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PROGRAMA DE PÓS-GRADUAÇÃO EM BIOLOGIA CELULAR E MOLECULAR
MESTRADO EM BIOLOGIA CELULAR E MOLECULAR

LISIÊ VALÉRIA PAZ

REVISÃO DOS MECANISMOS COMPORTAMENTAIS E FISIOLÓGICOS ENVOLVIDOS NA DEPRESSÃO CONTAGIANTE

Porto Alegre
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Dissertação apresentada como requisito para a obtenção do grau de Mestre pelo Programa de Pós-graduação em Biologia Celular e Molecular da Escola de Ciências da Saúde e da Vida da Pontifícia Universidade Católica do Rio Grande do Sul.

Área de concentração: Neurociências

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Por mais impetuoso que nosso progresso tenha sido, precisamos continuar inteiramente honestos com nós mesmos e reconhecer que só descobrimos uma minúscula fração do que há para saber do cérebro humano. Mas a modesta fração que descobrimos produz uma história mais excitante que qualquer romance de Sherlock Holmes. (RAMACHANDRAN, 2014, p. 10)

RESUMO

O transtorno depressivo maior (MDD, do inglês *Major Depressive Disorder*) é uma doença altamente incapacitante, com uma prevalência anual na população mundial que varia entre 3% a 11%. Os sintomas do MDD variam significativamente de paciente para paciente e vão de alterações de humor, falta de energia e anedonia até disfunções cognitivas e alterações metabólicas, endócrinas ou inflamatórias. A MDD é considerada uma doença muito heterogênea devido à sua alta complexidade de sintomas e alterações fisiológicas. Diversos tratamentos estão disponíveis, variando de psicoterapia a medicamentos antidepressivos, porém menos da metade dos pacientes diagnosticados apresentam melhora após a primeira intervenção farmacológica. Há décadas sabe-se que a depressão possui um aspecto contagiante, tendo uma ocorrência maior em indivíduos que compartilham de um mesmo ambiente de convivência. Infelizmente, os mecanismos pelos quais esse contágio ocorre não têm sido muito explorados. Pacientes depressivos possuem dificuldade em estabelecer uma comunicação emocional com os demais, o que contribui para o isolamento social, característico da doença. Em pacientes depressivos observa-se uma alteração dos padrões de ativação do córtex cingulado, região que integra informações emocionais, sensório-motoras e cognitivas além de desempenhar um papel fundamental em muitos aspectos da cognição social, da percepção da ação e do processamento da empatia. Neste projeto buscamos entender os mecanismos envolvidos no desenvolvimento da depressão contagiante através de uma abordagem teórica que culminou na produção de um artigo científico de revisão relacionando a depressão por contágio social, o mimetismo automático e o sistema de neurônios espelho.

Palavras-chave: Depressão contagiante, mimetismo automático, neurônios espelho, contágio emocional.

ABSTRACT

Major depressive disorder (MDD) is a highly disabling disease, with an annual world prevalence from 3% to 11%. MDD symptoms vary significantly among patients, ranging from mood swings, lack of energy and anhedonia, to cognitive dysfunction and metabolic, endocrine or inflammatory changes. MDD is considered a very heterogeneous disease due to its high complexity of symptoms and physiological changes. Several treatments are available, including psychotherapy and antidepressant medications, but less than half of the diagnosed patients show improvement after the first pharmacological intervention. For decades it is known that depression has a contagious aspect, having a greater occurrence between individuals who share the same living environment. Unfortunately, the mechanisms by which this contagion occurs has not been widely explored. Depressive patients have difficulty in establishing emotional communication with others, which contributes to the social isolation, a characteristic of the disease. In depressed patients, there is a change in the activation patterns of the Cingulate Cortex, a region integrating emotional, sensorimotor and cognitive information, in addition to playing a fundamental role in many aspects of social cognition, perception of action and processing of empathy. In this project we aimed to better understand the mechanisms involved in contagious depression through a theoretical approach that resulted in a scientific review article that connects contagious depression, automatic mimicry and the Mirror Neuron System.

Keywords: Contagious depression, automatic mimicry, mirror neurons, emotional contagion.

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LISTA DE ABREVIATURAS E SIGLAS

MDD – Do inglês *Major Depressive Disorder*, Transtorno Depressivo Maior;

OMS - Organização Mundial da Saúde;

DSM – Do inglês *Diagnostic and Statistical Manual*, Manual Diagnóstico e Estatístico de Transtornos Mentais;

ISRS – Inibidores seletivos da recaptação de serotonina;

IMAO – Inibidores da monoamina oxidase;

TCA – Antidepressivos tricíclicos;

rTMS – Do inglês *Repetitive Transcranial Magnetic Stimulation*, Estimulação Magnética Transcraniana Repetitiva;

HPA – Hipotálamo-hipófise-adrenal;

DmPFC – Córtex Pré-frontal Dorso Medial;

VmPFC – Córtex Pré-frontal Ventromedial;

DlPFC – Córtex Pré-frontal Dorsolateral;

VlPFC – Córtex Pré-frontal Ventrolateral;

ACC – Córtex Cingulado Anterior;

OFC – Córtex Orbitofrontal;

THAL – Tálamo;

AMY – Amígdala;

HPC – Hipocampo;

TSPO – Proteína translocadora;

TDCS – Do inglês *Transcranial Direct-Current Stimulation*, Estimulação Transcraniana por Corrente Contínua;

fNIRS – Do inglês *Functional Near-Infrared Spectroscopy*, Espectroscopia Funcional no Infravermelho Próximo.

fMRI – Do inglês *Functional Magnetic Ressonance Imaging*, Imagem por Ressonância Magnética Funcional;

MNS – Do inglês *Mirror Neunon System*, Sistema de Neurônios Espelho;

IFG – Giro frontal inferior;

PMv – Área pré-motora ventral;

PMd – Área pré-motora dorsal;

SMA – Área motora suplementar;

STS – Sulco temporal superior;

M1 – Córtex motor primário;

S1 – Córtex somatossensorial primário;

Pmtg – Giro temporal médio posterior;

FFA – Área fusiforme da face;

IPL – Lóbulo parietal inferior;

MT / V5 – Área temporal média;

ASD – Do inglês *Autism Spectrum Disorders*, Transtornos do Espectro Autista.

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1. CAPÍTULO 1

1.1 Transtorno Depressivo Maior

O transtorno depressivo maior (MDD – do inglês *major depressive disorder*) é um dos distúrbios psiquiátricos mais comuns, representando a principal causa de incapacidade em todo o mundo. Segundo o relatório de 2017 da Organização Mundial da Saúde (OMS) cerca de 322 milhões de pessoas sofrem de depressão no mundo, no Brasil essa doença atinge 5,8% da população (1).

O MDD é caracterizado não somente por alterações de humor como a falta de energia, humor depressivo, sentimento de culpa, baixa autoestima, baixa concentração e anedonia (1–3), mas também está associado a outros sintomas, como disfunção cognitiva, distúrbios do sono e apetite, fadiga, alterações metabólicas, endócrinas ou inflamatórias (Figura 1). A etiologia da depressão não é bem compreendida, podendo surgir espontaneamente, ter como gatilho um evento estressor traumático, ser relacionada ao abuso de drogas ou até decorrente de doenças prévias como o acidente vascular cerebral, a esclerose múltipla, a doença de Parkinson, a doença de Cushing ou o hipotireoidismo. Além disso, cerca de 50% dos fatores relacionados ao desenvolvimento da doença são genéticos (4). De acordo com o Manual Diagnóstico e Estatístico de Transtornos Mentais (DSM), existem 681 combinações possíveis de sintomas que poderiam atender aos critérios do diagnóstico de depressão maior, o que reflete a heterogeneidade e complexidade de sintomas e da fisiopatologia da doença (5). Existem inúmeras modalidades de tratamento disponíveis, desde a psicoterapia até medicamentos antidepressivos, porém menos da metade dos pacientes que são diagnosticados têm melhora na primeira abordagem clínica. Cerca de um terço dos pacientes com depressão maior não respondem adequadamente aos tratamentos convencionais disponíveis (6,7).

Os inibidores seletivos da recaptação de serotonina (ISRSs) são considerados tratamento de primeira linha para a depressão, e mesmo assim, somente pouco mais de 30% dos pacientes respondem ao tratamento. Dentre estes, mais de 50% voltam a apresentar os sintomas devido a uma perda de eficácia do medicamento (6,7). Por sua vez, os inibidores da monoamina oxidase (IMAO) são consideradas drogas clássicas para o tratamento do MDD. Descobertos nos anos 50 durante um ensaio clínico para

tratamento da tuberculose, os IMAO tiveram efeito positivo sobre o humor dos pacientes. A droga é responsável pelo aumento dos níveis de neurotransmissores monoaminérgicos, tais como a serotonina e a norepinefrina, e age inibindo a enzima que os degrada após sua liberação na fenda sináptica. Este mecanismo de ação também é utilizado por outra classe de antidepressivos como os tricíclicos (TCA). Os IMAOs e os TCAs são considerados antidepressivos de primeira geração e possuem muitos efeitos adversos, dificultando a aderência ao tratamento, entretanto possuem uma taxa de resposta clínica e remissão melhor que os ISRSs (7).

