAR E MOLECULAR

ESTUDO DE ASSOCIAÇÃO ENTRE O ÁCIDO ÚRICO E O TEMPERAMENTO

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Porto Alegre

2008

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Projeto de pesquisa das atividades desenvolvidas com a finalidade de obtenção de Título de Mestre em Biologia Celular e Molecular pelo PPGBCM - PUCRS

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Porto Alegre

2008

Agradecimentos

Aos meus pais, que tornaram isto tudo possível;

Ao meu orientador Diogo Rizzato Lara, por ter prontamente aceitado orientar-me, e por todo o auxílio e amizade durante a confecção deste trabalho;

Ao meu irmão Cláudio Lorenzi Ferreira, minha cunhada Elisabete Lorensi Ferreira e minha querida amiga Paula Simas Rocha, pela amizade e motivação durante o desenvolvimento do estudo.

À Daniela Borba por ter ajudado significativamente na validação da escala de temperamento.

Ao grupo de pesquisa que participo e em especial à Miriam Brusntein e Luísa Bisol pelo enorme incentivo e ajuda na preparação da defesa do trabalho.

Ao meu colega Gustavo Dutra, por ter aberto seu laboratório para coleta e análise dos dados desta pesquisa.

Às minhas colegas de curso, Josiane Bandinelli, Caroline Ruck e Liana Fernandez, pela amizade e aprendizado adquirido no decorrer do curso.

SUMÁRIO

LISTA DE ABREVIATURAS E SIGLAS

ADP - Adenosina difosfato.
AMP- adenosina monofosfato.
AMPc- Adenosina monofosfato cíclico.
APRT-adenina fosforribosil transferase.
ATP- Adenosina trifosfato.
AU **–** Ácido úrico.
AUS – Ácido úrico sérico.
DNA- ácido desoxirribonucleico.
ETAFE- Escala de temperamento afetivo e emocional.
GDP- guanosina difosfato.
GMP - guanosina monofosfato.
GTP- guanosina trifosfato.
HRPT - hipoxantina fosforribosil transferase.
IMP - inosina monofosfato.
NAD+ - dinucleotídeo nicotinamida-adenina .
PRPP - amidotransferase 5'-fosforribosil-1-pirofosfato.
PRS - PRPP sintetase.
RNA- ácido ribonucleico.
TDAH - transtorno de déficit de atenção.
XDH- xantina desidrogenase.
XO - xantina oxidase.
XOR-xantina oxireductase.

RESUMO

Lorenzi, Taise Michele. Lara, Diogo. Estudo de Associação entre ácido úrico e temperamento. Porto Alegre - RS, 2008. 78p. Dissertação de Mestrado – Faculdade de Biociência - Programa de Pós-Graduação em Biologia Celular e Molecular, Pontifícia Universidade Católica do Rio Grande do Sul.

O temperamento diz respeito à natureza emocional e ao humor basal. Propusemos uma integração dos construtos de temperamentos emocional e afetivo baseado no princípio de ativação (vontade e raiva) e inibição (medo) como as duas forças emocionais principais, que são reguladas por um sistema de controle (atenção e dever). A interação dessas forças resultaria no padrão de humor basal ou temperamento afetivo. O ácido úrico (AU) é o produto final do metabolismo de purinas e já foi associado com variáveis psicológicas como alta energia/vontade, afeto positivo, sucesso, alto desempenho, status social mais elevado e liderança. No presente estudo avaliamos 129 voluntários (44 homens e 85 mulheres) com a Escala de Temperamento Afetivo e Emocional, níveis séricos de AU e um questionário geral de saúde. Na amostra total, os níveis séricos de AU foram significativamente correlacionados com desinibição ($r=0.36$, $p<0.001$) e vontade ($r=0.25$, $p<0.01$), mas não com controle, raiva ou qualquer dos temperamentos afetivos. Entre homens, encontramos tendências de correlação ($p >0.05$ and <0.07) para controle ($r=0.27$) e os temperamentos afetivos irritável ($r=0.29$) e hipertímico ($r=0.27$). Entre mulheres, uma correlação significativa foi observada somente com desinibição ($r=0.34$, $p=0.001$). O tertil mais alto dos homens (AU sérico>6.0 mg/ml, n=16) apresentou significativamente mais vontade (29.9±5.9 X 26.0±3.6, $p=0.01$) e controle no nível de tendência (21.2±3.1 X 19.3±2.9, $p=0.054$) do que o resto da amostra. Entre mulheres, o tertil superior (AU sérico>4.0 mg/ml, n=29) apresentou maiores escores de desinibição (20.7±4.9 X 17.9±3.6, $p<0.01$) e mais frequentemente escolheram os temperamentos afetivos hipertímico (8/26 X 6/59, $p=0.023$) e irritável (7/26 X 5/59, $p=0.031$) do que o resto da amostra. Em suma, esses resultados confirmam que traços externalizados de temperamento estão associados com níveis mais altos de AU tanto em homens como em mulheres.

Palavras-chave

Temperamento, Ácido Úrico.

ABSTRACT

Temperament relates to the emotional nature and the quality of the prevailing mood. We have proposed an integration of emotional and affective temperament constructs based on the principle that activation (anger and drive/pleasure) and inhibition (fear) are the two main *emotional* forces, which are integrated by the control system (attention and duty). Their interaction would result in the prevailing mood or affective temperaments. Uric acid (UA) is the end-product of purine metabolism and has been associated with psychological features such as high energy/drive, positive affect, achievement, good performance, higher social status and leadership. In this study we evaluated 129 subjects (44 males, 85 females) with the Combined Emotional and Affective Temperaments Scale, serum UA levels and a general health questionnaire. In the whole sample, serum UA levels were significantly correlated with disinhibition ($r=0.36$, $p<0.001$) and drive ($r=0.25$, $p<0.01$), but not with control, anger or any of the affective temperament scores. Among males, we found correlations at trend level ($p >0.05$ and <0.07) for control ($r=0.27$), irritable ($r=0.29$) and hyperthymic ($r=0.27$) affective temperaments. Among females, a significant correlation was found only with disinhibition ($r=0.34$, $p=0.001$). The top tertile of males (serum UA>6.0 mg/ml, n=16) had significantly higher drive (29.9±5.9 X 26.0±3.6, $p=0.01$) and higher control at trend level (21.2±3.1 X 19.3±2.9, $p=0.054$) than the rest of the sample. Among women, the top tertile (serum UA>4.0 mg/ml, n=29) showed higher disinhibition scores (20.7±4.9 X 17.9±3.6, $p<0.01$) and more choices of hyperthymic (8/26 X 6/59, $p=0.023$) and irritable temperaments (7/26 X 5/59, $p=0.031$) than the rest of the sample. In conclusion, these results confirm that externalized traits of temperament are associated with higher serum UA levels both in men and women.

Keywords

Temperament, Uric Acid.

1. INTRODUÇÃO

1.1. TEMPERAMENTO

O temperamento diz respeito ao padrão emocional básico, que confere características de variações afetivas que tendem a perdurar durante toda a vida (Akiskal, 2005). O temperamento também pode ser considerado como a base do humor, do comportamento e da personalidade (Lara et al., 2006b). Alguns modelos foram propostos para caracterizá-lo e conceituá-lo.

O modelo psicobiológico dimensional de temperamento descrito por Cloninger e colaboradores (1993) (Cloninger et al., 1993) caracteriza o temperamento como os traços emocionais básicos que têm herança predominantemente genética. Cada dimensão do temperamento está relacionada às emoções básicas de medo (evitação de dano), raiva (busca de novidades), apego (dependência de reforço social) e ambição ou determinação (persistência). Nesse modelo, as dimensões apresentam distribuição normal, contemplando tanto a normalidade quanto as suas variações.

Já Akiskal concebe o temperamento a partir do padrão afetivo básico, que pode ser hipertímico, ciclotímico, irritável, depressivo ou ansioso (Akiskal, 2005). Esse modelo foi inspirado nas observações de (Kraeplin, 1921) e está mais voltado para a caracterização de pacientes com transtornos de humor, portanto carece de uma proposta para pessoas sem transtornos psiquiátricos.

Medo, vontade e raiva são as emoções mais básicas que constituem o temperamento, que são moduladas por uma função de controle (Lara and Akiskal, 2006). O modelo dimensional baseado em traços de medo, vontade/raiva proposto recentemente (Lara and Akiskal, 2006) adapta os conceitos de evitação de dano e busca de novidades de Cloninger e busca combinar as vantagens dessa abordagem ao modelo de Akiskal para temperamentos afetivos. Essa remodelação tem como objetivo diminuir as

limitações de ambos os modelos. Este novo modelo integrativo incorpora as dimensões normais e patológicas, concebe transtornos de humor, comportamento e personalidade concomitantemente, e fundamenta-se em funções cerebrais nos níveis comportamental, cognitivo, neuroquímico e anatômico.

A combinação dos traços de ativação (vontade/raiva), inibição (medo) e controle (dever-atenção) geraria os principais tipos de temperamentos afetivos propostos (Tabela 1) (Lara et al., 2006b).

Tabela 1: Temperamentos afetivos modulados por ativação e inibição emocionais

Temperamento afetivo	Ativação (vontade)	Ativação (raiva)	Inibição (medo)	Controle (dever-atenção)
Depressivo	↓↓	↔	↑	↔
Ansioso	↔	↔	↑	↔
Apático	↓	↓	↔	↓↓
Ciclotímico/disfórico	↔	↑↑	↔	↓
Eutímico	↑	↓	↔	↑
Irritável	↑	↑↑	↔	↑
Lábil	↓	↑	↔	↓↓
Desinibido	↔	↔	↓	↓
Hipertímico	↑↑	↔	↓↓	↑

↓ - baixo, ↓↓ - muito baixo, ↑ - alto, ↑↑ - muito alto,↔ médio

Esses temperamentos afetivos formariam a predisposição a transtornos

psiquiátricos, como transtorno bipolar do tipo I em hipertímicos e irritáveis, do tipo II em irritáveis e ciclotímicos, transtornos de ansiedade em ansiosos, depressão maior em depressivos, e TDAH (transtorno de déficit de atenção e hiperatividade) e seus subtipos em lábeis, apáticos e desinibidos (Lara and Akiskal, 2006).

Para testar o novo modelo, foi criada e validada a Escala de Temperamento Afetivo e Emocional (ETAFE - Anexo A) com questões auto-aplicáveis relacionadas aos traços de medo, raiva, vontade e controle, assim como aos temperamentos afetivos (manuscrito submetido – Anexo B). Esta escala possui questões auto-aplicáveis e possibilita a correlação entre os temperamentos afetivos e os traços emocionais de medo, vontade, raiva e controle. De maneira geral, as combinações dos traços de medo, vontade/raiva e controle proposta pelo modelo e os 10 tipos de temperamentos afetivos foi essencialmente confirmada.

1.2. PURINAS E ÁCIDO ÚRICO

As purinas são fundamentais nos processos relacionados à energia celular (principalmente ATP e ADP), na sinalização transmembrana (GTP e GDP), na sinalização intracelular (AMPc), e como parte do DNA e do RNA (adenina e guanina) (Hediger et al., 2005).

O produto final do metabolismo de purinas no ser humano é o ácido úrico (AU). O AU é um ácido fraco (pKa 5,8) que existe em grande quantidade como urato (sua forma ionizada) em pH fisiológico (Choi et al., 2005) e livre de qualquer proteína carreadora no plasma sanguíneo (Ngo and Assimos, 2007). A biosíntese de ácido úrico é catalisada pela enzima xantina oxidase ou pela sua isoforma, a xantina desidrogenase (Choi et al., 2005).

A excreção do ácido úrico permite eliminar o nitrogênio excedente do organismo (Pillinger et al. 2007). A produção endógena diária de urato gira em

torno de 300 a 400 mg, porém a excreção total pode variar dependendo da ingestão de purinas na alimentação (Ngo and Assimos, 2007). Os rins são responsáveis por 70% da excreção diária do AU e o restante é eliminado pelos intestinos, pele, cabelo e unhas (Anzai et al., 2005). No intestino, o AU é degradado em dióxido de carbono e amônia que são reabsorvidos ou liberados como gás intestinal.

Em muitos peixes, anfíbios e mamíferos não primatas, o ácido úrico é degradado pela uricase ou urato oxidase, enzima que catalisa a conversão de urato em alantoína (Choi et al., 2005). Na maioria dos mamíferos, a conversão de ácido úrico em alantoína resulta em níveis muito baixos de ácido úrico sérico (AUS) (menos do que 1mg/dL) (Eggebeen, 2007). A alantoína, por ser uma substância mais solúvel que o urato, é mais facilmente eliminada na urina (Terkeltaub et al., 2006).

Em humanos e na grande maioria dos macacos, o gene que produz a uricase sofreu mutações que o deixaram inativo (Wu et al., 1989). A vantagem evolutiva da inatividade da uricase em humanos e na maioria dos macacos não está clara, porém uma das hipóteses é que o urato pode remover a molécula de oxigênio e radicais livres tão efetivamente quanto a vitamina C (Choi et al., 2005). Um estudo proposto por Watanabe e colaboradores (Watanabe et al., 2002) sugere uma especial vantagem evolutiva na perda da uricase em humanos e em macacos. Eles notaram que no período Miocênico, nossos ancestrais tinham uma alimentação vegetariana, particularmente pobre em sódio. O nefrologista Richard Johnson, baseado nesses achados, propõem que a hipotensão é ocasionada pela dieta pobre em sódio. Mais adiante, Johnson hipotetizou que a perda da uricase e o acúmulo de AU pode, de certo modo, ter compensado o problema da hipotensão. E essa particularidade ocorre apenas em humanos e macacos porque esses são os únicos mamíferos que gastam a maior parte do tempo como bípedes e com isso são mais dependentes de maior pressão sanguínea que mantém a perfusão cerebral (Pillinger et al., 2007).

Watanabe e colaboradores (2002) propuseram que a perda da uricase

nos humanos e macacos favoreceu a manutenção da pressão sanguínea para manter a perfusão cerebral na postura bípede, especialmente em épocas de dieta pobre em sódio.

1.2.1. Síntese de novo e via de salvamento de purinas

A síntese de novo de purinas ocorre através de vários passos e requer a contribuição de 4 aminoácidos, sendo 1 molécula de amidotransferase 5'-fosforribosil-1-pirofosfato (PRPP), 2 folatos e 3 moléculas de adenosina trifosfato (ATP) para sintetizar uma molécula de inosina monofosfato (IMP) (Torres and Puig, 2007). A PRPP é produzida pela adição de um grupo fosfato do ATP ao açúcar modificado ribose-5-fosfato (Choi et al., 2005). O ponto inicial da síntese de novo é a conversão da ribose-5-fosfato (uma pentose derivada do metabolismo glicídico) em PRPP e fosforribosilamina, que será transformada em IMP. A partir desse IMP são derivados o AMP (adenosina monofosfato), o GMP (guanosina monofosfato), as bases púricas (adenina e guanina – úteis na síntese de DNA e RNA) e a inosina (que será degradada em hipoxantina e xantina até ácido úrico) (Cammalleri and Malaguarnera, 2007).