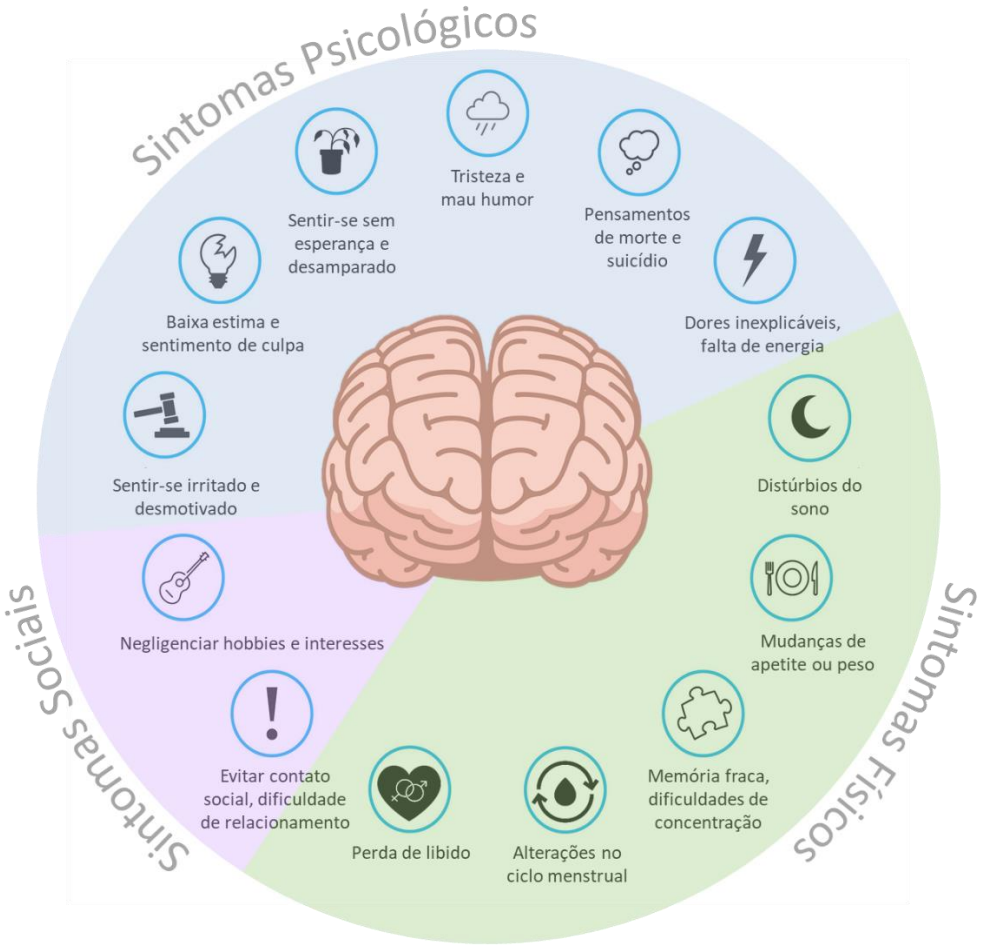


Figura 1. Principais sintomas da depressão. Subdivididos em sintomas físicos, psicológicos e sociais. (Adaptado de *Medical News Today, article: Common symptoms of depression: What to know*, disponível em: https://www.medicalnewstoday.com/articles/326769).

Outro tratamento que está ganhando aderência de pacientes com depressão é a estimulação magnética transcraniana repetitiva (rTMS do inglês *repetitive transcranial magnetic stimulation).* O rTMS se trata de um procedimento não invasivo onde uma sequência de pulsos magnéticos de alta intensidade são aplicados para a estimulação de neurônios corticais. Em pacientes com resistência aos tratamentos mais convencionais esse método parece fornecer melhoras significativas a curto prazo, além de fornecer outras vantagens como ter poucos ou nenhum efeito colateral (8).

O MDD vem sendo intensamente estudado nas últimas décadas, porém as alterações neurobiológicas bem como os mecanismos celulares envolvidos no desenvolvimento da doença ainda não foram completamente esclarecidos. As primeiras teorias relacionavam exclusivamente ao metabolismo e atividade da serotonina, seja quanto ao número de receptores, número de neurônios serotoninérgicos ou níveis do neurotransmissor no encéfalo. Atualmente são bem documentados os casos onde o metabolismo da serotonina parece não ser o fator determinante no desenvolvimento da doença (9,10). Muitos estudos recentes apontam que diversos outros fatores como alterações nos níveis das monoaminas, aumento da inflamação, anormalidades no eixo hipotálamo-hipófise-adrenal (eixo HPA), alterações vasculares e diminuição da neurogênese e neuroplasticidade estão envolvidos no desenvolvimento da doença (11). Além disso, diversos autores vêm alertando sobre a importância de fatores sociais e ambientais no desenvolvimento da depressão. O círculo social, o ambiente e contexto social em que o paciente está inserido podem ser determinantes não apenas para o desenvolvimento de um quadro depressivo mas também na recuperação do mesmo (12–15). Porém, diferentes pacientes irão apresentar um conjunto de sintomas e alterações fisiopatológicas, assim como suscetibilidade aos efeitos do ambiente, diferentes. Essas particularidades dificultam não somente o diagnóstico e tratamento dos pacientes, como também o entendimento da fisiopatologia da doença (11).

1.2 Neuroanotomia e neurofisiologia da depressão

A neuropatofisiologia da depressão é uma área extensamente estudada e muito se tem alcançado com estudos de neuroimagem (16). Muitos destes apontam para uma alteração no padrão de ativação de algumas áreas encefálicas em pacientes com

depressão, dentre elas o córtex pré-frontal dorsolateral e dorsoventral,, o córtex cingulado anterior, o córtex orbitofrontal, a ínsula, a amígdala, o hipocampo e o tálamo (figura 2) (17). Entre as alterações mais comuns está a diminuição do metabolismo do córtex pré-frontal de pacientes depressivos comparados ao grupo controle (18–21). Esse achado explica os bons resultados obtidos com o uso de estimulação magnética transcraniana na região pré-frontal como terapia para pacientes que não respondem aos tratamentos mais convencionais (22). Outros estudos também apontam uma diminuição no metabolismo do córtex cingulado e o aumento da atividade límbica com hiperativação da amígdala e do tálamo nesses pacientes. Além disso, a redução no volume do lobo pré-frontal, córtex orbitofrontal e hipocampo são alterações estruturais bastante relacionadas à morfologia cerebral de pacientes com depressão (17,23).

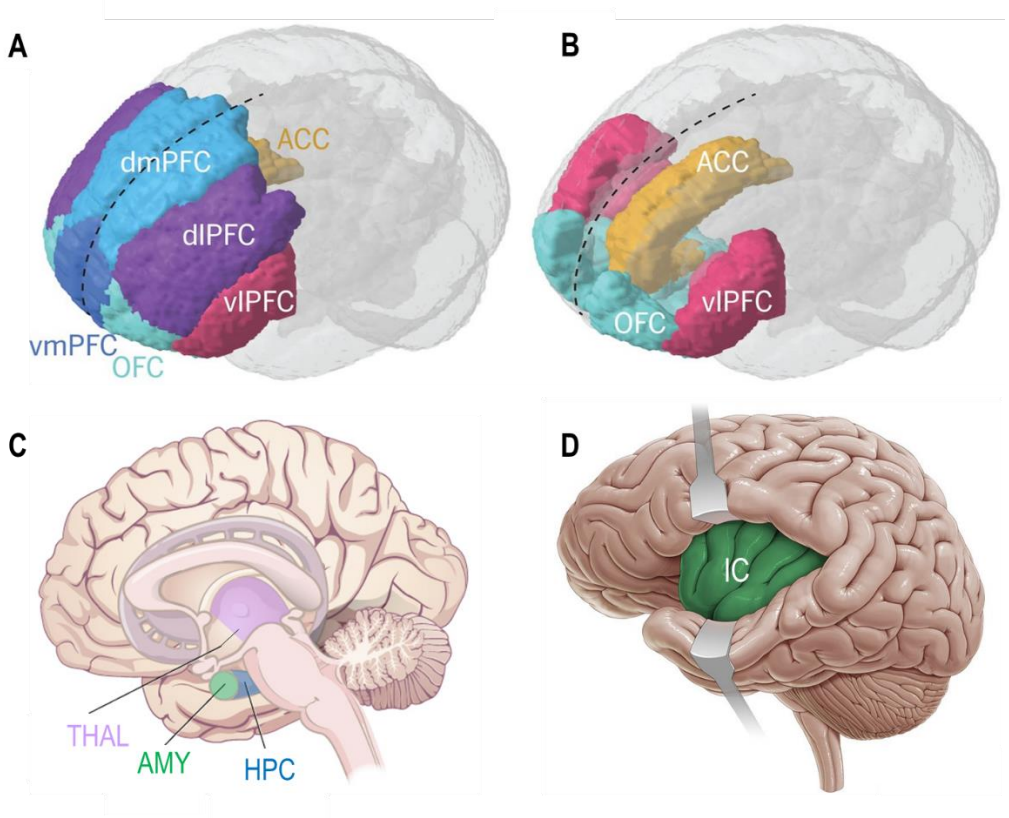


Figura 2. Regiões cerebrais envolvidas na fisiopatologia da depressão. A e B – Sub-regiões do Córtex Pré-frontal, dmPFC: Córtex Pré-frontal Dorso Medial, vmPFC: Córtex Pré-frontal Ventromedial, dlPFC: Córtex Pré-frontal Dorsolateral, vlPFC: Córtex Pré-frontal Ventrolateral, ACC: Córtex Cingulado Anterior, OFC: Córtex Orbitofrontal. C – THAL: Tálamo, AMY: Amígdala, HPC: Hipocampo. D – IC: Córtex Insular (Adaptado de *What constitutes the prefrontal cortex?* DOI: 10.1126/science.aan8868).

O córtex cingulado tem um papel chave na integração de informações importantes para funções emocionais, sensório-motoras e cognitivas (24). A porção dorsal do córtex cingulado parece estar envolvida em aspectos cognitivos da emoção incluindo resolução de conflitos relacionados a estímulos emocionais negativos. Já o córtex cingulado ventral faz conexões com regiões límbicas como a amígdala e o tálamo, além de conectar-se com áreas corticais responsáveis pela regulação do humor, como o córtex orbitofrontal e córtex pré-frontal medial. Essa conexão com o hipotálamo, envolvido na resposta ao estresse, e com demais áreas também envolvidas no desenvolvimento da depressão faz do córtex cingulado uma área de interesse no estudo da neuropatofisiologia da depressão (17). Interessantemente, estudos utilizando ressonância magnética funcional (fMRI,- do inglês *Functional Magnetic Ressonance Imaging*) atribuem o processamento da empatia ao córtex cingulado (25,26). Em um destes estudos, onde os pacientes deveriam observar outra pessoa sendo submetida a um estímulo de dor, o córtex cingulado anterior foi menos ativo em pacientes diagnosticados com psicopatia, distúrbio caracterizado pela falta de empatia, em comparação com o grupo controle (27).

Além de ser relacionado a uma diminuição da resposta empática, reduções na reatividade do córtex cingulado também vem sendo relacionadas a depressão maior (28–30). De fato, pacientes com depressão maior demonstram dificuldade em sustentar relações interpessoais, o que pode ser resultado d e uma incapacidade de entender e responder aos sentimentos e emoções dos outros (31). Ademais, ao serem submetidos a uma tarefa de resposta a dor de outras pessoas, durante fMRI, pacientes depressivos classificaram o estímulo de dor como menos doloroso comparado ao grupo controle e demonstraram menor ativação cerebral no córtex cingulado e córtex pré-frontal (26). Embora esses estudos sugiram que pacientes com MDD possuem o circuito do processamento da dor alterado, levando a uma alteração também da sua capacidade de reconhecimento da dor em outros indivíduos (32), um estudo recente sugeriu que essa alteração é devido aos fármacos usados no tratamento da depressão, e não da doença em si. Segundo os autores, os pacientes demonstram uma redução da resposta empática frente a tarefes cognitivas e afetivas, após o início do tratamento com antidepressivos, mas não na fase pré-tratamento (33).

Nesse sentido, um estudo recente sugeriu que a reatividade basal do córtex cingulado de pacientes depressivos anterior ao início da intervenção farmacológica pode servir como um biomarcador da eficácia do tratamento. Foi verificado que os sujeitos que

tinham maior ativação basal do córtex cingulado, responderam ao tratamento de 6 semanas com ISRS enquanto aqueles que tinham menor ativação não responderam ao tratamento (34,35). Outro achado interessante foi a observação do aumento da proteína translocadora (TSPO), predominante na micróglia, no córtex cingulado de pacientes com MDD. O aumento dessa proteína é indicativo de neuroinflamação, que tem sido associada a casos graves de depressão, inclusive quando há ideação suicida. Esse mesmo estudo afirma que altos níveis de TSPO em pacientes depressivos pode estar mais associado ao suicídio do que o próprio diagnóstico de MDD (36).

Quanto aos neurotransmissores envolvidos, além da desregulação serotoninérgica já bem estabelecida, recentemente tem sido reportado evidências de uma desregulação glutamatérgica. Em estudos de espectroscopia por ressonância magnética nuclear foi observado uma diminuição de glutamato e glutamina na região do córtex cingulado e pré-frontal de pacientes depressivos (37,38). Glutamato é mais comumente encontrado em neurônios enquanto glutamina é típico de astrócitos, importantes células gliais. Uma revisão de 2014 avaliou todos estudos recentes que quantificaram os níveis de glutamato e níveis absolutos de glutamato e glutamina combinados. Os resultados apontaram uma diminuição dos níveis absolutos em pacientes depressivos, mas sem diferença dos níveis de glutamato em relação aos grupos controles, indicando uma redução da glutamina. Esses dados apontam, mesmo que indiretamente, para uma alteração glutamatérgica de origem glial (39).

O desenvolvimento de um quadro depressivo também se relaciona com o grau de conexão entre diferentes áreas encefálicas envolvidas no processamento emocional e as redes neurais que as conectam. Através de estudos de ressonância magnética, é possível observar que a conexão entre o córtex pré-frontal direito e a amigdala é aumentada em pacientes com sintomas de depressão, mas que ainda não iniciaram nenhum tratamento, comparado a pacientes sadios (40). Uma maior ativação do córtex pré-frontal direito esta associado ao processamento de estímulos emocionais negativos, enquanto o córtex pré-frontal esquerdo demonstra maior ativação diante de estímulos emocionais positivos (41). Dessa forma, alterações funcionais do córtex pré-frontal direito (mas não do esquerdo) resultam em disfunções da regulação de emoções negativas, explicando o aumento da conexão com amigdala nesse lado do córtex em pacientes depressivos (42). Tal fato é corroborado pelo uso terapêutico da Estimulação Transcraniana por Corrente Contínua (TDCS, do inglês *transcranial direct-current stimulation*) utilizada em pacientes com

depressão. Nessa abordagem terapêutica é feito, ao mesmo tempo, uma estimulação do córtex pré-frontal esquerdo e inibição do córtex pré-frontal direito (43).

Outro método de imagem que vem sendo utilizado no âmbito da pesquisa, mas estima-se que seja utilizado no âmbito do diagnóstico da depressão dentro dos próximos anos é a espectroscopia funcional no infravermelho próximo (fNIRS – do inglês *functional near-infrared spectroscopy*). O fNIR permite a investigação da oxigenação periférica tecidual e hemodinâmica de forma não invasiva e contínua (44). Um estudo recente avaliou as alterações hemodinâmicas e de oxigenação no córtex pré-frontal de pacientes depressivos durante uma tarefa emocional de reconhecimento facial. Os resultados apontaram para uma alteração no padrão hemodinâmico do córtex pré-frontal esquerdo, assim como uma redução da oxigenação dessa área nesses pacientes (45). Esses resultados em adição aos os estudos citados anteriormente sugerem fortemente uma redução da ativação do córtex pré-frontal, principalmente do lado esquerdo.

1.3 Sistema de Neurônios Espelho

Os neurônios espelho foram descobertos na área F5 da região pré-motora de macacos em 1992 (46), o nome foi dado ao observar que estas células disparam ao observar uma ação sendo executada por outro indivíduo e imediatamente ao executar a mesma ação (47). Esse sistema foi detectado em áreas corticais do encéfalo humano via técnicas de neuroimagem e eletroencefalografia, sendo relacionado a compreensão de ações realizadas pelos outros e suas intenções (48). O Sistema de Neurônios Espelho (MNS do inglês *Mirror Neuron System*) vem sendo bastante estudado recentemente, porém conta com poucos métodos de análise disponíveis (49). Atualmente sabemos que o MNS pode desempenhar um papel chave em muitos aspectos da cognição social, desde a percepção da ação até a empatia (50).

O sistema de neurônios espelho humano engloba uma extensa rede neuronal, com diversas regiões e sub-regiões. A área motora suplementar (SMA), o lóbulo parietal inferior (IPL) e o sulco temporal superior (STS) são regiões chave dessa rede. A área pré-motora ventral (PMv), o giro frontal inferior (IFG) e o córtex motor primário (M1) são sub-regiões relacionadas a funções motoras no lobo frontal. Por sua vez, o córtex somatossensorial primário (S1), o giro temporal médio posterior (pMTG) e a área temporal média (MT/V5), são sub-regiões do lobo temporal, assim como a área fusiforme da face (FFA), relacionada as expressões faciais (figura 3) (51).

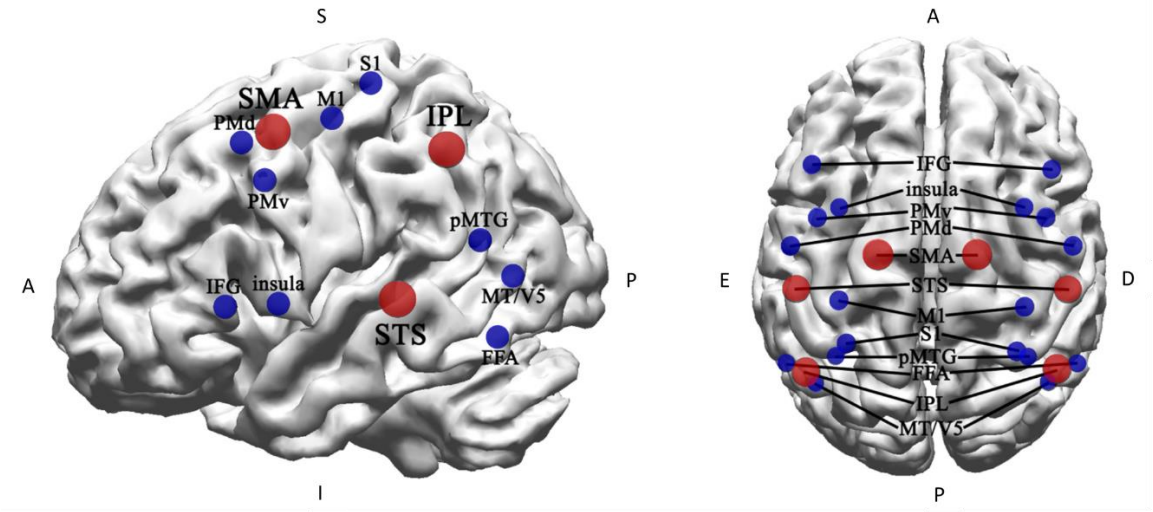


Figura 3. Sistema de neurônios espelho em humanos. Em vermelho as regiões principais e em azul as sub-regiões. A imagem à esquerda é a vista lateral esquerda e a imagem da direita é a vista superior de ambos os hemisférios. S, superior; I, inferior; A, anterior; P, posterior; E, esquerda; D, direita; IFG, giro frontal inferior; PMv, área pré-motora ventral; PMd, área pré-motora dorsal; SMA, área motora suplementar; STS; sulco temporal superior; M1, córtex motor primário; S1, córtex somatossensorial primário; pMTG, giro temporal médio posterior; FFA, área fusiforme da face; IPL, lóbulo parietal inferior; MT / V5, área temporal média. (Adaptado de *From Neurons to Social Beings: Short Review of the Mirror Neuron System Research and Its Socio-Psychological and Psychiatric Implications* DOI: 10.9758/cpn.2018.16.1.18).