Já a via de salvamento é mediada pela hipoxantina fosforribosil transferase (HRPT) e também pela adenina fosforribosil transferase (APRT). A HRPT catalisa a síntese de salvamento de IMP e GMP a partir das bases hipoxantina e guanina respectivamente (Torres and Puig, 2007). Somente uma pequena parte dos pacientes que sofrem de superprodução de ácido úrico possuem problemas genéticos, tais como a super atividade da enzima PRS (PRPP sintetase) e a deficiência da enzima HRPT (que resulta no acúmulo de hipoxantina e guanina e que são facilmente convertidas em ácido úrico através da enzima xantina oxidase) (Choi et al., 2005).

A deficiência na enzima HRPT leva à síndrome de Lesch-Nyhan, que caracteriza-se por hiperuricemia e hiperuricosúria e algumas manifestações neurológicas e psiquiátricas, como retardo mental, auto-mutilação e

coreoatetose (Jinnah et al., 2006).

Uma elevada atividade na enzima APRT pode contribuir para a superprodução de purinas (Torres and Puig, 2007). Condições associadas com a degradação do ATP conduzem ao acúmulo de adenosina difosfato (ADP) e adenosina monofosfafto (AMP), que podem ser rapidamente degradas até ácido úrico, podendo também causar hiperuricemia (Choi et al., 2005).

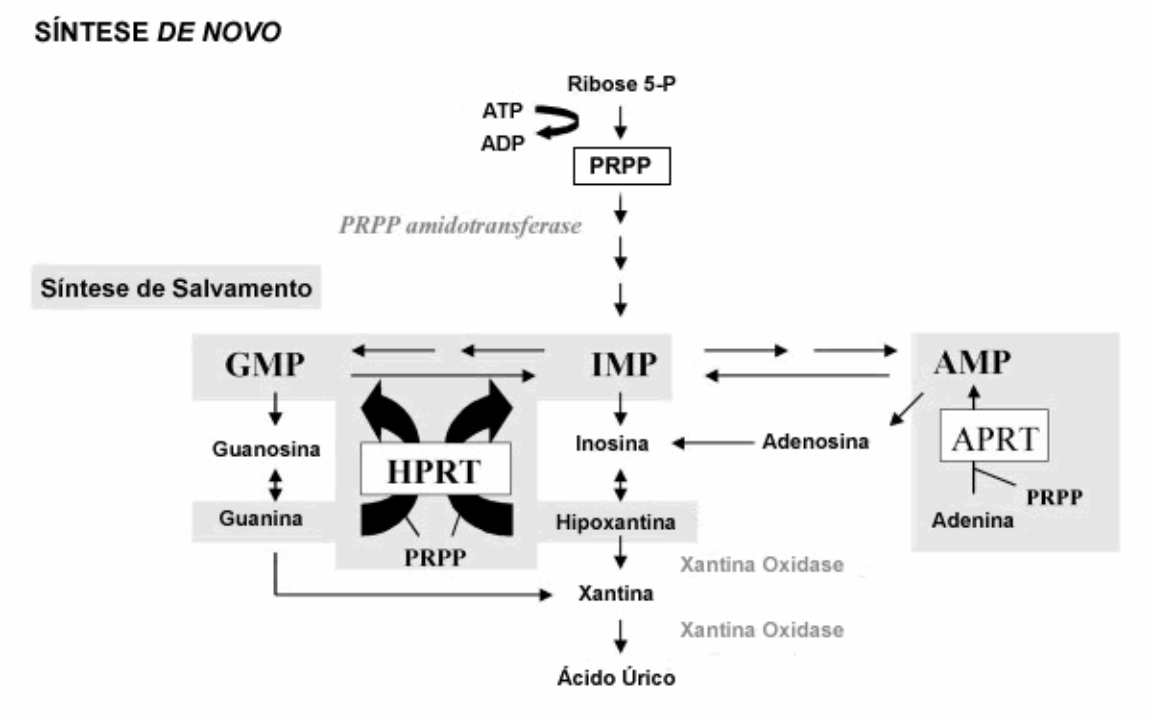

Figura 1 – Síntese de novo e de salvamento de purinas (retirado de (Torres and Puig, 2007)**.**

Entre as purinas, a adenosina é um importante neuromodulador a ser mais estudado na psiquiatria, uma vez que modula vários sistemas neurotransmissores e tem importantes funções por si só (Fredholm et al., 2005). A cafeína, que é um bloqueador não seletivo de receptores adenosinérgicos (A1 e A2), pode desencadear ou agravar vários sintomas associados à raiva e ao medo (ansiedade, ataques de pânico, hipomania e estados mistos) (Lara and Akiskal, 2006). Em contraste, agonistas adenosinérgicos apresentaram efeitos ansiolíticos, anti-agressivos e antipsicóticos (Fredholm et al., 2005). A ausência

de receptores A1 e A2 em camundongos foi associado ao comportamento agressivo e ansioso e à instabilidade emocional (Ledent et al., 1997; Gimenez-Llort et al., 2002; Lang et al., 2003).

1.3. HIPERURICEMIA E GOTA

Em 1776, o químico sueco Scheele (Scheele, 1776) identificou ácido úrico na urina de pacientes com gota. Em 1797, o químico inglês, Wollaston (Woolaston, 1797) percebeu que os tumores nas articulações causados pela doença continham ácido úrico (Nuki and Simkin, 2006). Fischer, no mesmo século, determinou a estrutura bioquímica do ácido úrico e sua relação com as purinas (Katz and Weiner, 1972).

Os humanos são os únicos mamíferos que desenvolvem gota, provavelmente em função dos altos níveis de uricemia em comparação a outras espécies (Johnson and Rideout, 2004), uma vez que em outros animais o ácido úrico é degradado pela uricase até alantoína. A ausência de uricase, combinada com a grande reabsorção do urato filtrado, resulta em altos níveis de ácido úrico no sangue (de 2 a 7 mg/dl normalmente, aproximadamente 10 vezes mais que em outros mamíferos) (Wu et al., 1992).

A hiperuricemia caracteriza-se por concentrações de ácido úrico sérico maiores que 7 mg/dl (miligramas por decilitro) em homens (Iwanaga et al., 2005) e maiores que 6 mg/dl em mulheres. É o principal fator de risco para desencadear a gota. Em um estudo de larga escala, com duração de 5 anos, o risco de desencadear a doença foi de 0.6% para os indivíduos que apresentaram níveis de AUS menores que 7 mg/dL e de 30.5% para aqueles que tinham níveis de AUS iguais ou maiores que 10 mg/dL (Falasca, 2006). É importante ressaltar que nem todos que desenvolvem hiperuricemia, desenvolvem gota (Hediger et al., 2005). Os níveis de AUS se elevam após a puberdade em homens e após a menopausa em mulheres, fatos que sugerem alguma relação com os hormônio sexuais. Na população geral, os níveis de

ácido úrico apresentam uma distribuição normal unimodal, sugerindo herança poligênica. A alimentação com altos níveis de purinas e o álcool, principalmente cerveja, que contém muita guanosina (Choi et al., 2005) pode causar hiperuricemia (Katz and Weiner, 1972).

A hiperuricemia resulta da superprodução de ácido úrico (que ocorre em 10% dos casos e está associada a defeitos congênitos e também relacionada com problemas no metabolismo de purinas), da baixa excreção do ácido úrico realizada pelos rins (que ocorre em 90% dos casos) ou de ambas as possibilidades (Choi et al., 2005). Uma pequena parte dos pacientes que apresentam superprodução de ácido úrico possuem problemas congênitos, tais como superatividade do PRS (enzima que sintetiza PRPP) ou deficiência na enzima HPRT.

Na gota, quando os limites locais de AUS ultrapassam o ponto crítico de solubilidade, os cristais monossódicos de urato depositam-se nas articulações, rins e tecidos moles. O acúmulo desta substância pode levar a artrites, formação de massa de tecido mole (também chamado de tofo), nefrolitíases e nefropatia de urato (Eggebeen, 2007). No entanto, nem todas as pessoas que possuem hiperuricemia desenvolvem a doença. Não há diferença entre homens e mulheres na chance de desenvolver gota nos vários níveis de ácido úrico (Katz and Weiner, 1972).

1.4. RELAÇÃO ENTRE HIPERURICEMIA, GOTA E VARIÁVEIS PSICOLÓGICAS

Hipócrates e outros médicos da antiguidade estavam familiarizados com os sinais e sintomas da gota, mas foi Paulo de Aegina, mil anos depois de Hipócrates, que observou que fatores emocionais poderiam precipitar ataques da doença. A partir daí também observou-se que excessos alimentares também poderiam induzir um episódio agudo de gota (Katz and Weiner, 1972).

Um fato curioso e importante é que muitas pessoas notáveis sofriam de gota, como: Édipo, Ulisses, Alexandre o Grande, Michelangelo, a família Medicy, Henrique VII e VIII, João Calvino, Martin Luther, Luis XIV, Isaac Newton, Thomas Sydenham, Benjamim Franklin e Theodore Roosevelt. Cullen (1778) observou que a gota ocorria mais freqüentemente “entre os sábios do que entre os tolos”, estando de alguma forma correlacionada com fama e notoriedade (Katz and Weiner, 1972).

Alguns estudos já a partir da década de 50 mostraram a correlação entre os níveis de AUS e aspectos sociais, psicológicos e de personalidade associados a sucesso, energia e alto desempenho (Rahe et al., 1974) e (Katz and Weiner, 1972). No entanto, nos últimos vinte anos essa área foi pouco estudada.

Um estudo realizado em 1959 (Stetten and Hearon, 1959) relacionou a inteligência com os níveis de AUS. Já Dunn e colaboradores (Dunn et al., 1963) relataram a correlação entre classe social e níveis de AUS. Consistente com outros estudos da literatura, eles mostraram que a variação diurna ou em períodos maiores de tempo nos níveis de AUS era insignificante em voluntários homens adultos saudáveis sob circunstâncias normais. Nesse estudo, dividiram os indivíduos nos seguintes grupos: gerentes, operários (artesões), cientistas (físicos e químicos) e estudantes (de medicina e ensino médio). Foram observados níveis mais altos de AUS entre os gerentes (5.73 mg%) comparados aos dos operários (4.77 mg%) e também entre os indivíduos com hiperuricemia contidos nesses dois grupos (42.5% e 12%, respectivamente). A média dos níveis de AUS dos cientistas (5.34 mg%) em relação aos artesões mostrou-se significativamente alta, porém mais baixa em relação aos executivos. A média de cientistas que apresentavam hiperuricemia era de 26.3%. Quanto ao grupo dos estudantes, não encontraram correlação entre os níveis de AUS e o exame de adminissão na escola de medicina porém constataram uma correlação entre os níveis de AUS e os altos escores em testes de inteligência. Encontraram também correlação positiva entre os níveis de AUS e a quantidade de atividades

extracurriculares. Os estudantes que apresentavam níveis altos de AUS tinham um perfil de maior liderança e responsabilidade.

Em 1966, Brooks e Muller (Brooks and Mueller, 1966) estudaram covariância entre níveis de AUS e características de vontade ou *drive*, ativação comportamental, realização e liderança positiva. Para isso realizaram um estudo com 57 professores da Universidade de Michigan. Observaram que a média de níveis de AUS encontrada no grupo de professores era de 5.66 mg% comparada ao grupo de gerentes e cientistas do estudo de Dunn e colaboradores. Perceberam também que a média de AUS no grupo de professores titulares era de 5,95 mg% enquanto que nos professores assistentes ou associados era de 5,50 mg%. Observaram relação entre os níveis de AUS e os itens de comportamento (*drive*, ativação comportamental, realização e liderança positiva) com um coeficiente de correlação de 0.66 ($p < 0.001$). Encontraram também correlação negativa entre níveis de AUS e níveis séricos de colesterol, e positiva entre os níveis de AUS com obesidade, apetite e consumo de álcool.

Outro estudo realizado na mesma época encontrou correlação positiva entre altos níveis de AUS, liderança e doenças coronárias (Montoye, 1967). Esses resultados foram confirmados também por Mueller e colaboradores (Mueller et al., 1970), mostrou a associação positiva entre altos níveis de AUS e variáveis psicossociais de vontade ou *drive*, realização e liderança.

Em uma pesquisa desenvolvida por Lanese e associados (Lanese et al., 1969), com um grupo de 210 empregados do sexo masculino, com idades variando de 40 a 59 anos, foi feito uma classificação por fatores de risco de doenças coronárias. Dos indivíduos que foram selecionados, 19,5% apresentavam hiperuricemia. Esses indivíduos foram classificados como sendo do grupo experimental enquanto que os demais indivíduos foram classificados como pertencentes do grupo controle. Identificou-se os indivíduos com altos níveis de AUS mudavam de emprego com mais freqüência, fumavam mais, eram obesos, tinham menos estabilidade na vida e tinham pressão arterial mais

elevada. Os autores desse estudo observaram que havia uma associação entre hiperuricemia e certos traços de comportamento, mas as causas e efeitos não puderam ser determinadas somente pelas covariações desses fatores.

Kasl e colaboradores (Kasl et al., 1966) encontraram uma correlação entre os níveis altos de ácido úrico com desejo de realização e de sucesso. Além disso, foi observada uma correlação positiva entre níveis de AUS e obesidade. O valor de AUS também se relacionou inversamente com os níveis séricos de colesterol. Esse estudo foi realizado em uma escola e também identificou que alunos que tinham notas altas apresentam níveis mais altos de ácido úrico e mais baixos de colesterol. Outro estudo realizado com 66 marinheiros demonstrou um aumento nos níveis de ácido úrico nos marinheiros que tinham grandes níveis de humor positivo (Rahe et al., 1976).

Em conjunto, estes estudos sugerem várias correlações entre os valores de AUS e variáveis sociais, psicológicas e de personalidade. No entanto, esses estudos utilizaram instrumentos de avaliação psicológica pontuais, baseados em construtos psicológicos antigos, e poucos estudos incluíram mulheres.

Já entre os transtornos psiquiátricos, o metabolismo purinérgico foi associado a humor patológico por estar envolvido no aumento da excreção de ácido úrico durante a fase de remissão do episódio maníaco (Anumonye et al., 1968). Cobb (1971) observou que indivíduos que apresentavam perfis emocionais mais lábeis tinham uma tendência à variação diária nos níveis de AUS (Rubin et al., 1969).