O MNS possui, também, uma rede límbica, que se conecta com a ínsula e o córtex cingulado anterior sendo considerado um importante sistema neural para o processamento emocional (52,53). Esse sistema foi associado ao processamento de empatia, através de estudos que avaliam a dor empática e aversão (54–56). Além disso, o MNS também é relacionado ao senso de moralidade, um estudo de 2002 mostrou que o STS teve maior ativação quando os participantes observavam imagens com violação moral do que quando observavam imagens emocionalmente desagradáveis (57).

Recentemente, uma revisão sistemática dos principais trabalhos publicados relacionando empatia e nosso sistema de neurônios espelho, demonstrou uma associação significativamente positiva entre a empatia cognitiva/emocional com esses neurônios, porém salientam que não existe uma metodologia padronizada para o estudo deste tópico e por isso os dados disponíveis ainda não são robustos o suficiente (49).

A ligação entre neurônios espelho e desordens do espectro autista (ASD, do inglês *autism spectrum disorders*) tem sido muito investigada. Pessoas com ASD geralmente possuem dificuldade de imitação, cognição social, comunicação social e empatia,

atividades relacionadas com o MNS (58). Alguns estudos já sugeriram uma disfunção do MNS nesses indivíduos, apontando diminuição da espessura de áreas que pertencem a esse sistema e ativação anormal dessas áreas (59,60) . Nesse sentido, diversas características de ASD e MDD se sobrepõem. Ambas doenças compartilham componentes genéticos associados aos seus desenvolvimentos e frequentemente pacientes depressivos e do espectro autista desenvolvem sintomas parecidos. Além disso, antidepressivos fazem parte do tratamento de parte dos indivíduos autistas, portanto é possível que as disfunções cerebrais de ambas doenças também se sobreponham (58). Yuan (2008) sugere essa ligação entre ambas as doenças e sua possível origem: disfunção do MNS. Além disso, afirma que ao considerar o papel do MNS em disfunções emocionais, como a MDD, também presente no diagnóstico autista, a estimulação das áreas pertencentes ao MNS pode ser uma ferramenta aliada na prevenção e tratamento dessas desordens emocionais (58).

A fim de testar essa hipótese, um grupo de pesquisa testou a estimulação de áreas ricas em neurônios espelhos do córtex parietal inferior com uso de rTMS em comparação com a estimulação do córtex pré-frontal esquerdo, área convencionalmente estimulada em pacientes com MDD, conforme citado anteriormente. O grupo que fez estimulação transcraniana (rTMS) nas áreas ricas em neurônios espelho teve melhora nos parâmetros de regulação emocional e empatia comparado ao grupo que fez estimulação padrão recomendada para pacientes depressivos. Esse estudo corrobora o envolvimento dos neurônios espelho, não apenas na regulação emocional mas na empatia, apresentando um padrão de ativação alterado em pacientes com MDD (61).

Empatia pode ser definida de várias formas, mas intrinsecamente é o que nos ajuda a compreender as intenções de outras pessoas (62). Alguns autores propõem que o MNS pode ser a base biológica da empatia, que seria uma resultante dos processos de espelhamento(62–64). Quando pessoas observam expressões faciais de bem estar durante estudos de empatia, os mesmos músculos são ativados ao imitar a expressão. Se essa imitação é inibida, sua capacidade de identificar a raiz emocional da expressão facial é reduzida (65). Além disso, já foi observado que as mesmas áreas cerebrais são ativadas tanto na tarefa de reconhecimento de expressões faciais quanto na tarefa de reprodução dessas expressões. Esses achados indicam que os substratos neurais responsáveis por sentir uma emoção e reconhecer uma emoção no outro podem ser os mesmos (66).

Alguns autores sugerem que graças aos neurônios espelho somos capazes de entender as ações dos outros através da simulação interna dessas ações. Nesse sentido a

imitação automática dos movimentos do outro nos possibilita compreender as intenções que deram origem a esse movimento funcionando como uma ferramenta para entender o que se passa na mente do outro (67). Lamm e Majdandzica (2015) salientam que devemos ter cuidado ao atribuir o fenômeno da empatia unicamente aos neurônios espelho, pois a linha de pesquisa ainda carece de evidência empírica que suporte esse tipo de afirmação (68).

1.4 Contágio Emocional

Emoções são contagiantes, diversos pesquisadores de várias áreas já chegaram nesse consenso (13,69–72). Durante interações sociais tendemos a tentar adivinhar o que o outro está sentindo ou pensando, utilizamos expressões corporais, faciais, gestos e microexpressões como dicas do nosso estado interno (73). Esse contágio emocional ocorre tanto para emoções de valência positiva quanto negativa, e aparentemente não temos controle dessa transmissão (69). Esse mecanismo parece ser uma importante ferramenta que facilita a comunicação e a conexão emocional entre membros de um grupo. O ambiente social pode ser imprevisível, por isso o desenvolvimento de habilidades de cognição social, comunicação afetiva e interpretação de pistas sociais foram selecionadas ao longo da evolução humana, gerando indivíduos capazes de contágio emocional (72).

Os mecanismos responsáveis pelo contágio emocional ainda estão sendo explorados, mas um dos mais citados pelos pesquisadores da área é o mimetismo automático. Mimetismo automático é a imitação automática e inconsciente da fala, movimentos, gestos, expressões faciais, movimento dos olhos e até de parâmetros autonômicos como dilatação pupilar, ritmos respiratórios e cardíacos (72). Esse fenômeno envolve um sujeito que envia a pista emocional, o “sender” e outro sujeito que recebe essas pistas, o “receiver”. Mas diferentemente do que se espera de um contágio viral, por exemplo, o contágio emocional não é indiscriminado, e depende de parâmetros sociais, interpessoais e individuais. Segundo a teoria de contágio emocional através de mimetismo automático, existem dois passos para o estabelecimento do contágio. Primeiro o “receiver” sem querer imita as expressões do “sender”; seguido de um feedback aferente causado pela imitação que estimula o mesmo estado emocional no “receiver” (74).

1.5 Depressão Contagiante

Foi proposto por Coyne em 1976 que pacientes depressivos provocam uma reação negativa em pessoas do seu convívio. Em seu estudo, foi demonstrado que 40% das pessoas que se relacionaram com alguém depressivo requisitaram atendimento psiquiátrico (75). Sua teoria era simples e previa que depressão era capaz de induzir depressão em outras pessoas do mesmo convívio. Em 1994, Thomas Joiner afirmou a existência de depressão por contágio em um estudo controlado com 48 pares de estudantes colegas de quarto. Verificou também que o contágio é específico para sintomas da depressão, não ocorrendo com outros transtornos psiquiátricos como a ansiedade, por exemplo (15,76,77).

Desde então muitos estudos demonstrando que a depressão tem um efeito negativo em indivíduos do mesmo convívio social têm sido publicados, com alta frequência em membros de uma mesma família, colegas, parceiros e amigos de um mesmo ciclo de convivência (12,75,78–81). Infelizmente, os mecanismos pelos quais esse "contágio" ocorre não têm sido muito investigados. Um estudo recente estabeleceu um modelo animal para o estudo pré-clínico da depressão por contágio. Essa descoberta certamente amplia as possibilidades de pesquisas futuras, possibilitando o estudo dos mecanismos celulares e morfológicos envolvidos neste fenômeno (82).

Tanto estados emocionais de valência positiva quanto estados emocionais de valência negativa se disseminam entre grupos sociais, como uma doença infecciosa, daí o uso do termo "contágio emocional". Apesar de ser uma doença multifatorial, a depressão parece ter um aspecto contagiante. Estudos apontam que se um amigo ou familiar tem depressão, as chances de o indivíduo desenvolver a doença aumentam (70,83,84). Além disso, o desenvolvimento da doença em um indivíduo do círculo social pode ter efeitos de longo prazo no humor dos outros indivíduos (70). Fowler e Christakis (2012) observaram que pessoas depressivas procuram se relacionar com outras pessoas nas mesmas condições, alterando o estado de humor uma das outras após longos períodos de convivência (13). Bastiampillai (2013) sugere a existência de mecanismos conscientes e inconscientes atribuindo os mecanismos inconscientes ao mimetismo automático e o sistema de neurônios espelhos, e os mecanismos conscientes a estilos específicos de comunicação como a co-ruminação (12).

2 JUSTIFICATIVA

Segundo o ministério da saúde, a prevalência de depressão ao longo da vida do brasileiro é em torno de 15,5% e esse número vêm crescendo rapidamente. É considerada uma doença extremamente debilitante, que atrapalha o convívio social, impossibilita o seguimento de atividades laborais e é a principal responsável pelos casos de suicídio no mundo. Ademais, segundo a OMS, depressão e ansiedade geram um impacto na economia mundial de quase 1 trilhão de dólares.

Sabe-se que a depressão é multifatorial, onde somam-se fatores genéticos, ambientais, traumas, aspectos sociais, presença de doenças prévias, abuso de substâncias entre outros fatores envolvidos. São conhecidos apenas alguns dos mecanismos responsáveis pelos sintomas, porém muitos pacientes permanecem sem um tratamento eficaz pois ainda não se entende por completo a fisiopatologia da doença. Diversos estudos na literatura concluem que a depressão pode ser transmitida dentro de um círculo de convívio social. Entretanto pouco se tem conhecimento a respeito dos mecanismos envolvidos no estabelecimento deste modelo de depressão.

Dessa forma, se faz necessário, pra o entendimento aprofundado da depressão contagiante, o levantamento dos dados já existentes na literatura. É necessária a compreensão desses resultados e a conexão dos mesmo com outras linhas de conhecimento também possivelmente associadas a esse modelo de estabelecimento da doença.

3 OBJETIVOS

3.1 Objetivo Geral

O presente projeto tem como objetivo uma revisão bibliográfica e a produção de um artigo científico de revisão a respeito da depressão contagiante.

3.2 Objetivos Específicos

a) Levantar dados, informações, teorias e resultados relacionados aos aspectos ainda pouco explorados da depressão contagiante.
b) Utilizar esses materiais na confecção de um artigo de revisão que ilustre aspectos da depressão contagiante, como o mimetismo automático e o sistema de neurônios espelho.

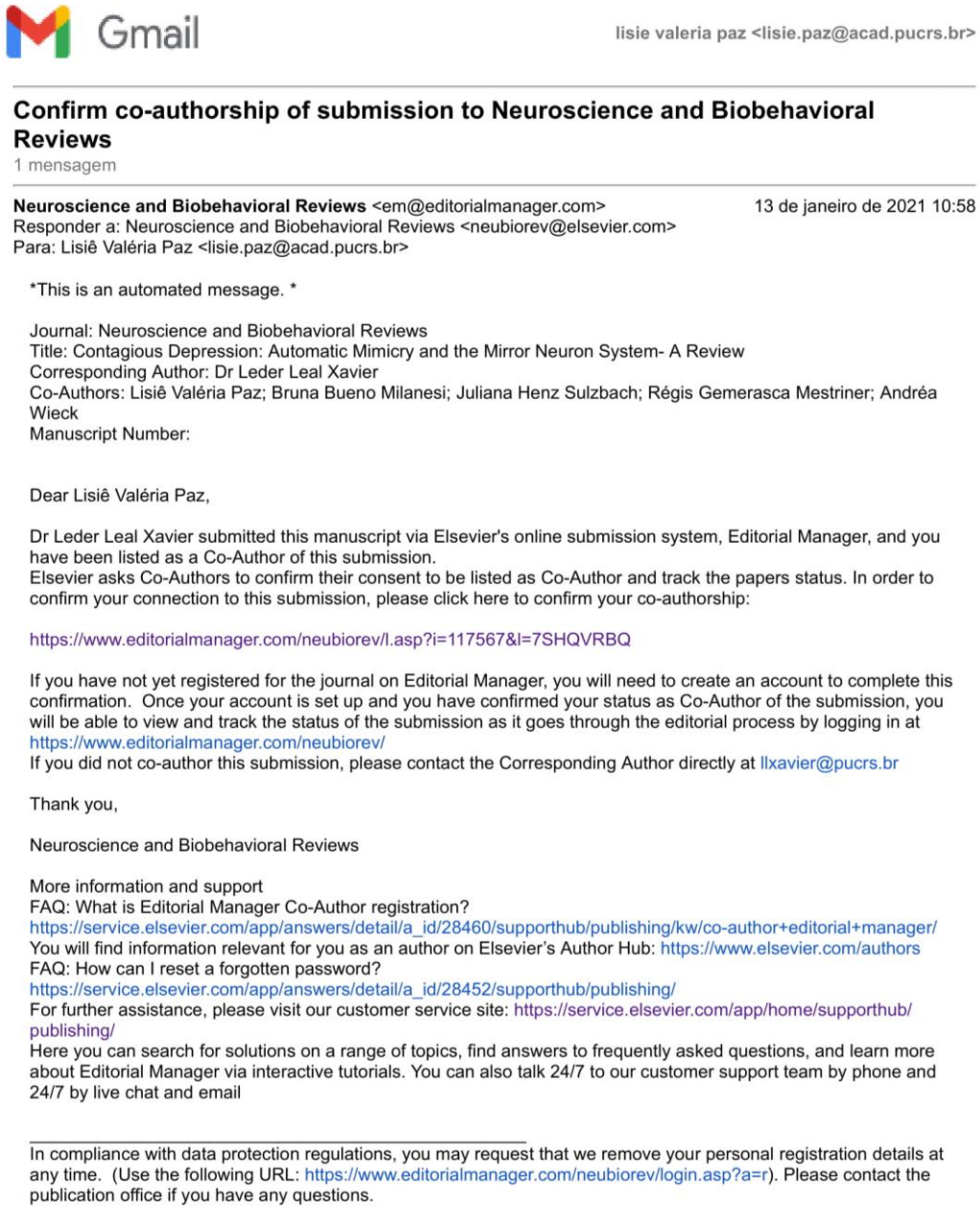
4 METODOLOGIA

O artigo científico de revisão produzido durante esse mestrado e apresentado no próximo capítulo trata-se de um estudo descritivo que segue o modelo de revisão narrativa. Este foi produzido através da busca por palavras-chave em diversas plataformas científicas de busca como: *Pubmed, Scielo, Google Scholar, Web of Science* e *Medline*. Os artigos foram selecionados conforme sua adequação ao tema da revisão e as respectivas datas de publicação variam entre 1969 e 2020. Devido ao baixo número de publicações que se encaixavam na proposta do tema de pesquisa, não foram aplicados filtros específicos nos sistemas de busca.

5 CAPÍTULO 2

5.1 Artigo Científico

O artigo científico foi submetido ao periódico "*Neuroscience and Biobehavioral Reviews*", FI: 8,330, em 13 de janeiro de 2021.



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Neuroscience and Biobehavioral Reviews

Contagious Depression: Automatic Mimicry and the Mirror Neuron System- A Review

--Manuscript Draft--

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Abstract:	Contagious depression is a theory proposing that depression can be induced or triggered by our social environment. This theory is based on emotional contagion, the idea that affective states can be transferred during social interaction, since humans can use emotional contagion to communicate feelings and emotions in conscious and unconscious ways. This review presents behavioral, physiological, and neuroanatomical aspects of two essential contagious depression mechanisms, automatic mimicry and the mirror neuron system.
Suggested Reviewers:	Elisa Brietzke Queen's University Elisa.Brietzke@kingstonhsc.ca Dr Brietzke is a renowned researcher in the psychiatric field. Her research accomplishes an integrated abordation and, therefore, we think that her contributions will be important for our manuscript.
	Nicholas Christakis Harvard Medical School christakis@hcp.med.harvard.edu Dra Christakis is a renowned researcher on social networks and social contagion. We strongly agree that his knowledge is important for this review.
	Delia Lenzi University of Rome La Sapienza: Universita degli Studi di Roma La Sapienza delia.lenzi@gmail.com Dr Lenzi knowledge on neural basis of emotional processing is of great importance for this review.
	James Fowler University of California San Diego jhfowler@ucsd.edu Dr Fowler knowledge on the spreading of emotions is of great importance for this review.

Contagious Depression: Automatic Mimicry and the Mirror Neuron System- A Review

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ABSTRACT

Contagious depression is a theory proposing that depression can be induced or triggered by our social environment. This theory is based on emotional contagion, the idea that affective states can be transferred during social interaction, since humans can use emotional contagion to communicate feelings and emotions in conscious and unconscious ways. This review presents behavioral, physiological, and neuroanatomical aspects of two essential contagious depression mechanisms, automatic mimicry and the mirror neuron system.

Keywords: Contagious depression, emotional contagion, mimicry, mirror neuron system, empathy.

1. INTRODUCTION

Forty-four years ago, James Coyne first described the role social environment plays in depression (Coyne, 1976). Social neuroscience seeks to investigates how the brain engages in social activities, and answer critical questions regarding how depression can be transmitted from one individual to another (Spitzer and Brüne, 2011). However, the complexities of human behavior and social relationships mean investigations into contagious depression are scarce.

Thus, there are some critical questions that remain to be answered, such as 1-How can affective states interfere in interactions between people ?; 2- Can one person's emotional state "infect" another's?; 3-What mechanisms are involved in the transmission

of emotions? 4-How can a social network be influenced by its members' mental state?; 5-What determines who is the sender and who is the receiver of emotions ?

Like many others, we are social animals, and social interaction is essential in our lives since it offers better chances for survival through communication and cooperation (Prochazkova and Kret, 2017). Our brain has a default network that gets spontaneously activated during rest and engages areas related to social activities, leading us towards social learning whenever we are not engaged in some other task (Meyer et al., 2019). Moreover, humans enjoy engaging in social interactions, which engage the brain reward system, in a similar way to monetary or food rewards (Tomova et al., 2019).

During social interaction, humans become aware of the other's sensations, emotions, or thoughts. Emotions such as embarrassment, shame, pride, and guilt are shared through cues such as facial and body expressions, gestures, posture, and sounds. This seems to explain why, when watching another person being socially rejected, we can elicit strong empathic feelings of social pain, thus feeling encouraged to help the person get personal relief from the situation. The receiver of emotions (hereafter "the receiver") can also have a positive, rewarding experience by observing somebody win a game, for example, without any personal material benefit for the receiver (Laura Müller-Pinzler, Sören Krach and Paulus, 2016).

Our affective state influences our social network, which can be either positive or negative. It has been suggested that happiness, can be extended to your contacts, like a social infection. For example, if your friend is happy, you will be more likely to be happy for a period of time (Fowler and Christakis, 2009). A cohort study of an extensive social network for over 20 years that gathered more than 12 thousand connections found that a person is 15% more likely to be happy if someone close to him is happy. In other words,

happy people tend to be connected, and moreover, those people tend to be the center of their local social networks (Fowler and Christakis, 2009).