Pfeiffer e colaboradores (1969) observaram elevados níveis de AUS em pacientes esquizofrênicos não tratados, que foi interpretado como relacionado ao cérebro em estado de alta excitação. Os níveis diminuíram com o tratamento exceto em 3 pacientes que tinham síndrome de Tourette. Os autores sugeriram que o estresse causado pelo estado psicótico havia aumentado o *turnover* de ácidos nucléicos no SNC e que contribuíram para a elevação dos níveis de AUS (Pfeiffer et al., 1969).

1.5. ALOPURINOL: UM FÁRMACO HIPOURICEMIANTE

A xantina oxidase (XO) e xantina desidrogenase (XDH) são formas interconvertidas de uma mesma enzima conhecida como xantina oxireductase (XOR) (Pacher et al., 2006.). A diferença entre essas enzimas é que XO pode reduzir apenas oxigênio, enquanto que XDH pode reduzir tanto oxigênio como NAD+ (Stirpe and Della, 1969). No entanto ambas as formas catalisam a conversão de hipoxantina em xantina e xantina em AU nas duas reações finais da via de degradação de purinas (Berry and Hare, 2004).

A superprodução de ácido úrico pode ser controlada com o fármaco alopurinol, um inibidor de xantina oxidase que bloqueia as conversões de xantina em hipoxantina e desta em ácido úrico (Hediger et al., 2005). Ao reduzir os níveis de AUS, o tratamento com alopurinol previne as doenças associadas à hiperuricemia, como gota e nefrolitíase (Torres and Puig, 2007).

Na neuropsiquiatria foi observado que o alopurinol tem atividade anticonvulsivante, antiagressiva, antipsicótica e antimaníaca possivelmente decorrente do efeito inibitório na degradação de purinas, aumentando a atividade adenosinérgica (Lara et al., 2006a).

Na esquizofrenia o alopurinol foi eficaz como tratamento adjuvante em casos isolados de pacientes esquizofrênicos (Machado-Vieira and Lara et al., 2001) e em 2 ensaios clínicos recentemente publicados (Akhondzadeh et al., 2005; Brunstein et al., 2005).

Foi observada melhora após o tratamento com alopurinol em dois pacientes com mania refratária associada a hiperuricemia (Machado-Vieira et al., 2001). Recentemente esses achados foram confirmados em dois ensaios clínicos randomizados em que o alopurinol foi comparado a placebo como medicação adjuvante ao lítio na mania aguda (Akhondzadeh et al., 2006; Machado-Veira et al., 2008).

2. OBJETIVO

O objetivo principal desta pesquisa é avaliar a correlação entre os níveis de AUS e as medidas de temperamento avaliadas com a Escala de Temperamento Emocional e Afetivo recentemente criada e validada pelo nosso grupo de pesquisa. Desse modo, pretendemos especificar quais traços de temperamento estão associados aos níveis ácido úrico utilizando um instrumento psicológico que avalia globalmente variáveis emocionais e afetivas, tanto dimensional como categorialmente.

3. ARTIGO

Manuscrito a ser submetido para o Journal of Affective Disorders.

CORRELATION OF SERUM URIC ACID LEVELS WITH EMOTIONAL AND AFFECTIVE TEMPERAMENTS

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ABSTRACT

Temperament relates to the emotional nature and the quality of the prevailing mood. We have proposed an integration of emotional and affective temperament constructs based on the principle that activation (anger and drive/pleasure) and inhibition (fear) are the two main *emotional* forces, which are integrated by the control system (attention and duty). Their interaction would result in the prevailing mood or affective temperaments. Uric acid (UA) is the end-product of purine metabolism and has been associated with psychological features such as high energy/drive, positive affect, achievement, good performance, higher social status and leadership. In this study we evaluated 129 subjects (44 males, 85 females) with the Combined Emotional and Affective Temperaments Scale, serum UA levels and a general health questionnaire. In the whole sample, serum UA levels were significantly correlated with disinhibition ($r=0.36$, $p<0.001$) and drive ($r=0.25$, $p<0.01$), but not with control, anger or any of the affective temperament scores. Among males, we found correlations at trend level ($p >0.05$ and <0.07) for control ($r=0.27$), irritable ($r=0.29$) and hyperthymic ($r=0.27$) affective temperaments. Among females, a significant correlation was found only with disinhibition ($r=0.34$, $p=0.001$). The top tertile of males (serum UA>6.0 mg/ml, n=16) had significantly higher drive (29.9±5.9 X 26.0±3.6, $p=0.01$) and higher control at trend level (21.2±3.1 X 19.3±2.9, $p=0.054$) than the rest of the sample. Among women, the top tertile (serum UA>4.0 mg/ml, n=29) showed higher disinhibition scores (20.7±4.9 X 17.9±3.6, $p<0.01$) and more choices of hyperthymic (8/26 X 6/59, $p=0.023$) and irritable temperaments (7/26 X 5/59, $p=0.031$) than the rest of the sample. Controlling for daily intake of meat and grains, which could lead to higher UA levels, did not change these results using a general linear regression model. In conclusion, these results confirm that externalized traits of temperament are associated with higher serum UA levels both in men and women.

INTRODUCTION

Temperament relates to the emotional nature and the quality of the prevailing mood, being mostly inherited and relatively stable over time (Allport ,1961; Cloninger et al., 1993). Two of the most intensively studied temperament constructs in psychiatry are the psychobiological model by Cloninger, with a focus on behaviors and basic emotions (Cloninger et al., 1993), and the model of affective temperaments by Akiskal, based on Kraepelin fundamental states. Recently we have proposed an integration of emotional and affective temperament constructs with clinical (Lara et al., 2006), neurobiological and treatment implications (Lara and Akiskal, 2006). This model is based on the principle that activation (anger and drive/pleasure) and inhibition (fear) are the two main *emotional* forces, which are integrated by the control system (attention and duty). Their interaction would result in the prevailing mood or affective temperament, namely depressive, anxious, apathetic, cyclothymic, dysphoric, euthymic, irritable, labile, desinhibited and hiperthymic (Lara et al., 2006).

Uric acid is the end-product of purine metabolism. Purines are essential for all human cells, but the CNS seems to be particularly affected in situations of purine metabolism dysfunction, such as Lesch-Nyhan disease. This disorder is due to impaired purine salvage, leading to hyperuricemia and reduced purine pool, with severe consequences such as self-mutilation, mental retardation and choreatethosis (Oslon and Houlihan, 2000). Purinergic neurotransmission mediated mainly by ATP on P2 receptors and adenosine on P1 receptors have an important role on its own and by modulating other neurotransmitters (Burnstock, 2007). Behaviorally, the purinergic system affects sleep, motor activity, cognition, attention, aggressive behavioral and mood (Lara et al., 2002). Interestingly, the xanthine oxidase inhibitor allopurinol, which inhibits uric acid production, has been shown to produce antimanic (Lara et al., 2002; Machado-Veira et al., 2008) and antipsychotic effects (Akhondzadeh et al., 2005; Brunstein et al., 2005).

Several studies, mostly from the 60's, have shown an association of

serum uric acid with behavioral and psychological traits such as high energy/drive, positive affect, achievement, good performance, higher social status and leadership (Katz and Weiner, 1972). To our knowledge, there are no studies evaluating the relationship between uric acid levels and modern constructs of temperament.

We have recently developed and validated the Combined Emotional and Affective Temperament Scale (CEATS), which integrates both Cloninger's and Akiskal's temperament constructs in a single and shorter scale. In this study, we assessed the relationship between uric acid levels and temperament variables in a sample from the general population.

Materials and Methods

This study was approved by the IRB of Hospital São Lucas of Pontifícia Universidade Católica do Rio Grande do Sul. The research goals and procedures were explained to all volunteers, who signed an informed consent form.

Temperament was assessed with the CEATS and demographic data and an evaluation of habits and general health was evaluated with a structured self-applied questionnaire. Blood samples were collected with a vacutainer system in a laboratory of clinical analysis, centrifuged at 2.000 rpm for 15 min, and serum uric acid was determined within 2 hours in the routine of the laboratory

To be included, volunteers had to be between 18 and 60 years old and sign the informed consent form. Exclusion criteria were TSH (thyroid stimulating hormone) > 5 μUI/mL, acute and chronic diseases and current treatment with drugs that may affect uric acid levels (Choi et al., 2005), such as beta-blockers, pirazinamide, salicilates, diuretics, cyclosporine, ethambutol and tracolimus.

Statistical analysis

The correlation between uric acid levels and dimensional temperament

variables was performed with Pearson correlation test. Comparisons between two variables, such as age between genders and top tertile versus the rest of the sample, were conducted with t-test. Comparison of the top tertile with the rest of the sample was also conducted with general linear regression, with meat and grain intake as covariates. Distribution of the categorical affective temperaments was compared with Fisher Exact test. Alpha level for significance was $p<0.05$. All tests were conducted with the software SPSS 15.0.

RESULTS

The sample consisted of 129 subjects, with 85 females (mean age 35.1 ± 10.6) and 44 males (26.5 ± 10.3 years). Age was different between genders ($p<0.001$).

In the whole sample, serum uric acid levels (in mg/ml) were significantly correlated with disinhibition ($r=0.36$, $p<0.001$, Figure 1) and drive ($r=0.25$, $p<0.01$), but not with control, anger or any of the affective temperament scores.

Among males, no statistically significant correlation was found, but we found correlations at trend level ($p >0.05$ and <0.07) for control ($r=0.27$), irritable ($r=0.29$) and hyperthymic ($r=0.27$) affective temperaments. Among females, a significant correlation was found only with disinhibition ($r=0.34$, $p=0.001$).

As a secondary analysis, we compared temperament scores between the top tertile of uric acid levels with the rest of the sample separately for males and females. The top tertile of man (serum uric acid>6.0, n=16) had significantly higher drive (29.9 ± 5.9 X 26.0 ± 3.6, $p=0.01$) and higher control at trend level (21.2 ± 3.1 X 19.3 ± 2.9, $p=0.054$) than the rest of the sample. Among women, the top tertile (serum uric acid>4.0, n=29) showed only higher disinhibition than the rest of the sample (20.7 ± 4.9 X 17.9 ± 3.6, $p<0.01$). Controlling for daily intake of meat and grains, which could lead to higher uric acid levels, did not change these results using a general linear regression model.

Regarding the choice for categorical affective temperaments, as shown in Figure 2, men within the top tertile less often chose the euthymic temperament (1/16 X 9/28, p=0.045), whereas women in the higher tertile more often chose the hyperthymic (8/26 X 6/59, p=0.023 Fisher exact test) and irritable temperaments (7/26 X 5/59, p=0.031).

DISCUSSION

In general agreement with the literature, we found that uric acid levels were associated with disinhibition (particularly in women) and drive (more in men), as well as irritable and hyperthymic temperaments.

Dunn et al. (1963) has found a significant difference in mean values of serum uric acid levels between the executives (5.73 mg%) and craftsmen (4.77 mg%) and between the number of subjects with hyperuricemia in these two groups (42.5 and 12.0%, respectively). Brooks e Muller (Brooks and Mueller, 1966) observed a correlation coefficient of 0.66 between uric acid levels and overall scores of motivation and drive and SUA levels *(P* < .001) in a study with university professors. Similarly, Fowler reported higher motivation, drive and leadership in men with hyperuricemia (>7.0 mg/ml) compared to normouricemics. Another study found a positive correlation between a motivation score and serum uric acid levels (Rahe et al., 1976). As can be seen, these early studies point out in the same direction, but are mostly restricted to males. Our results extend these findings to women, whose uric acid levels were correlated with disinhibition, which also leads to more externalized behavior.

Uric acid is under high genetic heritance (Emmerson et al., 1992; Yang et al., 2005; Nath et al., 2007), with heritability ranging from 0.42 to 0.87, which is also a characteristic of temperament (Cloninger et al., 1993). Hyperuricemia results from increased absorption of precursor purines, increased de novo purine production, diminished excretion of uric acid or some combination of these mechanisms. Our study does not allow the evaluation of which mechanism accounts for the higher uric acid levels in those with more disinhibited or driven

temperaments.

Orowan (Orowan, 1955) has suggested that uric acid has psychostimulant properties similar to those of other xanthines, such as caffeine and theophylline. Inhibition of uricase in rats leads to increased uric acid levels and locomotion in rats (Barrera et al., 1989). Uric acid has also been shown to increase memory in rats (Essman, 1967). Alternatively, uric acid may just reflect the activity of the purinergic system or may be an index of metabolic activation as the end-product of ATP catabolism. Uric acid excretion also increased along the remission of manic episodes (Anumonye et al., 1968) and (Cobb, 1971) observed that those with more marked mood lability also showed more daily variations of serum uric acid levels (Rubin et al., 1969). Conversely, the xanthine inhibitor allopurinol can exert antimanic (Machado-Vieira et al., 2002; Akhondzadeh et al., 2005), antiaggressive (Lara et al., 2000; Lara et al., 2003) and antipsychotic effects (Lara et al. 2001; Akhondzadeh et al., 2005; Brunstein et al., 2005).

This study has limitations that may have affected the results. Our questionnaire had no data on alcohol consumption and weight, which are variables that could be associated with higher serum uric acid (Choi et al., 2005). Also the sample size, especially for males, was relatively small. Compared to previous studies, however, our sample included females. Despite their lower baseline levels compared to males, uric acid was also correlated with temperament in a similar direction.

In conclusion, serum uric acid seems to be a biochemical marker of temperament both in males and females. Its role as a cause or consequence of externalized emotions remains to be established. Since this is a routine laboratory exam, it would be interesting to investigate if baseline uric acid levels can predict response to treatment, particularly in those with externalized behaviors and disorders. Also, these results add a rational basis for the use of uric acid lowering drug allopurinol as a psychiatric treatment for externalized disorders.