Emotions can spread like an infectious disease across social networks in a phenomenon called emotional contagion, which can be defined as a tendency to acquire affective states from our social contacts (Hatfield, Cacioppo, and Rapson, 1994). This is the main finding of a 2010 study that used a mathematical model approach to demonstrate that an individual's probability of becoming "discontent" increases with the number of discontent contacts. That is also true, but with lower rates, among "content" subjects. (Hill et al., 2010). This indicates that the social network is a potential source of both positive and negative moods. Furthermore, emotional contagion seems to occur mostly between family members, partners, roommates, close friends, or co-workers that have strong ties and frequent contact (Bastiampillai et al., 2013; Hill et al., 2010).

It is not only emotions that seem to be contagious, complex mood disorders such as depression, anxiety, or loneliness, are also thought to spread in a similar way (Fowler and Christakis, 2009). A study involving 96 pairs of roommates supports this theory with experimental evidence, demonstrating that the roommates of depressed college students became more depressed after three weeks living together. Additionally, students with high reassurance-seeking behavior were more vulnerable to experience contagious depression, showing that an individual's susceptibility to the emotions of others or their sensitivity to adverse experiences is an important aspect to be taken into consideration (Joiner, 1994).

Here we will discuss two important aspects of emotional contagion that may be imperative in developing contagious depression, elucidating the mechanisms that seem to be involved in transferring emotions, namely automatic mimicry and the mirror neuron

system (MNS). Additionally, we will explore other aspects that may be involved, such as empathic concern, the direction of contagion, and why this phenomenon has been selected during human evolution.

2. MECHANISMS OF CONTAGION

Numerous studies from a wide range of scientific fields have discussed the possibility that emotional states can be transferred between persons (Christakis and Fowler, 2013; Fowler and Christakis, 2009; Hill et al., 2010; Lundqvist and Dimberg, 1995; Prochazkova and Kret, 2017). Among the many mechanisms implicated in emotion contagion is the conscious processing of emotional information, whereby people imagine how they would feel in another person's position and thus come to share their feelings (Stotland, 1969). Conscious processing is recognized as a potent determinant of emotional contagion, especially between individuals who love, like, or identify with others or share their goals (Hatfield et al., 1994). Another hypothesis is that emotional contagion could result from conditioned or unconditioned emotional responses. In this scenario, the mere sight of facial expressions or postures previously associated with angular movements, shrill, high-pitched voices, or intense vocalizations and movements, for instance, may come to evoke fear, panic, or similar emotions in the receiver. These reactions may be similar to or even opposite to the target emotion, which may be dependent on the relationship between the individuals involved, previous experiences, and the environment itself (Hatfield et al., 1994). Here, we will be focusing on two mechanisms that have been strongly suggested to be linked to emotional contagion: automatic mimicry and the MNS.

2.1.SHARING EMOTION THROUGH AUTOMATIC MIMICRY

The current literature agrees that one of the mechanisms allowing humans to share emotions is automatic mimicry (Decety and Lamm, 2006; Hatfield et al., 1994; Schuler et al., 2016). Automatic mimicry allows an emotional synchronization between two or more individuals that seems to occur at different levels, integrating motor and autonomic responses (Prochazkova and Kret, 2017). In other words, automatic mimicry is the unconscious and automatic imitation of speech, movements, bodily postures, gestures, facial expressions, eye gaze, and the synchronization of those with another person (Prochazkova and Kret, 2017). This unconscious behavior allows people to recognize and share emotions, and therefore, might have an essential role in emotional contagion (Prochazkova and Kret, 2017). Forms of motor mimicry and autonomic mimicry, such as heart rate, pupil dilation, blushing, and even crying and yawning can be synchronized and have critical social roles (Prochazkova and Kret, 2017).

A two-stage model for emotional contagion, involving automatic mimicry, is proposed (Hatfield, Cacioppo, and Rapson, 1994). Briefly, it implicates basic automatic mimicry and facial feedback where, first, people automatically mimic or synchronize with the facial expressions, vocal expressions, postures, and movements of those around them. And second, the receiver adopts the facial, vocal, and postural expressions sent by the other person (afferent feedback). This feedback then elicits the receiver's corresponding emotional state (Hatfield et al., 1994; Olszanowski et al., 2020) (Figure 1). For example, during a conversation, people can anticipate others' actions and frequently infer their feelings, often without any conscious awareness, while frequently using this information to contextualize. When people observe an emotionally intense facial expression, they experience partial activation in the corresponding neural circuit, evoking the perceiver's corresponding emotion (Figure 1A -2) (Lawrence et al., 2006; Preston and Waal, 2002; Schippers et al., 2010). Put briefly, first, we observe the face and body expression, and

then we mimic it to evoke the same emotion. Apart from the facial muscle movements, we also send autonomic cues during the emotional experience (Figure 1B). This autonomic type of mimicry, over which we have little or no control, includes synchronization of heart rate, breathing rhythms, pupil diameter, blushing, sweating, and even hormonal levels (Kret, 2015; Prochazkova and Kret, 2017). It is not yet clear how these autonomic neurovegetative reactions impact emotional perception, but one suggestion is that they modulate the perception of the emotion by intensifying it or providing more context (Kret, 2015).

It has been suggested that the two-stage emotional contagion model is too simplistic to explain something that is probably highly complex. In fact, emotional contagion has been shown to occur without any emotional mimicry, and it is thought the change in the receiver's emotion after an interaction with the sender of emotions may be triggered by different mechanisms like social appraisal rather than automatic mimicry (Hess and Blairy, 2001; Lishner et al., 2008). In contrast to mimicry, appraisal is a conscious, not completely automatic, assessment of someone's facial expression, made in an attempt to evaluate the current situation (Bruder et al., 2014; Parkinson, 2011). One reason for questioning whether emotional contagion is purely automatic is the evidence that it can be modulated by social factors (Epstude and Mussweiler, 2009; Wróbel and Królewiak, 2017). During unusual or uncertain social situations, the receiver may intentionally seek emotional cues from others to grasp the emotional meaning of these situations (Bruder et al., 2014). But regardless of the initially controllable nature of appraisal, this may become automatic after sufficient repetition, thus being considered an involuntary assessment (Wróbel and Imbir, 2019).

Complicating this matter further, the type of social connection between receiver and sender seems to affect emotional contagion. When is a positive valence relationship

(i.e., family connections, close friends), the probability of emotional contagion is higher. By contrast, this convergence may not happen in a nonaffiliated interaction or even have a different outcome than expected (van der Schalk et al., 2011). People only seem to mimic emotions with whom they are minimally affiliated to; the reactions evoked by the emotion are dependent on these affiliations, social meaning, and the relationship itself (Fischer and Hess, 2017; Hess and Fischer, 2013). Emotional mimicry can be triggered not only by the observed expression but also by the overall interpretation of this expression in a specific social context, based on prior knowledge of the social interactions and subjects involved (Hess and Fischer, 2013)

Several others criticisms have been leveled at the two-stage emotional contagion model. For instance, the contagion model holds that emotional spread is a replicative process, that is the receiver's emotional response is always the same as that experienced by the sender. However, this emotional similarity is unlikely to be the default response to every interaction between any given pair of individuals. Someone expressing anger, for instance, will not evoke the same feeling in the receiver, who might be expected to display fear or submission. Emotional response seems to depend on the personality of the individuals involved, the nature of their relationship, and the context of their interaction (Figure 2). If the conditions for stable emotional communication are met, then emotional replication is likely to emerge in some, but not in all cases (Figure 1A). If the sender expresses anger, pride, or sadness, for example, the receiver is more likely to produce a complementary response than to replicate the sender's emotion (Figure 2B). So, according to this idea, the sender's emotion may be replicated, complemented, or generate no response at all (Figure 1C) (Dezecache, Jacob, and Grèzes, 2015).

It is important to point out that most of the available studies regarding emotional contagion are based on the visualization of short videos or pictures while researchers

identify the receiver's emotions. Those studies reveal a co-occurrence between emotional contagion and mimicry but not a causal relationship. A recent study evaluated the role of facial mimicry in emotional contagion, based on indirect evaluation of the impression of the sender's mood state. The strategy was adopted to eliminate the positive feeling of performing the task correctly, because simply linking someone's facial expression to the corresponding emotion may be too easy a task. The results showed the participants displayed and felt emotions that corresponded to those of the senders. According to this study, facial activity seems to be essential to comprehend the relationship between the observed and felt emotions, but does not seem to be the only mechanism involved, the authors mention the influence of appraisal (Olszanowski et al., 2020).

The social top-down response-modulation (STORM) theory presupposes the existence of a mentalizing system that performs top-down control of emotional mimicry by social signals. This system would supervise the mirror neuron activity and inhibit mimicry any time that it is considered socially inappropriate. This theory highlights that the mechanisms responsible for mimicry are activated regardless of the meaning of the action, perhaps due to the simple perception of the action itself. The STORM model holds that receivers use explicit and implicit social cues to evaluate the sender's intent (Wang and de Hamilton, 2012). Those social cues do not influence the tendency to mimic *per se* but the processes controlling it (Wróbel and Imbir, 2019).

2.2.THE ROLE OF EMPATHY IN EMOTIONAL SHARING

There is no consensus in the literature regarding the concept of empathy. Different types of categorization with varying levels of complexity have been used over the decades. It is very well represented by what Heyes (2018) recently defined as empathy: *"feeling what others are feeling"* (Heyes, 2018). De Waal and Preston (De Waal and

Preston, 2017) say that empathy is "*any process that emerges from the fact that observers understand others' states by activating personal, neural and mental representations of that state, including the capacity to be affected by and share the emotional state of another; assess the reasons for the other's state; and identify with the other, adopting his or her perspective".* Moreover, De Waal and Preston propose empathy as an umbrella term, containing different layers that need to be comprehended in a fully integrated model with various components such as motor mimicry, emotional contagion, empathic concern, consolation, perspective-taking, and targeted helping (De Waal and Preston, 2017).

Although the definitions vary in complexity and details, we can split empathy into two different types, emotional empathy, and cognitive empathy. Emotional empathy is considered more primitive, described as the tendency to take on the sensory, motor, physiological and affective states of others. It is also used as a synonym of emotional contagion since it cannot be controlled, it is fast, automatic, and can be found in many other animals (De Waal and Preston, 2017; Heyes, 2018; Prochazkova and Kret, 2017). Empathy demands an emotional stimulus, like a facial expression, a body gesture, a vocalization, or an emotive situation sent to the receiver. When this stimulus is automatically picked up by the receiver and triggers correspondent neural circuits, it produces automatic responses that lead to emotional synchronization. This emotional empathy, and the automatic reactions produced in this scenario serve as the basis for the incitement of cognitive empathy. What takes place next is an assessment of the context of the emotional stimulus, the relationship of the sender towards the receiver, and the sender's priorities, while also taking into account prior experiences (Heyes, 2018). The current literature suggests that emotional contagion plays a crucial role in cognitive empathy and that the latter rarely takes place without the former (Heyes, 2018).

As the name suggests, cognitive empathy involves perspective-taking and mental processes that allow us to relate to other people's emotions, thoughts, and intentions. It is not innate, starts to develop later in childhood and is probably unique to humans (De Waal and Preston, 2017; Heyes, 2018; Prochazkova and Kret, 2017). Emotional empathy engages brain areas involved with affective and motor-motivational tasks like the insula, anterior cingulate cortex, thalamus, amygdala, somatosensory, and motor cortices, among others. On the other hand, cognitive empathy will engage brain areas involved in executive, working memory, and visuospatial processes such as the dorsolateral region of the prefrontal cortex, superior temporal regions, among others (De Waal and Preston, 2017).

A recent review suggests the innate drive to mimic others precedes emotional understanding and alignment. This convergence of emotions between two or more group members allowed empathy to develop during human evolution. (Prochazkova and Kret, 2017). It is plausible that during human evolution, empathy was selected due to the need for prolonged parental care and group cooperation, being a trait that remains in our DNA until the present time (De Waal and Preston, 2017; Heyes, 2018; Preston and Waal, 2002).

Other authors suggest that despite the similarities between emotional contagion and emotional empathy there are also dissimilarities. Emotional contagion will always refer to copying others' emotions, while emotional empathy will include spontaneous arousal of a different emotion from the one the sender's expressing. For instance, having a positive emotion by perceiving others' negative emotions is an example of emotional empathy that is not emotional contagion (Nakahashi and Ohtsuki, 2015).

2.3.SHARING EMOTIONS THROUGH MIRROR NEURONS

Mimicry might facilitate social interactions by helping people to connect with each other and even induce some affection. Therefore, people who are good at recognizing others' emotions using automatic imitation may also be good at showing empathy, suggesting a correlation between the tendency to automatic mimicry and the ability to empathize. The neural mechanism that may explain the link between those two is the MNS (Iacoboni, 2009).

Although it cannot fully explain empathy, the MNS is responsible for the feedback between the observation of affective expression and neural activation associated with emotional states (De Waal and Preston, 2017). Mirror neurons were first discovered during the 1990s in the F5 area of the monkey premotor cortex. Researchers observed a group of neurons that were discharged not only when the monkey performed a goal-oriented action, such as grasping an object, but also when he observed another monkey perform the same task (di Pellegrino et al., 1992; Gallese et al., 1996). In humans, the mirror neurons are present in a few areas, including the inferior frontal gyrus (IFG) and Brodmann area 44 (Broca's area), a brain region with crucial aspects related to language, thus emphasizing the importance of mirror neurons to human communication (Rizzolatti and Arbib, 1998). Although the neurons can be found in specific regions, they seem to be part of a larger and broader network that includes areas like the inferior parietal lobule, superior temporal sulcus (STS), and some regions of the limbic system. The main function of this network is to address perceptions of the environment to internal sensorimotor representations (Oberman et al., 2007).

Initially, mirror neurons were associated with the comprehension of an action, linking the observation of a particular scene to a corresponding movement. But further experiments showed this interpretation to be over simplistic and a more complex system was conceived for the shared coding of motor and perceptual aspects of actions of the self

and others (Rizzolatti and Craighero, 2004). A study revealed that mirror neurons could be triggered even in the absence of visual input; in this case, the sound of an action was enough to make the neurons fire (Kohler et al., 2002). In humans, mirror neurons do not merely represent actions, but also their underlying intentions. For instance, during an interaction, much more than the information regarding physical movements is picked up, but also the overall context is assimilated, with the intentions, thoughts, and feelings motivated the action (Oberman et al., 2007). Iacoboni and colleagues (2005) demonstrated the activation of the right inferior frontal cortex for the intention aspect, suggesting that this mirror neuron area actively participates in understanding the intentions behind observed actions. This finding indicates that the same task in different contexts can have different activation patterns (Iacoboni et al., 2005). Therefore, apart from being sensitive to intentions, the MNS is also responsive to social cues in a stimulus, being more activated when the stimulus is not only social but interactive. Further than that, when the subject has a sense of identification with the stimuli, the degree of social interaction is higher (Oberman et al., 2007). Together, this evidence demonstrates the role the MNS plays in sophisticated social skills such as the theory of mind, empathy, and language.

Mirror neurons are responsible for many aspects of social cognition, including our understanding of emotions displayed by others. A functional Magnetic Resonance Imaging (fMRI) investigation into the role of mirror neurons in imitation and facial emotional expressions showed that a large-scale neural network involving the MNS together with the limbic system and insula is responsible for empathy (Carr et al., 2003). According to Goldman (Goldman, 2006), this network provides a simulation-based empathy, and several fMRI studies corroborate the positive association between empathic concern and mirror neuron areas (Gazzola et al., 2006; Iacoboni, 2009; Kaplan and

Iacoboni, 2006; Pfeifer et al., 2008). fMRI studies analyzing empathy and imitation in humans showed MNS activation primarily in two different areas, the IFG and rostral posterior parietal cortex (Rppc) (Iacoboni, 2009; Shamay-Tsoory et al., 2009). Studies show IFG activity is interconnected with the insula activation and may be associated with the process of empathic pain (Lamm et al., 2011). For instance, during a painful stimulus, the anterior cingulate cortex and anterior insula activate the perception of physical pain.

Interestingly, the same areas seem to activate during the experience of emotional pain and when observing a loved one receiving painful stimuli (Bastiaansen et al., 2009). Therefore, it seems there is not merely an overlap between the physical and emotional pain processing mechanisms. In fact, some brain areas seem not to distinguish between pain inflicted on the own person or the loved one. Intriguingly, a recent article showed that acetaminophen, one of the world's most used physical pain suppressants, effectively reduces the pain caused by social rejection. Acetaminophen reduced the neural responses in the dorsal anterior cingulate cortex and anterior insula, which are regions responsible for processing social pain, and the affective component of physical pain (DeWall et al., 2010).

3. DIRECTION OF CONTAGION

During social interaction, all involved subjects will be acting as both sender and receiver of emotional cues. What will define which one will infect and which one will be infected? Will their personal traits and behavior characterize their susceptibility? Or perhaps their mental health, emotional intelligence, or even their capacity to empathize? (Doherty, 1997; Hatfield et al., 1994; Sonnby-borgström, 2002).

Emotional contagion can be thought of like the spread of a virus. It seems reasonable to suppose that some people may have a natural ability to infect others with

this "virus" while others are especially vulnerable to contagion (Hatfield et al., 1994). Hatfield et al. (1994) proposed potent senders could possess at least three characteristics: they must feel strong emotions; they must be able to express those strong emotions; and they must be relatively insensitive to others' feelings (that are not compatible with their own) (Hatfield et al., 1994). Both individual variations and social factors are important determinants of differences in emotional expressiveness (Cacioppo et al., 1992). The individual variances refer mostly to the differences in physiological activity (e.g., reactivity measures, systolic and diastolic blood pressures, skin conductance, heart rate) in response to a situation. This response may vary from very consistent to unique across individuals. By their own physiology, those who are inclined to respond strongly, visibly, and consistently in emotional situations are thought to be more likely to initiate emotional contagion due to their expressiveness in emotional situations (Hatfield et al., 1994). And those who are prone to respond strongly, but not visibly, in emotional situations (i.e.: although they feel the physiological changes, they do not show emotional signs of distress) are more likely to be influenced by the visible signs of other's emotional reactions (Hatfield et al., 1994). The same authors suggest a few features in personality can predict or influence emotional contagion. Externalizers, those whose emotions can be "read" on their faces, yet who show little autonomic nervous system (ANS) sympathetic response, are more likely to infect (to be the senders of emotions). By contrast, internalizers, those whose faces seems emotionless but shows strong ANS activation, are more likely to be infected (to be the receivers). Similarly, extroverts, individuals who have high threshold for arousal, are more likely to be strong carriers of emotional contagion, while introverts, those who are easily aroused, are easier to condition (Hatfield et al., 1994).

Personality, self-construal, genetic heritage, and early experiences predispose some people to be more susceptible to emotional contagion and others to be more resistant to it. Susceptibility to emotional contagion can be measured as the frequency with which emotional stimuli elicit an emotional expression characteristic of the eliciting emotion. Besides such personality traits, especially susceptible people pay close attention to others (being able to read others' emotional expressions); see themselves as interrelated with others rather than independent and unique; tend to mimic all types of expressions; and experience conscious emotions that are powerfully influenced by peripheral feedback (Doherty, 1997; Hatfield et al., 1994).