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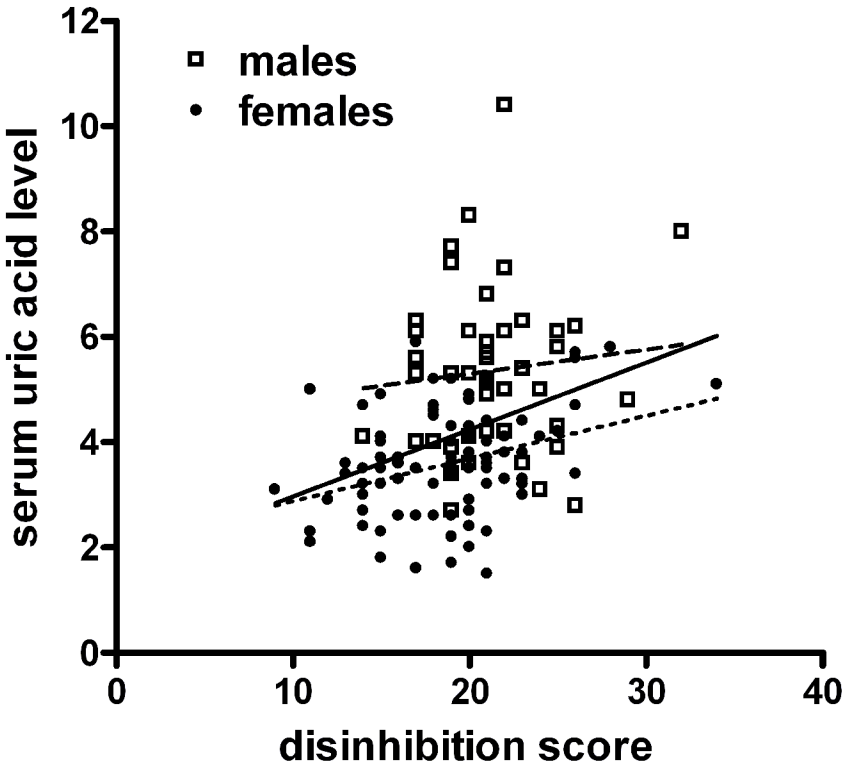

Figure1: Correlation between disinhibition score and uric acid levels. Top, middle and low lines show the correlation for males, the whole sample and females, respectively.

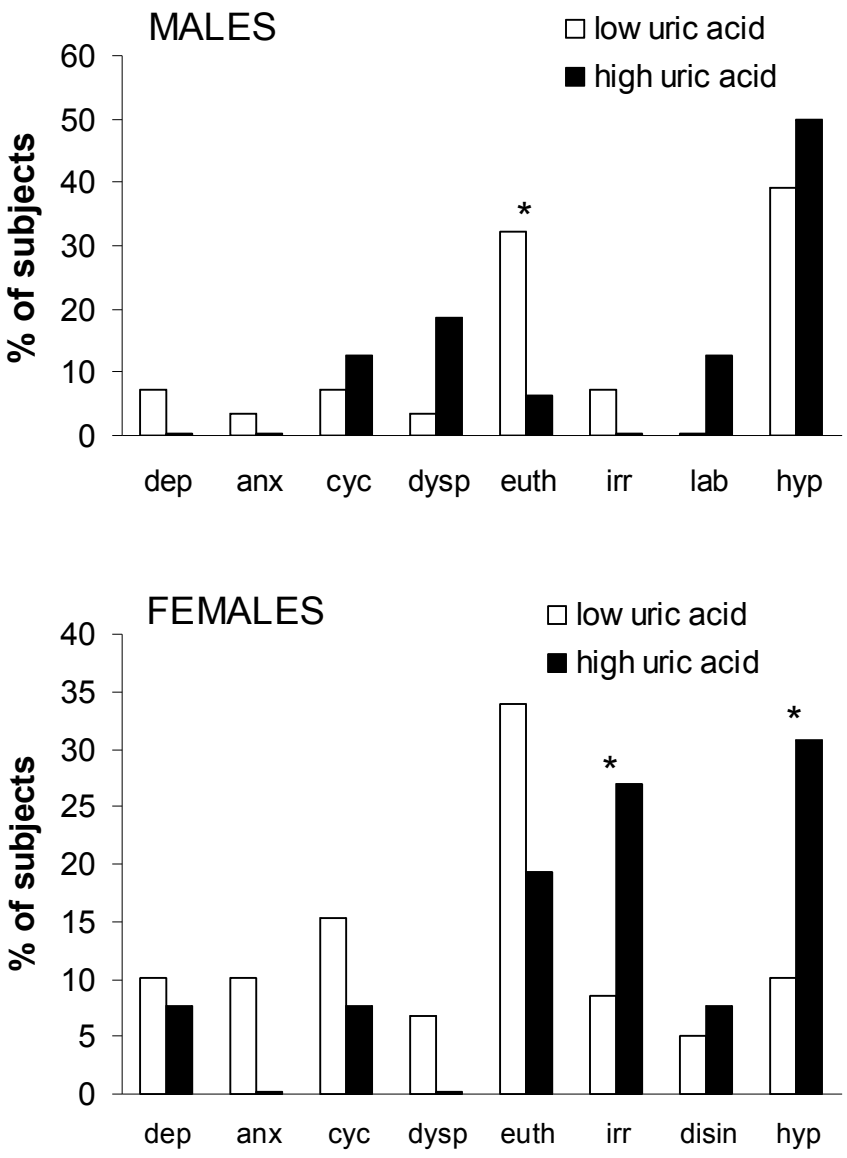

Figure 2. Comparison of affective temperament choice between top tertile of uric acid levels and rest of the sample in males (top) and females (bottom). Dep=depressive, anx=anxious, cyc=cyclothymic, dysp=dysphoric, euth=euthymic, irr=irritable, disin=disinhibited, hyp=hyperthymic. *=P<0.05, Fisher exact test.

4. DISCUSSÃO E CONCLUSÃO

Nosso estudo apresenta algumas limitações. Não inserimos no questionário perguntas referentes ao consumo de álcool e à obesidade. Esses fatores podem influenciar os níveis séricos de AU (Choi et al., 2005). Não temos como avaliar se esses itens afetaram os resultados.

Um estudo de larga escala demonstrou os efeitos da ingestão de álcool em relação aos níveis de urato e o risco de desenvolver gota (Choi et al., 2004). O quadro abaixo mostra o risco de desenvolver gota em relação ao consumo diário de álcool comparado com a abstinência:

Consumo diário (g)	Risco de desenvolver gota (%)
>10 e <14,9	32
> 15 e < 29,9	43
> 30 e < 49,9	96
>= 50g	153

Dados retirados de (Choi et al., 2004).

Estudos recentes evidenciam a hiperuricemia, aparentemente causada pela redução de excreção do AU (López-Suárez et al., 2006) como uma característica importante em pacientes com síndrome metabólica (Puig and Martınez, 2008). A síndrome metabólica caracteriza-se por resistência a insulina, obesidade, hipertensão e hipertrigliceridemia (Choi et al., 2005). A redução na excreção de AU parece ser decorrente da hiperinsulinemia com aumento da reabsorção de sódio. Essa condição relaciona-se com a obesidade e hipertensão, que são as principais doenças associadas com a síndrome metabólica (Puig and Ruilope, 1999; Strazzullo et al., 2006; Strazzullo and Puig, 2007).

Por fim, os resultados do nosso estudo mostraram associação positiva entre AU e desinibição nas mulheres e vontade nos homens, confirmando achados de estudos anteriores. Identificou-se também uma tendência de

associação entre níveis de AUS e controle nos homens. Em relação à literatura existente, nosso estudo acrescentou dados principalmente em mulheres, que mesmo tendo níveis médios de AU mais baixos, apresentaram correlação entre AU e variáveis psicológicas.

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ANEXO A – Escala de Temperamento Afetivo e Emocional (ETAFE)

Curso/profissão:_____

SEXO: ( ) M ( ) F IDADE:_____

INSTRUÇÕES:

1) **Em cada uma das questões abaixo, marque a alternativa que mais corresponde ao seu jeito de ser e de agir em geral.**
2) **Leia todas alternativas de cada questão antes de marcar a que mais se aproxima ao seu perfil. Responda a todas as questões e assinale somente uma alternativa.**
3) **Procure responder com atenção, mas não demore muito em cada afirmação.**
4) **Lembre-se que não existem respostas certas ou erradas. Você deve responder de acordo com o que você é, não com o que você desejaria ser.**

1.
   a) Sou uma pessoa medrosa
   b) Sou um pouco mais medroso do que a maioria das pessoas
   c) Sou um pouco mais ousado do que medroso
   d) Sou ousado
   e) Sou muito ousado

2.
   a) Sou muito tímido
   b) Sou mais tímido do que a maioria das pessoas
   c) Sou um pouco mais extrovertido do que tímido
   d) Sou extrovertido
   e) Sou muito extrovertido

3.
   a) Sou bastante prudente e cauteloso; é raro eu me arriscar
   b) Sou prudente e cauteloso; me arrisco pouco
   c) Em algumas situações sou prudente e cauteloso, mas em outras me arrisco
   d) Em geral, me arrisco um pouco mais do que os outros
   e) Sou pouco prudente e cauteloso; é comum eu me arriscar

4.
   a) Sou muito inibido
   b) Sou inibido; tenho alguma dificuldade em me sentir à vontade
   c) Às vezes, sou um pouco inibido, mas, em geral, consigo me sentir à vontade
   d) Sou desinibido e espontâneo
   e) Sou muito desinibido e espontâneo, algumas vezes até demais

5.
   a) Penso demais antes de agir; demoro demais para tomar decisões
   b) Costumo pensar muito antes de agir; raramente me precipito para tomar decisões
   c) Penso antes de agir, mas não demoro muito para tomar decisões
   d) Algumas vezes ajo sem ter pensado o suficiente; decido rapidamente
   e) Muitas vezes ajo sem pensar, tomo decisões impulsivamente

6.
   a) Me preocupo demais com as coisas
   b) Me preocupo com as coisas mais do que a maioria das pessoas
   c) Me preocupo com as coisas como a maioria das pessoas
   d) Me preocupo menos com as coisas do que as outras pessoas
   e) Me preocupo pouco com as coisas

7. Em situações de perigo, minha reação natural é:
   a) ficar paralisado e tenso mesmo depois do perigo passar
   b) ficar paralisado até o perigo passar
   c) ficar paralisado no começo, mas logo consigo me soltar e agir
   d) ter alguma reação rápida, quase não fico paralisado
   e) ter reações rápidas, nunca fico paralisado

8.
   a) Sou pessimista
   b) Sou mais pessimista do que otimista
   c) Sou um pouco mais otimista do que pessimista
   d) Sou otimista
   e) Sou muito otimista

9.
   a) Não costumo ficar entusiasmado e excitado com novas atividades
   b) Poucas atividades me deixam entusiasmado e excitado
   c) É razoavelmente comum eu ficar entusiasmado e excitado com novas atividades
   d) É comum eu ficar entusiasmado e excitado com novas atividades
   e) É muito comum eu ficar muito entusiasmado e excitado com novas atividades

10.
a) Sinto pouco a sensação de prazer
b) Sinto menos prazer do que a maioria das pessoas
c) Sinto prazer como a maioria da pessoas
d) Sinto mais prazer do que a maioria das pessoas
e) Sinto prazer de forma muito intensa

11.
a) Sou triste e desanimado
b) Sou um pouco triste e desanimado
c) Sou razoavelmente alegre e animado
d) Sou alegre e animado
e) Sou muito alegre e muito animado

12.
a) Meus planos são modestos, tendo a pensar pequeno
b) Meus planos são mais modestos do que os dos outros
c) Tenho alguns planos ambiciosos
d) Meus planos em geral são ambiciosos
e) Meus planos são muito ambiciosos, penso grande

13.
a) Qualquer dificuldade já me desanima
b) É comum eu desanimar frente a dificuldades
c) Desanimo um pouco em algumas situações mais difíceis ou complicadas
d) É difícil alguma coisa me desanimar
e) É muito difícil alguma coisa me desanimar

14.
a) Sou muito inseguro
b) Sou mais inseguro do que a maioria das pessoas
c) Me sinto razoavelmente seguro
d) Sou mais confiante do que os outros
e) Sou muito autoconfiante

15.
a) Tenho poucos objetivos definidos e vou atrás de poucos deles
b) Tenho alguns objetivos definidos e consigo ir atrás de alguns deles
c) Tenho alguns objetivos definidos e vou atrás da maioria deles
d) Tenho vários objetivos claros e vou atrás deles
e) Tenho muitos objetivos, inclusive alguns muito difíceis, e vou atrás deles até o fim

16.
a) Sou pouco disciplinado
b) Sou menos disciplinado do que a maioria das pessoas
c) Sou razoavelmente disciplinado
d) Sou mais disciplinado do que a maioria das pessoas
e) Sou muito disciplinado

17.
a) sou pouco organizado e isso às vezes me atrapalha
b) sou menos organizado do que a maioria das pessoas
c) sou organizado em algumas coisas
d) sou mais organizado do que a maioria das pessoas
e) sou muito organizado, às vezes até demais

18.
a) sou muito dispersivo e distraído, e isso freqüentemente me atrapalha
b) sou dispersivo e distraído; às vezes isso me atrapalha
c) fico dispersivo e distraído por alguns momentos, mas isso não chega a me atrapalhar
d) sou menos dispersivo e distraído do que a maioria das pessoas
e) sou muito pouco dispersivo e distraído

19.
a) Muitas vezes não concluo as tarefas que começo
b) Tenho alguma dificuldade em completar as tarefas que começo
c) Concluo boa parte das tarefas que começo, mas desisto de algumas mais difíceis
d) Costumo concluir as tarefas que inicio, inclusive algumas mais difíceis
e) Sempre concluo as tarefas que inicio, até mesmo as mais longas ou difíceis

20.
a) Tenho dificuldade de manter a concentração e o interesse
b) Consigo manter a concentração somente se estou interessado
c) Mantenho a concentração se estou razoavelmente interessado
d) Mantenho a concentração mesmo estando pouco interessado
e) Mantenho *bem* a concentração mesmo estando pouco interessado

21.
a) Sou pouco responsável
b) Sou menos responsável do que a maioria das pessoas
c) Sou razoavelmente responsável
d) Sou mais responsável do que a maioria das pessoas
e) Sou muito responsável

22.
   a) É raro eu me irritar com alguma coisa
   b) Não costumo me irritar
   c) Às vezes, me irrito, mas isso não me gera grandes problemas
   d) Sou mais irritado (bravo) do que a maioria das pessoas
   e) Sou muito irritado (bravo) e isso freqüentemente me causa problemas

23.
   a) Não sou nada agressivo e isso às vezes me atrapalha
   b) Sou pouco agressivo
   c) Sou um pouco menos agressivo do que as outras pessoas
   d) Sou um pouco mais agressivo do que os outros
   e) Sou agressivo em várias situações

24. Quando me irrito, minha raiva dura:
   a) pouquíssimo tempo; é raro eu ficar muito irritado
   b) pouco tempo, logo fico bem de novo
   c) um pouco menos tempo do que para as outras pessoas
   d) mais tempo do que para as outras pessoas
   e) muito tempo (“estraga o meu dia”)

25.
   a) Nunca sou explosivo
   b) Sou menos explosivo do que os outros
   c) Às vezes, sou explosivo
   d) Sou mais explosivo do que os outros
   e) Sou muito explosivo

26. Penso que estou sendo traído ou que estão armando algo contra mim:
   a) Nunca
   b) Quase nunca
   c) Poucas vezes
   d) Algumas vezes
   e) Freqüentemente

27.
   a) sou muito paciente, tolero bem esperar
   b) sou paciente
   c) sou um pouco impaciente
   d) sou impaciente
   e) sou muito impaciente, não tolero esperar

28. Marque para cada descrição abaixo a alternativa que mais corresponde a você (marque somente uma alternativa).

A) Tenho uma tendência à tristeza e à melancolia; vejo pouca graça nas coisas; tendo a me desvalorizar; não gosto muito de mudanças; prefiro ouvir a falar.

a) tudo a ver comigo
b) muito a ver comigo
c) algumas coisas a ver comigo
d) pouco a ver comigo
e) nada a ver comigo

B) Sou muito cauteloso e precavido; freqüentemente me sinto inseguro e apreensivo; imagino que coisas ruins estão prestes a acontecer; tento evitar situações de risco; estou sempre alerta e vigilante.

a) tudo a ver comigo
b) muito a ver comigo
c) algumas coisas a ver comigo
d) pouco a ver comigo
e) nada a ver comigo

C) Meu humor é imprevisível e instável (altos e baixos), muda rapidamente ou de maneira desproporcional aos fatos; tenho fases de grande energia, entusiasmo e agilidade que se alternam com outras fases de lentidão, perda de interesse e desânimo.

a) tudo a ver comigo
b) muito a ver comigo
c) algumas coisas a ver comigo
d) pouco a ver comigo
e) nada a ver comigo

D) Tenho uma forte tendência a me sentir agitado, ansioso e irritado ao mesmo tempo.

a) tudo a ver comigo
b) muito a ver comigo
c) algumas coisas a ver comigo
d) pouco a ver comigo
e) nada a ver comigo

E) Tenho pouca iniciativa; com freqüência me desligo do que os outros estão dizendo ou fazendo; muitas vezes não concluo o que comecei; tendo à passividade e sou um pouco lento.

a) tudo a ver comigo
b) muito a ver comigo
c) algumas coisas a ver comigo
d) pouco a ver comigo
e) nada a ver comigo

F) Meu humor é equilibrado e previsível, costuma mudar só quando há um motivo claro; tenho boa disposição e, em geral, me sinto bem comigo mesmo.

a) tudo a ver comigo
b) muito a ver comigo
c) algumas coisas a ver comigo
d) pouco a ver comigo
e) nada a ver comigo

G) Sou muito sincero, direto e determinado, mas também irritado, explosivo e desconfiado.

a) tudo a ver comigo
b) muito a ver comigo
c) algumas coisas a ver comigo
d) pouco a ver comigo
e) nada a ver comigo

H) Sou inquieto e dispersivo; com freqüência me desligo do que os outros estão dizendo ou fazendo; muitas vezes ajo sem pensar nas conseqüências; às vezes sou inconveniente e só me dou conta tarde demais; mudo de humor ou de interesse rapidamente, e não concluo muitas coisas que começo; quando me irrito, logo fico bem de novo.

a) tudo a ver comigo
b) muito a ver comigo
c) algumas coisas a ver comigo
d) pouco a ver comigo
e) nada a ver comigo

I) Sou inquieto, ativo, espontâneo e distraído; muitas vezes ajo de maneira precipitada e inconseqüente; é muito comum eu deixar para fazer as coisas na última hora; quando me irrito, logo fico bem de novo.

a) tudo a ver comigo
b) muito a ver comigo
c) algumas coisas a ver comigo
d) pouco a ver comigo
e) nada a ver comigo

J) Estou sempre de bom humor, me sinto muito confiante e me divirto facilmente; adoro novidades e estou sempre pronto para novas atividades; faço várias coisas sem me cansar; quando quero alguma coisa, vou atrás e consigo conquistá-la; tenho forte tendência à liderança.

a) tudo a ver comigo
b) muito a ver comigo
c) algumas coisas a ver comigo
d) pouco a ver comigo
e) nada a ver comigo
f)

29. Escolha a descrição da questão 28 acima que mais se aproxima do seu perfil (somente uma alternativa). Leia bem todas as 10 descrições antes de optar pela resposta (páginas 5 e 6).

A)

B)

C)

D)

E)

F)

G)

H)

I)

J)

30. Em que medida você tem ou já teve problemas ou prejuízos pessoais em função do seu jeito de ser, do seu comportamento e/ou do seu padrão de humor?

a) nenhum problema e nada de prejuízo

b) poucos problemas e prejuízos pequenos

c) problemas e prejuízos moderados

d) problemas e prejuízos sérios ou graves

31. Em que medida você tem ou já teve vantagens ou benefícios pessoais em função do seu jeito de ser, do seu comportamento e/ou do seu padrão de humor?

a) quase nenhuma vantagem e benefícios mínimos

b) poucas vantagens e benefícios pequenos

c) algumas vantagens e benefícios moderados

d) muitas vantagens e grandes benefícios

ANEXO B – Termo de Consetimento

Termo de Consentimento Livre e Esclarecido

“Estudo das bases genéticas do temperamento”

A Justificativa da Pesquisa

Este estudo visa caracterizar a base genética do temperamento, que é nosso padrão emocional básico. Para isso, será necessária a aplicação de uma escala de auto-avaliação do temperamento, assim como coleta de sangue para análise genética. O objetivo deste estudo é avaliar o quanto traços do temperamento se relacionam com os parâmetros biológicos que serão investigados. Os resultados poderão colaborar para a compreensão das causas de diversos transtornos mentais, que frequentemente apresentam variações de temperamento.

Os procedimentos a serem utilizados

Os meios utilizados para realizar este trabalho consistem no preenchimento de duas escalas auto-aplicáveis e coleta de sangue por punção venosa (1 tubo de 5 ml).

III. Os procedimentos ou riscos esperados

A coleta de sangue por punção venosa é um procedimento invasivo corriqueiro e de risco mínimo, podendo ocorrer pequeno hematoma autolimitado em local da punção.

IV. Os benefícios que se pode obter

Essa pesquisa busca o melhor entendimento do temperamento, auxiliando

assim no acúmulo de informações necessárias para que se possa reconhecer e tratar melhor os transtornos mentais. Individualmente, o benefício nesse tipo de estudo é ainda limitado.

V. Garantia de resposta a qualquer pergunta

Os pesquisadores garantem que responderão a qualquer pergunta referente a esta pesquisa.

VI. Liberdade de abandonar a pesquisa sem prejuízo para si

O voluntário tem a liberdade de abandonar a pesquisa a qualquer momento, sem prejuízo para si.

VII. Garantia de privacidade

Será mantida a privacidade do voluntário em todas as fases da pesquisa. Todos os dados coletados serão mantidos sob sigilo.

VIII. Consentimento para pesquisas futuras

O voluntário consente que o material coletado (escalas e amostras de sangue) poderá ser utilizado para futuras pesquisas com o fim de caracterizar e compreender a base genética dos traços de personalidade e dos transtornos mentais.

_____

Local e data

_____

Assinatura do voluntário

_____

Assinatura do pesquisador

ANEXO C - Artigo de desenvolvimento e validação da ETAFE

Development and validation of the Combined Emotional and Affective Temperament Scale (CEATS): a brief self-report instrument

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ABSTRACT

Background: Temperament relates to both emotional dimensions and prevailing mood, but these different views are rarely integrated. Based on a model where temperament works as a system with activation, inhibition and control (inspired in Cloninger's and Rothbart's models), which produce the affective tone (inspired by Akiskal's and Kraepelin's model), we developed and validated the Combined Emotional and Affective Temperament Scale (CEATS). *Methods*: 1007 subjects (28% males) from the general population and university students filled in the instrument either in the internet or in a pen and paper version. The CEATS has an Emotional section (dimensional only), an Affective section (both dimensional and categorical) and an evaluation of problems and benefits related to temperament. The data was analyzed with standard psychometric batteries and different sections were compared. *Results*: In the Emotional section, 4 factors with Eingenvalue>1 explained 46% of the variation. These factors were interpreted as drive, control, disinhibition-fear and anger, had a normal distribution and had satisfactory Chronbach's alphas (0.70-0.82). Anger was particularly associated with

problems and drive with benefits. In the Affective section, all 10 categorical affective temperaments were selected, being euthymic and hyperthymic the most prevalent (18-23%), followed by cyclothymic and irritable (11-13%), anxious and depressive (8-9%) and dysphoric, disinhibited, labile and apathetic temperaments (3-7%). The dimensional evaluation of affective temperaments showed 95% of the sample was able to ascribe to at least one affective temperament. Only the euthymic and hyperthymic temperaments were clearly associated with a favorable problem/benefit profile. The comparison between the emotional and affective sections revealed that each affective temperament had a particular emotional configuration. *Limitations*: both computerized and pen and paper versions were used. The sample was not evaluated for psychiatric symptoms. Quantification of the dimensional assessment of affective temperament is limited. *Conclusions*: the CEATS is a brief and adequate instrument to evaluate emotional and affective aspects of temperament simultaneously.

INTRODUCTION

Temperament relates to the emotional nature and the quality of the prevailing mood, being mostly inherited and relatively stable over time (Allport, 1961; Cloninger et al., 1993). Since the four humours of Hippocrates and Galen, the concept of temperament has had new interpretations by Eysenck (1987), Gray (Pickering and Gray, 1999), Cloninger (Cloninger et al. 1993), Akiskal (Akiskal et al. 1989) and others. Two of the most intensively studied temperament constructs in psychiatry are the psychobiological model by Cloninger, with a focus on behaviors and basic emotions, and the model of affective temperaments by Akiskal, based on Kraepelin fundamental states.

In Cloninger's model, the combination of four dimensions comprises the temperament (Cloninger et al. 1993). They are named as behaviors that are routed in basic emotions (in brackets): novelty seeking (anger), harm avoidance (fear), reward dependence (attachment) and persistence (ambition). They are normally distributed dimensions that can occur in any combination, as they are independently inherited. This construct can be objectively assessed with the Temperament and Character Inventory (TCI) and was conceived more specifically for personality disorders. However, several studies have shown that in virtually all psychiatric disorders, including mood, behavioral and personality disorders, at least one these temperament dimensions is altered compared to a mentally healthy control group (see Lara et al. 2006 for review). Most

commonly novelty seeking (NS) and/or harm avoidance (HA) is either high or low, and self-directedness from the character section is often reduced in psychiatric disorders.

Akiskal has conceived temperament as the affective predisposition or reactivity, based on the original descriptions by Kraepelin (1921) of fundamental states, which could be either manic (currently called hyperthymic), irritable, cyclothymic or depressive (Akiskal et al., 1989). More recently, Akiskal added the concept of anxious temperament (Akiskal, 1998). These five affective temperaments would be the predisposing ground for the development of mood disorders. The TEMPS has been developed and validated as the self-report scale to assess this construct (Akiskal et al., 2005). Indeed, these affective predispositions are present in individuals that develop mood disorders, as well as in their relatives, with different distributions according to the type of mood disorder (e.g. more hyperthymic traits in bipolar I disorder, cyclothymic traits in bipolar II disorder and depressive traits in unipolar depression) (Evans et al., 2005; Kesebir et al, 2005; Akiskal et al, 2005).

As Rothbart et al. (2000), our view coincides with Allport's (1961) definition of temperament as 'an individual`s emotional nature, including his susceptibility to emotional stimulation, his costumary strength and speed of response, and the quality of prevailing mood, these phenomena being regarded as dependent upon constitutional make-up'. However, current temperament models assess *either* the emotional nature or the prevailing mood. Rothbart et al. (2000) thoughtfully incorporated and studied the role of attention and self-regulation to the concept of temperament, but have not directly addressed the prevailing mood or affective predisposition.

Recently we have proposed an integration of emotional and affective temperament constructs, named as the fear and anger model, with clinical (Lara et al, 2006), neurobiological and treatment implications (Lara and Akiskal, 2006). This model is based on the principle that activation (anger and drive/pleasure, related to NS) and inhibition (fear and caution, related to HA) are the two main *emotional* forces or 'vectors of the mind', as coined by Thurstone (1934). Their interaction would produce a resulting *affective* trend or prevailing mood. In our construct, we consider desire and pleasure as part of the emotional terrain, at odds with other concepts that ascribe them to motivation, as if motivation did not have a strong emotional/affective component.

Three studies (Maremmani et al. 2005; Akiskal et al. 2005; Rósza et al., 2007) have been conducted with simultaneous assessment with the TCI and the TEMPS, showing essentially that: hyperthymic temperament is associated with high NS and low

HA; irritable with high NS and moderate HA; cyclothymic with both high; anxious with moderate NS and high HA and finally that depressive temperament is associated with low NS and high HA. Reward dependence and persistence are weakly correlated with these five affective temperaments. For practical reasons, the dimensions of activation and inhibition can be conceived as high, moderate and low, as they are normally distributed in the population. Therefore, nine combinations can arise from their 2X2 interactions. In order to complete the other putative combinations of activation and inhibition, we have proposed and predicted four new affective temperaments: disinhibited (originally called hyperactive) with moderate NS and low HA; labile with both low; apathetic or passive with low NS and moderate HA, and euthymic with both moderate (Lara et al. 2006). After pilot versions of the scale and clinical observations, we also conceived a dysphoric predisposition, which would also be associated with the mixture of high activation and inhibition, similar to cyclothymic temperament. Based on other models and our preliminary versions of the scale, we also included a factor that is related to regulation of activation and inhibition, which we called control. This concept is highly attributed to frontal lobe function and is similar to consciousness in the big five model (McCrae and Costa, 1985), some aspects of persistence and self-directedness in Cloninger's model (Cloninger et al. 1993) and also executive functions and effortful control in Rothbart's concept (Rothbart et al. 2000). Although control is not emotional per se, this factor is included in the emotional construct due to its proposed role in emotional regulation and behavioral adaptation (Rothbart et al. 2000).

Here we present the validation data of a scale developed to evaluate emotional and affective temperaments simultaneously, trying to keep the original concepts by Cloninger and Akiskal/Kraepelin, but making the necessary adaptations and changes to allow for their integration. Named as the Combined Emotional and Affective Temperament Scale (CEATS), the emotional section consists of twenty seven 5-item multiple choice questions on disinhibition-fear, drive, control and anger, whereas the affective section includes 10 descriptions of affective temperaments with a dimensional 5-point scale and a categorical choice of the best description. We also included two questions that subjects could rate in a 4-point scale according to the degree of problems and benefits related to their temperament.

MATERIALS AND METHODS

Preliminary versions of the scale were reviewed by psychologists familiar to current concepts of temperament. Four preliminary pen and paper versions were developed with around two thousand subjects of Porto Alegre, mostly university students. The final version for construct validation was developed in a pen and paper version with 124 university students from the city of Belém (Pará, Brazil) and 245 subjects from the city of Porto Alegre, as well as with an internet version that was completed by the general population of the city of Porto Alegre (638 subjects). Subjects became acquainted with the study by word of mouth and announcement of our website through a local TV talk-show. As the overall results were similar in all samples, the results were combined to increase statistical power (1007 subjects). The internet version has the advantage that all items are necessarily answered and no mistakes of data transfer are expected to occur. All participants gave their informed consent (signature or electronic) before completing the scale. This form was elaborated to fulfill the requirements of the National Health Council of Brazil (Resolution 196/1996). Their participation was voluntary and they could cancel their participation at any moment without justification. The study was approved by the Institutional Review Board of Hospital São Lucas from Pontifícia Universidade Católica do Rio Grande do Sul.

DESCRIPTION OF THE CEATS

The CEATS (see Appendix) consists of an emotional and an affective section, as well as two questions to evaluate problems and benefits associated with temperament. It has 40 items total, and typically takes 20-30 min to be completed.

Emotional section

The 27 five-item multiple choice questions were developed in the preliminary versions and arranged in the final version in following order: disinhibition-fear (7 items), drive (8), control (6) and anger (6). The first alternative was a description of low and the last with high expression of the trait. In order to facilitate application and rating, we chose to reverse the fear factor as disinhibition-fear, so that low scores represent high fear/inhibition. In this way, the order of the alternatives of disinhibition-fear, drive and anger go from more internalizing to more externalizing traits. This principle is not easily applied to control, but we chose to align the alternatives from low to high control since

we consider it a proactive trait (e.g., concludes tasks, pays attention even if uninterested, self-regulation), although they may reduce the expression of externalizing traits. The total score of each dimension is the sum of scores from 1 to 5 for each question.

Affective section

Ten short descriptions of the affective temperaments based on previous studies of the TEMPS, theoretical concepts, clinical observation and preliminary versions of the CEATS were presented with a 5-item likert scale, from 'everything to do with me' (rated as 5) to 'nothing to do with me` (rated as 1). This was called the dimensional assessment of affective temperaments. After these 10 descriptions, one question asked the subject to select which of these profiles was the most suitable to represent his/her temperament. This allows for a categorical evaluation of affective temperaments. Instead of using a statistical approach to define someone's affective temperament, this categorical choice results from the selection of one profile in detriment of the other nine profiles, but the dimensional part allows for a more refined understanding of the chosen category (e.g. subjects from the cyclothymic category may have different levels of the other affective temperaments).

Problems and benefits

Two final questions assessed the degree of problems and benefits that one conceives to have with his/her temperament with a 4-point scale (no, minimal, moderate and marked problems or benefits). This strategy was used because problems and benefits are not mutually exclusive and adaptation can be conceived as the result of both. This is in contrast to other scales and current practice of psychiatry, which focus mostly on problems.

Statistical analysis

The emotional section was analyzed for the evaluation of factorial structure and internal consistency. Exploratory factorial structure was analyzed with Varimax rotation, which allowed the selection of items in agreement with the theoretical construct that showed a higher load for a specific factor. Only factors with an Eigenvalue>1 and items with factorial load over 0.40 were kept in the final version of the scale. These factors were interpreted in accordance with the theoretical construct and their means, standard deviations and Chronbach's alphas were calculated. Gender differences in age were

compared with Student's t-test. Gender differences in emotional factors were compared using Multivariate General Linear Model, with age as covariate.

The affective section was analyzed with Pearson's correlation test. Also, the number of 'everything to do with me' answers were counted. In those subjects who had no such answer, we counted how many chose the 'much to do with me' in order to evaluate if the 10 descriptions covered most of the population's affective temperaments.

Comparisons between emotional and affective temperaments were performed with ANOVA with Tukey`s test as *post hoc* for the categorical and Pearson's correlation test for the dimensional affective temperament. Age, problems and benefits scores were also compared with emotional and affective temperaments using Pearson's correlation test. Statistical significance was considered if $p<0.05$. The SPSS 15.0 software was used for all analyses.

RESULTS

Our final sample consisted of 1007 subjects, with mean age of 34.9 ± 11.9 years (16-80), being 284 (28.2%) males (32.3 ± 11.7 years) and 723 (71.8%) females (35.9 ± 11.8 years) ($p<.01$, Student's t test).

EMOTIONAL SECTION

Exploratory factorial analysis revealed that the best solution involved four factors with Eigenvalues>1, as shown in Table 1. These factors were interpreted as drive, anger, disinhibition-fear and control. In some preliminary analysis a fifth factor arose involving only 2 items (related to shyness-extroversion and inhibition-spontaneity, or social fear – see Table 2), which in the final sample loaded well to the factor associated with questions of disinhibition-fear. Twenty-seven items remained in the final version of the scale, accounting for 46.0% of the total variation. The factors had Chronbach's alphas between 0.70 and 0.82 and showed normal distributions, with Liliefords with $p<0.01$ (see Table 1). The factorial matrix, item descriptions and loadings are shown in Table 2.

Table 3 shows that there was a moderately high correlation between the factors disinhibition-fear and drive ($r=0.51$), and drive and control ($r=0.34$). Other correlations

between emotional factors, even if statistically significant, were weaker. Regarding age, there was a weak but statistically significant negative correlation with drive and anger and a weak positive correlation with control (Table 3). The perception of problems with own mood and temperament was associated with higher anger, lower drive and lower control, but not with disinhibition-fear. In contrast, the perception of benefits was associated with higher drive, disinhibition-fear and control and lower anger (Table 3). Problem and benefit scores were significantly but weakly correlated ($r=-0.17$, $p<0.01$).

Regarding gender differences, using age as covariate, males had higher scores of disinhibition-fear and females were higher in control scores (Table 4). Males had numerically but non-significantly higher drive and lower anger than females.

AFFECTIVE SECTION

The frequencies of the categorical choices of affective temperaments are shown in Figure 1. Euthymic (≅23%) and hyperthymic (≅18%) temperaments were the most prevalent, followed by cyclothymic, irritable and anxious temperaments. The remaining affective temperaments were all present, with apathetic and labile temperaments as the less prevalent (3-4%). To our surprise, the frequency of the euthymic temperament, even in previous versions of the scale solely in university students, never exceeded 30%. The major numerical differences in gender distribution were the predominance of males among hyperthymics, labiles and disinhibited temperaments, and of females among cyclothymic, dysphoric and irritable temperaments. The dimensional score of affective temperaments showed that males show significantly higher scores on disinhibited ($p<0.01$) and apathetic ($p<0.05$) temperaments, and labile temperament at trend level ($p=0.07$).

As we postulate that the 10 proposed affective temperaments arise from combinations of activation, inhibition and control, we expected that most people would recognize at least one description as a perfect or good match (‘everything to do with me’ or ‘a lot to do with me’, respectively). Indeed, 595 subjects (59%) found at least one or more perfect matches, and 6% found from 5 to 7 perfect matches (Figure 2). Among those 412 (41%) individuals who failed to point out one perfect match, 364 (36% of the total sample) found at least 1 good match. Thus, less than 5% (48 subjects) failed to identify at least one satisfactory description for their affective temperament.

The correlations of the dimensional part of the Affective Section are shown in

Table 5. Except for a positive correlation with hyperthymic temperament, euthymic temperament was negatively correlated with all temperaments, particularly with cyclothymic, depressive, dysphoric and labile temperaments. Depressive, anxious, cyclothymic, dysphoric, apathetic and labile temperaments were positively correlated. Labile and disinhibited temperaments as well as dysphoric and cyclothymic temperaments were particularly correlated ($r>0.50$). Inter-correlations between externalized temperaments (hyperthymic, irritable and disinhibited) were low to moderately positive. As expected, all categorical choices of affective temperaments were associated with higher score of the respective temperament in the dimensional part of Affective Section, with statistical separation from all the other groups ($p<0.05$), except for labile score from categorical disinhibited temperament, labile score from dysphoric and hyperthymic score from euthymic temperament.

Problems and benefits associated with categorical affective temperaments are shown in Figure 4 and with dimensional affective temperament scores at the bottom of Table 6. Only euthymic and hyperthymic temperaments are associated with a perception of little problems and high benefits. Hyperthymic and euthymic temperaments had lower problem scores than all the other temperaments ($p<0.05$), except for apathetic temperament, which was not different from any other temperament. The remaining affective temperaments were not significantly different among them ($p>0.1$). In terms of benefits, depressive temperaments had significantly lower scores than all other temperaments ($p<0.05$), except for anxious and cyclothymic, whereas hyperthymic temperament had significantly higher scores than all others ($p<0.05$), except for euthymic and disinhibited temperaments.

COMPARISON BETWEEN EMOTIONAL PROFILE AND AFFECTIVE TEMPERAMENTS

The emotional profiles of categorical affective temperaments are shown in Figure 3 and the correlations between emotional factors and dimensional scores of affective temperaments are shown in Table 6. In general, each affective temperament was associated with a fairly specific emotional signatures, with the exception of dysphoric and cyclothymic temperaments, which had similar profiles. The irritable temperament was also similar to these two temperaments, but with numerically higher scores in the 4 factors. ANOVA with Tukey's as the post hoc test showed 6 different statistical groups for disinhibition: dep=anx≤apa=cyc≤eut≤dysp≤irr=lab=htm=disin. For drive, 7 statistical

groups were found: dep<anx=apa≤lab=cyc≤dysp≤irr=eut=disin<htm. For control, 5 statistical groups were found: lab≤apa=disin≤dep=cyc≤dysp≤anx=irr=eut=htm. For anger, 5 groups emerged: eut≤htm=apa≤anx≤disin=dep≤lab≤cyc=dysp=irr. As can be seen, each emotional factor is associated with a different ranking of affective temperaments.

DISCUSSION

The emotional section of the CEATS showed 4 four factors with satisfactory reliability coefficients as shown by Chronbach's alpha values between 0.70 and 0.82. The item insecure/self-confident was kept in the drive factor despite a slightly higher loading in the disinhibition factor based on theoretical ground, but especially because this item 'behaved' as a drive item when it was analyzed in relation to affective temperaments. Also, when only disinhibition and drive questions were analyzed, this question loaded much more heavily on the drive factor (data not shown).

Compared to Cloninger's model, there were some differences regarding features of harm avoidance compared to disinhibition-fear, and novelty seeking compared to drive and anger. The harm avoidance dimension includes energy and pessimism/optimism (Cloninger et al. 1993), which loaded in the drive factor in CEATS. Cloninger also attributes impulsivity to novelty seeking, whereas we consider impulsivity as a possible outcome of disinhibition/low fear, or lack of control, or even as excessive drive (pleasure seeking), which we have called appetitive impulsivity (Lara et al, 2006). However, in the strict sense of impulsivity as acting without enough forethought or reflection, impulsivity was ascribed to the disinhibition-fear factor. Also, many features of Cloninger's self-directedness, which is considered part of the character domain, are similar to our drive factor. Indeed, both high harm avoidance and low self-directedness have been the factors associated with unipolar major depression (Richter et al., 2000; Cloninger et al., 2006), whereas in our scale, the depressive temperament was associated with high inhibition (low disinhibition/high fear) and low drive. However, concurrent validation between both scales is necessary to adequately address this topic.

The CEATS' emotional factors were similar to Rothbart's 4 main temperament factors developed after decades of studies across the whole life span, with emphasis on early development (Rothbart et al., 2000). These factors are fear, approach-positive affect, anger-frustration and effortful control. As in our model, Rothbart's construct

avoids factors associated with socialization, which is in contrast to Cloninger's inclusion of reward dependence/attachment. Although socialization factors are surely important for personality, reward dependence is weakly associated with affective disorders and affective temperaments (Maremanni et al, 2005; Akiskal et al, 2005; Rósza et al. 2007).

There were significant correlations between some but not all emotional factors (Table 3). Our interpretation for the moderately high correlation (r=0.51) between drive (activation) and disinhibition is that a combination of 'emotional synchrony' is favored, i.e. a bias to avoid ambivalence between approach (drive) and avoidance (inhibition). The positive correlation between drive and control and their negative correlation with anger suggests that higher control favors the expression of activation as drive rather than anger, although these two are not mutually exclusive.

The Affective Section of the CEATS included five new prototypes of affective temperaments to be validated. Categorical euthymic temperament (≅23%) arouse as the most common, but less often than we expected. The results of the preliminary versions in university students showed the same pattern (data not shown). The other newly proposed affective temperaments, namely labile, disinhibited, apathetic and dysphoric, had lower frequencies in the range of 3 to 7% of subjects. Depressive and anxious temperaments were chosen by 7-9% of subjects, whereas higher prevalence was found for hyperthymic (≅18%), cyclothymic (≅13%) and irritable (≅11%) temperaments. This suggests that affective temperaments related to bipolar spectrum disorders are more common than those related to unipolar depression or attention-deficit and hyperactivity disorders.

The categorical choice of an affective temperament relies on the idea that the subject has to choose *one* description among 10 prototypes *instead* of the other 9 descriptions, i.e., the best fit. This is a different approach than stratification through standard deviations. The dimensional assessment of the affective temperaments identified 95% of the subjects with either a perfect match (59% as everything to do with me) or a good match (36% as mostly to do with me), and a minority (6%) chose more than 5 perfect matches. Given that conceptually there are no 'zones of rarity' between 'neighbor' temperaments, it is quite possible that someone considered dysphoric, cyclothymic, irritable and anxious temperaments as perfect matches, for example. We conceive affective temperaments as essentially related to or even a product to these 4 the emotional factors (drive, disinhibition-fear, anger and control), which are usually thought to be relatively independent. If they are categorized as low, moderate or high to

grossly reflect their normal distribution, theoretically there would be 81 combinations or affective temperaments, or at least 27 if control and disinhibition influence the expression of activation as drive or anger (therefore counting drive and anger as only one activation factor). The 95% rate of perfect/good matches with only 10 affective temperaments and the correlations between the emotional factors discussed above suggest that these emotional combinations do not occur randomly.

The correlations between dimensional scores of affective temperaments were essentially in agreement with the proposed bidimensional model (Lara et al, 2006). 'Neighbor' temperaments had higher positive correlations, especially the cyclothymic and dysphoric temperaments, which were conceived as closely related, but distinct expressions of conflicting emotional forces (ups and downs X dysphoria-agitation). Also, moderately positive correlations were found between the most unstable temperaments, namely cyclothymic and labile, and moderately high negative correlations were found between hyperthymic and depressive temperaments, as expected.

Both emotional and affective temperaments were associated with gender differences. Males showed higher disinhibition and lower control. Considering the hypothesis that temperament differences underlie most psychiatry disorders, this profile is compatible with the higher prevalence of externalizing and lower prevalence of internalizing disorders in males than in females (see Lara et al, 2006 for review). This emotional profile was also in general agreement with the numerically higher prevalence of hyperthymic and disinhibited temperaments in males and higher cyclothymic temperament in women. Ageing was associated with a slight decline in drive and anger and an increase in control, and reduction of cyclothymic, dysphoric and irritable affective temperaments, which is mostly coherent taking into account the emotional-affective interactions. This is in general agreement with the findings in novelty seeking using the TCI (Cloninger et al., 1993) and the TEMPS (Rósza et al. 2007), although we did not find a decline in hyperthymic traits with age. Activation both as drive and anger have a high influence of dopaminergic tone, which declines steadily with age (Lara and Akiskal, 2006).

In general, our results comparing the original five affective temperaments (depressive, anxious, cyclothymic, irritable and hyperthymic) with the emotional factors are in line with previous results comparing the TEMPS and the TCI (Maremanni et al, 2005; Akiskal et al, 2005; Rósza et al, 2007). Of note, these studies have shown that cyclothymic temperament is associated with high harm avoidance and high novelty

seeking. Using the categorical cyclothymic temperament, we indeed found high anger, which is probably related to high novelty seeking, but disinhibition (conceived as the reverse of harm avoidance) was not low as we predicted. Disinhibition scores of cyclothymics were similar to those of euthymic temperament, and both were intermediate between depressive/anxious and hyperthymic temperaments. One possibility is that 'sunny' (disinhibited) and 'dark' (inhibited) cyclothymics (Akiskal 2005) cancel each other and produce an average score of disinhibition-fear. However, the dimensional score of cyclothymic temperament showed a significant negative correlation with disinhibition (i.e., the more cyclothymic, the more inhibited). Interestingly, although the most characteristic feature of the cyclothymic temperament was high anger, the description of this affective temperament is strictly on cycling, without any reference to anger or irritability.

Cyclothymic, dysphoric and irritable temperaments were highly intercorrelated. However, careful inspection reveals a gradient from cyclothymic to dysphoric to irritable temperament from more internalizing to more externalizing features (higher disinhibition, drive and anger) and higher control (see Figure 4 and Table 6). The irritable temperament of the TEMPS seems to correspond to the CEATS description of dysphoric rather than irritable temperament. Besides irritability and explosive outbursts, the CEATS description of irritable temperament also focuses on assertiveness and goal-direction, similar to the original observations on the irritable fundamental state by Kraepelin (1921).

Clearly the only affective temperaments associated with a perception of favorable problem/benefit ratio were the euthymic (particularly associated with little problem) and hyperthymic temperaments (particularly associated with high benefit). This profile is probably due to expression of activation in these subjects as drive, rather than anger. Depressive, cyclothymic, dysphoric and labile temperaments were particularly problematic, and depressive temperament was more specifically associated with lack of perceived benefit.

This study and the scale have some limitations. Data collection was done using both internet and pen and paper versions, being part of them in university students. Although the distribution of emotional and affective temperaments was not clearly different between these versions and subjects, this sample cannot be considered representative of the general population. Thus, prevalence estimates and emotional dimensions can be different in other samples. Also, no psychiatric evaluation was conducted in the sample. As a self-report instrument, this instrument may include some

degree of desirability, although more than half of the subjects chose affective temperaments that were not associated with a particularly favorable profile in terms of problems and benefits. The emotional section contains multiple choice questions rather than phrases in a 5-point likert scale. This approach allows for better specification of items, but at the cost of time to fill in the scale. The two types of ratings and the selection of a category in the affective temperament section also requires the subject to adapt to new presentations and rules for answering. In terms of results, the drive factor was not as pure as the other factors, with some loadings from all the other factors. Even so, drive was differently expressed in affective temperaments than the other emotional factors. Finally, the dimensional assessment of affective temperaments is based on only one question, which has limitations for quantification compared to other scales such as the TEMPS, which has many items and wider scores.

In conclusion, the CEATS showed a satisfactory profile to assess the emotional factors that are thought to reflect affective expression. Thus, it may be helpful to evaluate emotional and affective temperaments in a wide range of psychiatric patients. Application of the Harm avoidance, Novelty Seeking, Persistence and Self-Directedness items of the TCI together with the TEMPS would typically require more than one hour, whereas the CEATS usually takes less than 30 min to be completed. Thus, CEATS may be a convenient instrument for both clinical and research ends to evaluate emotional and affective temperaments simultaneously, but this requires further testing.

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Table 1. Psychometric properties of the Emotional Section of the CEATS.

Scale Factor	Number of items	Total variation explained (%)	Mean score ± S.D	Alpha	Skewness	Kurtosis
1.Drive	8	20.2	24.8 ± 5.8 (8-40)	.82	-.13	-.29
2. Anger	6	12.5	17.7 ± 4.6 (6-30)	.74	.16	-.34
3. Disinhibition-fear	7	8.3	19.7 ± 4.2 (7-35)	.70	-0.05	.00
4. Control	6	5.0	19.8 ± 4.1 (6-30)	.71	-.31	-.03
Total scale	27	46.0	81.9 ± 10.8 (27-135)	.76	-.06	-.13

Table 2. Factorial matrix of CEATS – Emotional Section.

Factor/items	Factorial load: F1	Factorial load: F2	Factorial load: F3	Factorial load: F4
Factor 1: DRIVE				
Pessimistic/optimistic	.56	-.32.	.31	
Low/high excitement with novelty	.64			
Low/high sense of pleasure	.68			
Sad/cheerful	.63		.32	
Modest/ambitious plans	.63			
Easily/hardly gives up	.46		.36	.30
Insecure/self-confident	.42		.49	.31
low /high drive and goal direction	.67			.37
Factor 2: ANGER				
Hardly/easily irritable		.80		
Non-aggressive/very aggressive		.68		
Short/long duration of anger		.56		
Non explosive/very explosive		.73		
Rarely/often gets suspicious		.44		
Patient/very impatient		.65		
Factor 3: DISINHIBITION-FEAR				
Fearful/daring	.32		.58	
Shy/extroverted	.31		.59	
Cautious/risk-taking			.48	
Inhibited/spontaneous			.63	
Thoughtful/impulsive			.53	
Worried/unworried			.51	
Freezing in danger – reactive in			.48	
Factor 4: CONTROL				
Non/very disciplined				.63
Non/very organized				.67
Distractful/ non distractful				.60
Fails to finish tasks/finishes long				.67
Low concentration and interest/high concentration even without interest				.45
Irresponsible/very responsible				.63

Only loadings ≥0.30 and ≤-0.30 are shown.

Table 3. Correlation between emotional factors, problems, benefits and age.

	Disinhibition-fear	Drive	Control	Anger
Drive	.51**	-		
Control	.02	.34**	-	
Anger	.07*	-.17*	-.22**	-
Problem	-0.03	-0.28**	-0.31**	0.42**
Benefits	0.31*	0.52*	0.19*	-0.14**
Age	0.00	-0.13**	0.07*	-0.09*

* Correlation is significant at the 0.05 level.
** Correlation is significant at the 0.01 level.

Table 4. Gender differences for mean scores of emotional factors of CEATS.

FACTOR	Males (n=284)	Females (n=723)	F	p
Disinhibition-fear	20.5±4.2	19.3±4.3	13,186	<0.001
Drive	25.1±5.8	24.1±5.8	2,712	0.10
Control	19.2±4.2	20.0±4.1	5,945	0.015
Anger	17.5±4.6	17.9±4.7	2,048	0.15

Table 5. Correlations between dimensional scores of affective temperaments.

	Depr	**Anx**	**Cyclo**	**Dysph**	**Apath**	**Euthy**	**Irrit**	**Labil**	**Disin**
Anxious	**.46**	-							
Cyclothymic	**.42**	.30	-						
Dysphoric	.24	.27	**.51**	-					
Apathetic	**.45**	.28	.32	.20	-				
Euthymic	**-.43**	-.22	-.53	-.37	-.28	-			
Irritable	*.01*	.12	.26	**.46**	*-.05*	-.12	-		
Labile	.18	.10	**.41**	.35	**.41**	-.34	.27	-	
Disinhibited	*-.01*	*.02*	.25	.30	.23	-.12	.27	**.58**	-
Hyperthymic	**-.54**	-.28	-.30	-.14	**-.41**	**.48**	.11	-.13	*.05*

Values >0.40 and <-0.40 are in **bold**. Values in *italics* were statistically non-significant (p>0.05).

Table 6. Correlation of dimensional affective temperaments with emotional factors, problems, benefits and age.

	Depr	Anx	Cycl	Dysp	Apat	Euth	Irrit	Lab	Disi	Htm
Disinhib-fear	**-.46**	**-.41**	-.12	*.00*	-.32	.13	.13	*.05*	.21	.39
Drive	**-.65**	-.38	-.31	-.16	**-.46**	.33	.07	-.17	*.01*	**.65**
Control	-.20	*-.05*	-.30	-.21	**-.52**	**.41**	-.07	**-.48**	**-.40**	.33
Anger	.21	.22	**.43**	**.53**	.09	-.32	**.52**	.30	.20	-.17
Problems	.27	.16	.32	.29	.24	-.38	.19	.28	.20	-.25
Benefits	-**.44**	-.23	-.28	-.11	-.35	.32	*.02*	-.18	*-.02*	**.44**
Age	*.02*	*.02*	-.15	-.12	*-.01*	.08	-.13	-.07	-.09	*-.01*

Values ≥0.40 and ≤-0.40 are in **bold**. Values in *italics* were statistically non-significant (p>0.05).

FIGURE LEGENDS

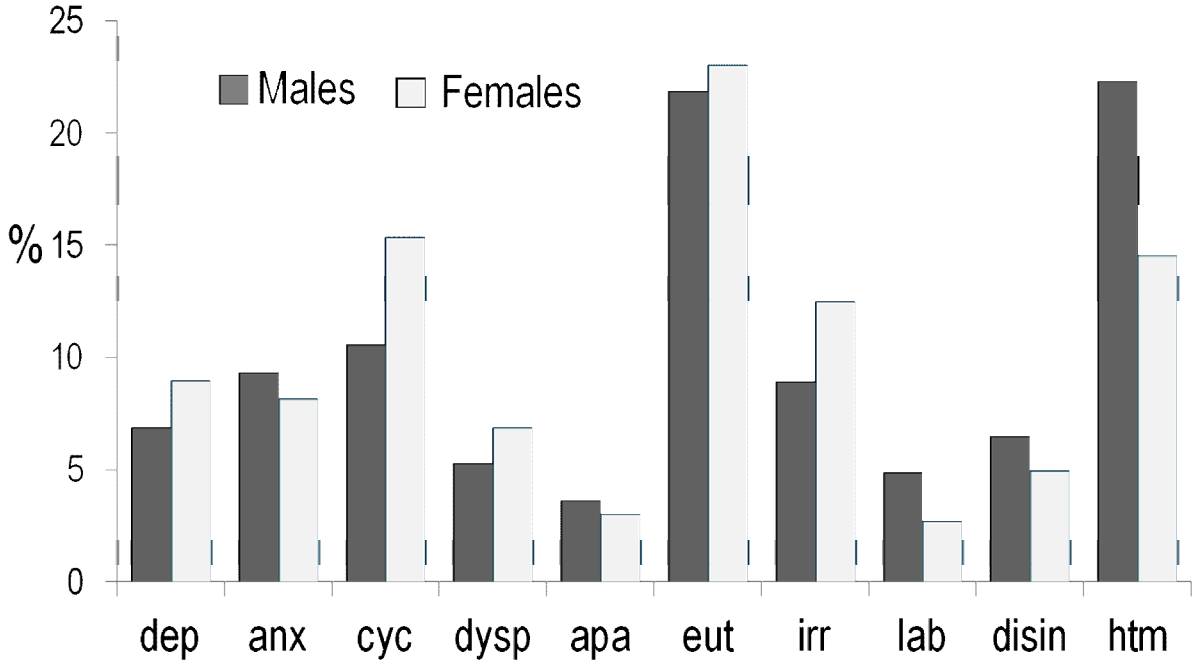

Figure 1. Prevalence of categorical affective temperaments in males and females. Subjects had to choose the affective temperament description that best fitted their profile. N = 1007, males = 284 (28.2%) females = 723 (71.8%). Dep = depressive, anx = anxious, cyc = cyclothymic, dysp = dysphoric, apa = apathetic, eut = euthymic, irr = irritable, lab = labile, disin = disinhibited, htm = hyperthymic.

Figure 2a – Total Sample (n=1007)

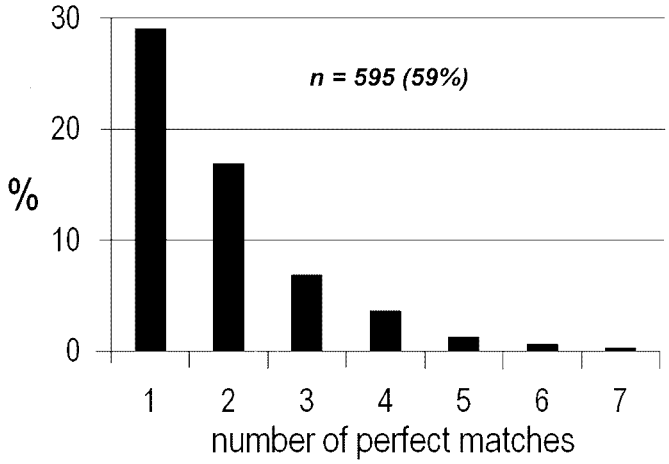

Figure 2b – Sample without a perfect match (n=412)

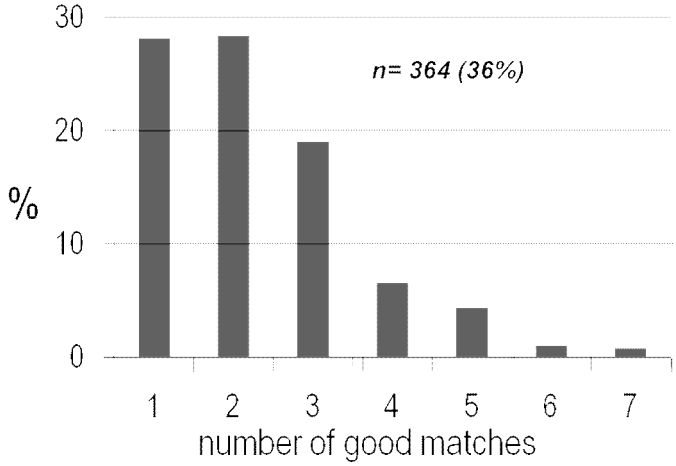

Figure 2a and Figure 2b. Frequency of perfect and good matches in the dimensional choice of affective temperaments. Perfect and good match are the descriptions marked as 'everything to do with me' and 'a lot to do with me', respectively. A = number of perfect matches in the whole sample; B = number of good matches among those without a perfect match.

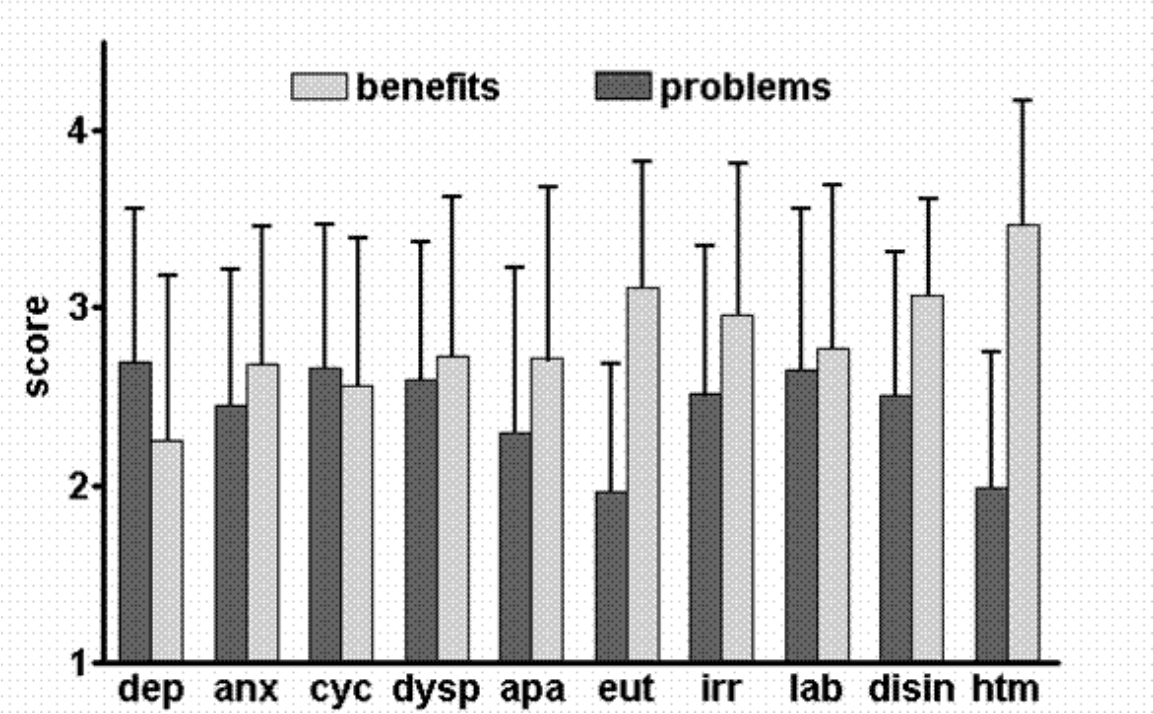

Figure 3. Problems and benefits scores associated with categorical affective temperaments. Score ranges from 1 (no problems or minimal benefits) to 4 (marked problems or benefits). Results are shown as mean ± s.d. For statistical differences, see Results. Dep = depressive, anx = anxious, cyc = cyclothymic, dysp = dysphoric, apa = apathetic, eut = euthymic, irr = irritable, lab = labile, disin = disinhibited, htm = hyperthymic.

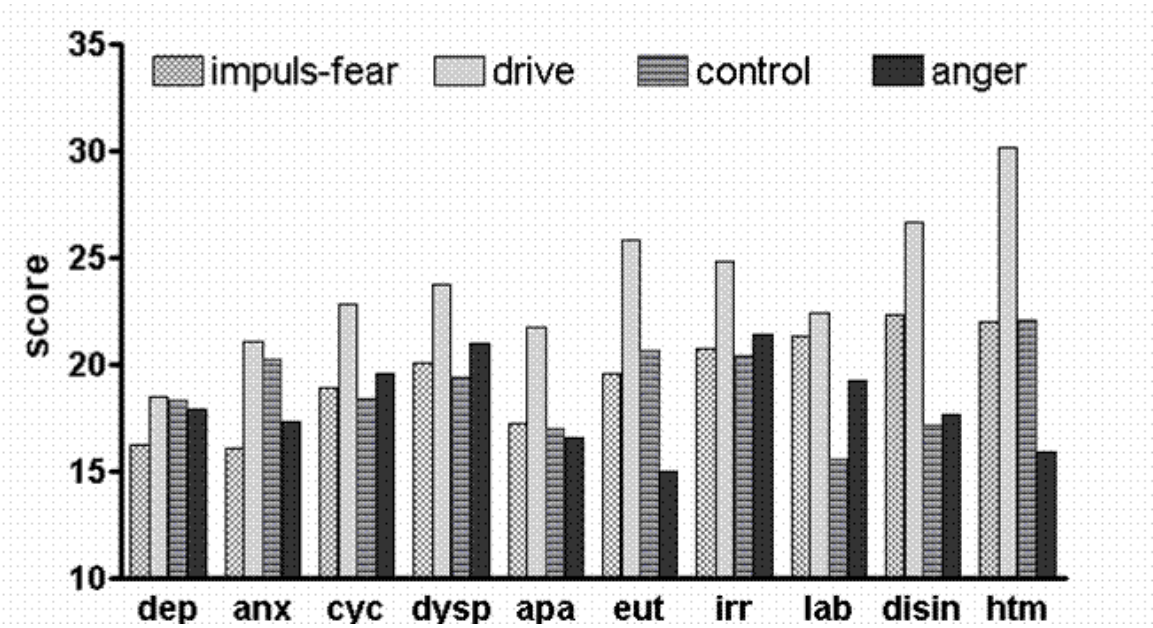

Figure 4. Emotional profile of categorical affective temperaments. Scores of disinhibition-fear (7-35), drive (8-40), control (6-30) and anger (6-30) are shown. For statistical differences, see Results. Dep = depressive, anx = anxious, cyc = cyclothymic, dysp = dysphoric, apa = apathetic, eut = euthymic, irr = irritable, lab = labile, disin = disinhibited, htm = hyperthymic.

APPENDIX

COMBINED EMOTIONAL AND AFFECTIVE TEMPERAMENT SCALE (CEATS) (this version has been translated, back translated and checked to correct for discrepancies from the original version in Brazilian Portuguese, but it has not been validated in English).

INSTRUCTIONS:

1) For each of the questions below, please mark the alternative that best matches the way you usually are and behave.
2) Read all the alternatives for each question before marking the one that most closely represents your profile. Answer all the questions and tick only one alternative.
3) Please answer carefully, but do not take too long to answer the questions.
4) Remember that there are no right or wrong answers. You must answer according to how you are, not how you wish you were.

1.
A) I am fearful
B) I am slightly more fearful than most people
C) I am slightly more daring than fearful
D) I am daring
E) I am very daring

2.
A) I am very shy
B) I am shier than most people
C) I am slightly more outgoing than shy
D) I am outgoing
E) I am very outgoing

3.
A) I am very careful and cautious; I rarely take risks
B) I am careful and cautious, I take few risks
C) In some situations I am careful and cautious, but in others I take risks
D) In general, I take more risks than most people
E) I am not careful and cautious; I often take risks

4.
A) I have great difficulty to feel at ease; I am very inhibited
B) I am inhibited, I have difficulty to feel at ease
C) Sometimes I feel a little awkward, but in general I feel at ease
D) I am spontaneous easygoing
E) I am very spontaneous, sometimes even too much

5.
A) I think too much before I do things; I take longer than others to make decisions

B) I think a lot before I do things; I rarely make decisions impulsively
C) I think before I do things, but I don't take long to make decisions
D) Sometimes I do things without having thought enough; I make decisions quickly
E) I often do things without thinking, I make decisions impulsively

6.
A) I worry too much
B) I worry more than most people
C) I worry as much as most people
D) I worry less than other people
E) I practically don't worry

7. In dangerous situations, my natural reaction is:
A) to freeze and remain tense even after the danger passes
B) to freeze until the danger is gone
C) to freeze at the beginning, but I soon manage to loosen up and act
D) to have some kind of quick reaction, I usually do not freeze
E) to react quickly, I never freeze

8.
A) I am pessimistic
B) I am more pessimistic than optimistic
C) I am a little more optimistic than pessimistic
D) I am optimistic
E) I am very optimistic

9.
A) I rarely get excited and lively about new activities
B) Sometimes I get excited and lively about new activities
C) It is fairly common for me to get excited and lively with new activities
D) It is common for me to get excited and lively with new activities
E) It is very common for me to get very excited and very lively with new activities

10.
A) I feel little pleasure and joy
B) I feel less pleasure and joy than most people
C) I feel as much pleasure and joy as most people do
D) I feel more pleasure and joy than most people
E) I feel pleasure and joy intensely

11.
A) I often get sad and miserable
B) I often get a little sad and miserable
C) I am fairly happy and content
D) I am happy and cheerful
E) I am very happy and very cheerful

12.
A) My plans are modest, and I think small
B) My plans are more modest than those of others
C) I have some ambitious plans
D) My plans are usually ambitious
E) My plans are very ambitious, I think big

13.
A) Any problem I have is enough to discourage me and to make me give up
B) I often get discouraged and give up when I face difficulties
C) I feel a bit discouraged when the situation is difficult or complicated
D) It is quite rare for me to feel discouraged and give up on things
E) I rarely feel discouraged and I almost never give up

14.
A) I am very insecure
B) I am less confident than most people
C) I feel reasonably confident
D) I am more confident than others
E) I am very self-confident

15.
A) I have few goals and it is hard for me to go after them
B) I have some goals and go after some of them
C) I have some goals and go after most of them
D) I have many goals and go after them
E) I have many goals, including difficult ones, and I go after all of them with vigor

16.
A) I have little discipline
B) I have less discipline than most people
C) I am reasonably disciplined
D) I have more discipline than most people
E) I have a lot of discipline

17.
A) I am disorganized and it sometimes brings me problems
B) I am less organized than most people
C) I organized in some things
D) I am more organized than most people
E) I am very organized, sometimes too much

18.
A) I easily get distracted and it often brings me problems
B) I often get distracted and sometimes it brings me problems
C) Sometimes I get distracted but it is not enough to disturb me

D) I get distracted less often than most people
E) I hardly get distracted

19.
A) I often fail to conclude that the tasks I start
B) I have some difficulty in completing the tasks I start
C) I conclude many of the tasks I start, but I usually give up the hard ones
D) I often complete the tasks I start, including some hard ones
E) I always conclude the tasks I start, even long or difficult ones

20.
A) It is difficult for me to keep my concentration and interest
B) I can only keep my concentration if I am interested
C) I can keep my concentration if I am fairly interested
D) I can keep my concentration even if I am not interested
E) I can keep my concentration *well* even I am not interested

21.
A) I am fairly irresponsible
B) I am less responsible than most people
C) I am reasonably responsible
D) I am more responsible than most people
E) I am very responsible

22.
A) It is rare for me to get irritated with something
B) I usually don`t get irritated
C) Sometimes I get irritated, but it rarely brings me problems
D) I get irritated more often than most people
E) I often get very irritated, and it often brings me problems

23.
A) I am not at all aggressive and sometimes it is a problem for me
B) I am not aggressive
C) I am a little less aggressive than most people
D) I am a little more aggressive than most people
E) I am quite aggressive in various situations

24. When I get angry, my anger lasts:
A) for a short time and I rarely get angry
B) shortly, I quickly calm down
C) slightly less than other people
D) longer than other people
E) a long time (‘it ruins my day’)

25.
A) I am not explosive at all
B) I am less explosive than others
C) Sometimes I am explosive
D) I am more explosive than others

E) I am very explosive

26. I …… feel I am being betrayed or someone is planning to do something against me:
A) Never
B) Almost never
C) Hardly ever
D) Sometimes
E) Often

27.
A) I am very patient
B) I am patient
C) I am a little impatient
D) I am impatient
E) I am very impatient

28. For each description below check the alternative that best corresponds to you (check only one alternative).
A) I have a tendency towards melancholy and sadness, I see little fun and joy in things; I tend to put myself down; I don't like changes; I prefer to listen than to talk.
a) everything to do with me
b) a lot to do with me
c) some things to do with me
d) little to do with me
e) nothing to do with me

B) I am very cautious and careful; I often feel insecure and apprehensive; I keep imagining that bad things are about to happen, I try to avoid high-risk situations; I am always alert and vigilant.
a) everything to do with me
b) a lot to do with me
c) some things to do with me
d) little to do with me
e) nothing to do with me

C) My mood is unpredictable and unstable (ups and downs or mood swings); my mood changes very quickly or out of proportion to the facts; I have periods of great energy, enthusiasm and energy that alternate with other phases of sluggishness, loss of interest and discouragement.
a) everything to do with me
b) a lot to do with me
c) some things to do with me
d) little to do with me
e) nothing to do with me

D) I have a strong tendency to feel agitated, anxious and angry at the same time.
a) everything to do with me
b) a lot to do with me
c) some things to do with me

d) little to do with me
e) nothing to do with me

E) I have little initiative; I often drift away from what others are saying or doing; I often fail to finish what I have started; I tend to be passive and a bit slow.
a) everything to do with me
b) a lot to do with me
c) some things to do with me
d) little to do with me
e) nothing to do with me

F) My mood is balanced and predictable, I usually have mood changes only when there is a clear reason, I have good spirits and, in general, I feel good about myself.
a) everything to do with me
b) a lot to do with me
c) some things to do with me
d) little to do with me
e) nothing to do with me

G) I am very frank, direct and determined, but also angry, suspicious and explosive.
a) everything to do with me
b) a lot to do with me
c) some things to do with me
d) little to do with me
e) nothing to do with me

H) I am restless and easily distracted; often I switch off or drift away from what others are saying or doing, I often do things without thinking about the consequences, and sometimes I am inconvenient and only realize it when it is too late; I quickly loose interest, and I often fail to finish what I have started; when I loose my temper, I soon calm down.
A) everything to do me
B) a lot to do with me
C) some things to do me
D) little to do me
E) nothing to do me

I) I am restless, active, spontaneous and distracted; I often rush and do careless things; I often leave things for the last minute; when I loose my temper, I soon get well again.
a) everything to do with me
b) a lot to do with me
c) some things to do with me
d) little to do with me
e) nothing to do with me

J) I am always in good spirits, I feel very confident and I have fun easily; I love novelty and I am always ready for new activities; I do many things without getting tired; when I want something, I go after and get it; I have a strong tendency for leadership.
a) everything to do with me
b) a lot to do with me
c) some things to do with me

d) little to do with me
e) nothing to do with me

29. Choose the description (A to J) from the question 28 above that is closest to your profile (only ONE alternative). Please read all the 10 descriptions before choosing the alternative.

[ ] A)
[ ] B)
[ ] C)
[ ] D)
[ ] E)
[ ] F)
[ ] G)
[ ] H)
[ ] I)
[ ] J)

30. To what extent have you had problems or personal losses due to your usual mood and the way you are and behave?

A) no problem / no losses
B) few problems / small losses
C) some problems / moderate losses
D) marked problems/ serious losses

31. To what extent have you gained benefits and had personal advantages due to your usual mood and the way you are and behave?

A) almost no advantage / minimal benefits
B) few advantages / small benefits
C) some advantages / moderate benefits
D) many advantages / marked benefits