To measure the individual differences in susceptibility to emotional contagion, Doherty et al. (1997) proposed the Emotional Contagion Scale. This scale evaluates the likelihood of catching others' affective states and considers genetics, gender, early experience, and personality characteristics. Further elements such as temperament, distractibility, attention, and intensity of responsiveness also influence the probability to "catch" an emotion. Susceptibility showed a positive association with affective orientation, emotionality, sensitivity to others, self-esteem, and was found to be strongly associated with emotional rather than cognitive types of empathy. However, it did not correlate with self-assertiveness, emotional stability, alienation, masculinity, and approval motivation. Self-centered people tend to be more susceptible to any kind of emotion. By contrast, introverted people tend to be more susceptible to positive emotions, while extroverts are more affected by others' negative emotional expressions (Doherty, 1997) (Figure 3).

Pinilla et al. proposed a mathematical model to describe how the affective states influence people's abilities to judge others' affective states. In this experiment, the subjects were negatively or positively induced by watching a video clip with positive or negative

content. Briefly, after watching the video, the researchers asked the participants how the scene made them feel. In the second phase, the subjects had to rate different pictures of random faces according to what they thought the person was feeling. The results indicate that negatively induced people show more emotional contagion to angry than happy faces, while positively induced people showed more emotional contagion to happy than angry faces (Pinilla et al., 2020). This finding suggests a pattern behind the mechanisms of emotional contagion that differs when triggered by positive versus negative emotions. In the same study, the highest emotional contagion was observed for the negative induced participants towards angry faces, suggesting that negative affective states trigger more behavioral responses than positive ones (Pinilla et al., 2020).

Along the same lines, a thought-provoking study proposed that susceptibility to negative rather than positive emotions could play an essential role in distinguishing between a fake and a sincere smile. Their findings showed that people with high susceptibility to contagion by negative emotions performed better in identifying an authentic smile and rarely rated a fake smile as sincere. On the other hand, people with high susceptibility to contagion by positive emotions showed a reduced capacity to detect authentic emotions, being more prone to rate fake smiles as sincere. Their findings also suggest that susceptibility to emotional contagion is influenced by emotional content (Manera et al., 2013).

4. SHARING BAD EMOTIONS – MAJOR DEPRESSIVE DISORDER

We have already spoken about how an individual's social network and environmental circumstances can significantly influence the contagion of emotions, mood, and behavior. Since first being described in the 1970s (Coyne, 1976), a few studies have been tested the hypothesis that depression can be as contagious as an infectious

disease (Abela et al., 2009; Bastiampillai et al., 2013; Coyne, 1976; Joiner, 1994; Karp, 2017; Kiuru et al., 2012). Joiner et al. (1994) investigated the possibility that negative emotions were contagious among roommates. Their findings showed that while depressive symptoms were contagious, anxiety and negative affect were not, and people with high reassurance-seeking behavior showed greater vulnerability to contagion (Joiner, 1994). In their research with elderly couples, Goodman et al. (2002) found that when one partner suffered vision loss any consequent depressive symptoms were shared (Goodman and Shippy, 2002). When analyzing family relationships, we also see patterns linked to depression; studies have shown children of parents with a history of major depressive episodes are four to six times more likely than other children to develop major depression (Beardslee et al., 1993; Weissman et al., 1997). Those symptoms seem to be temporally associated as well, since increased depressive symptoms in parents during the 1-year follow-up interval were significantly associated with increased depressive symptoms in their children. The results also suggest that children who live with high levels of negative attachment are more likely to develop depression when they have depressive parents than children who do not live in such conditions (Abela et al., 2009). Weissman et al. (2016) recently published a 30-year follow-up of children from depressed parents. Their results show the offspring of depressed parents were at a 10-fold higher risk of developing depression in the prepubertal phase, had overall lower functioning and a higher risk for depression, morbidity, and mortality that persisted into their middle years (Weissman et al., 2016).

This effect appears to be even stronger among teenagers, since co-rumination, a behavior especially typical between adolescents seems to facilitate depression contagion (Schwartz-Mette and Rose, 2012). A recent study demonstrates that co-rumination plays an important role in the contagion of depressive symptoms, facilitating peer influence

within friendships in some contexts, such as an adolescent experiencing personal distress, when confronted with the distress of others, or excessively seeking reassurance from friends, and having a high positive quality friendship. They also suggest that individuals who are easily triggered by others' distress are more susceptible to contagion processes via co-rumination than others (Schwartz-Mette and Smith, 2018). Another investigation reinforced those findings and showed that co-rumination exacerbates the deleterious effects of major stressful life events (Hruska et al., 2017). Kiuru et al. (2012) found that adolescents tended to show similar depressive symptoms as their friends. Moreover, adolescents initiated relationships with peers who reported similar depression levels and were more likely to end relationships with peers who became less similar in terms of depression symptoms over time (Kiuru et al., 2012).

Those findings provide essential insights that may help elucidate the apparent surge in adolescent suicide clusters, which has a significant impact on society. Hazell et al. suggested that suicide clusters may behave like an infectious disease model occurring through contagion. He assumes that individuals will be differentially affected by exposure to suicide, and some will be more susceptible to imitative suicidal behavior than others (Hazell, 1993). A recent study assessed the influence of attempted suicide on the ideation of suicide among family members. The prevalence of suicidal ideation among individuals in this situation was found to be more than twice that of people who did not have a family member that attempted suicide (Jang et al., 2016). Mueller et al. (2015) also reported that emotional distress is contagious in adolescence and can be increased, along with suicidal ideation, by having a close friend attempt suicide (Mueller and Abrutyn, 2015).

4.1. THE ROLE OF THE MIRROR NEURON SYSTEM IN CONTAGIOUS DEPRESSION

Major depressive disorder patients (MDD) have been shown to present alterations in processing emotional information, finding it more difficult to differentiate faces with positive emotional stimuli and stimuli with no emotional content (Goodin et al., 2019). Depressive patients also report having greater difficulty coping with and regulating their emotions, engaging in social interactions, and being empathic. Furthermore, this condition seems to persist, even if the symptoms of depression decrease (Visted et al., 2018). Accordingly, poor emotional regulation and lower social competencies might be a latent risk factor for relapse.

There is considerable evidence to show that brain areas rich in mirror neurons are involved in emotional regulation, social abilities, and empathy (Lamm and Majdandžić, 2015). In comparison with healthy people, individuals with major depressive disorders show lateralization in the right hemisphere neural activity. During the research, it was observed that repetitive transcranial magnetic stimulation (rTMS) on the left dorsolateral prefrontal cortex ameliorated symptoms of depression compared to a sham condition (Lam et al., 2008). This finding helps to elucidate the previous discovery that patients with MDD have hypoactivity in the left PFC, which is associated with a lack of positive emotion processing (Davidson et al., 2002, 2000; Korgaonkar et al., 2013; Zhong et al., 2011). Moreover, a recent study showed that, compared to rTMS on the left dorsolateral prefrontal cortex, the same type of stimulation on a mirror-neuron-rich area on the left inferior parietal lobe, improved empathy and reduced some depressive symptoms. This demonstrates that the stimulation of areas with a higher density of mirror neurons appeared to improve specific dimensions of emotion regulation and empathy (Jahangard et al., 2019).

Dysfunctional MNS has been associated with human social cognition disorders, including autism spectrum disorders (ASD) (Williams et al., 2006). This hypothesis is

reinforced by imaging studies showing a significant thinning in MNS-related areas, such as the inferior frontal cortex (IFC), the inferior parietal lobule (IPL), and STS, in individuals with ASD. An fMRI study also showed that highly-functioning children with ASD demonstrated markedly weaker activation in the IFG than the control group during a task involving the imitation of emotional expressions (Dapretto et al., 2006). Since the understanding of facial expressions is important for emotional processing, a dysfunctional MNS may well hamper the ability of ASD patients to understand emotions (Golarai et al., 2006; Khalil et al., 2018; Sasson, 2006). Interestingly, ASD and mood disorders, such as depression and anxiety, share some genetic variables related to serotonin transporter transcription, suggesting some overlapping mechanisms in both diseases (Muhle et al., 2004; Yuan and Hoff, 2008). Moreover, patients with ASD frequently present depressive symptoms, while MDD patients also present some difficulty in emotional processing (Munesue et al., 2008; Towbin et al., 2005). Yuan and Hoff (2008) suggested that it is possible to observe-learning-based brain activation or even rehabilitation of the MNS. They proposed using computerized displays or virtual reality environments to present scenarios designed to specifically modulate various brain regions (Yuan and Hoff, 2008).

Although Hatfield (Hatfield et al., 1994) found no major gender differences regarding emotional contagion, a few studies have shown that women seem to have a certain advantage in decoding non-verbal emotional cues as well as better scores on self-report measures of empathy (Baron-cohen and Wheelwright, 2004; Hall, 1978; Hall et al., 2010; Olderbak et al., 2019; Reyes-Aguilar and Barrios, 2016). Those differences might be due to a different pattern of brain activation during emphatic-associated situations. Schulte-Ruther used fMRI to measure changes in brain activity during a face recognition task. Their results showed that regions involved in the human MNS, such as the IFG, are recruited during an emotional perspective-taking task in both genders. But

in women, the neural activation is more robust in the right IFG and right STS, evidencing a different pattern of activation and an enhanced MNS activation in emotional perspective taking (Schulte-Rüther et al., 2008).

Another study analyzed mothers who self-reported depressive symptoms. The subjects were asked to perform a task requiring the recognition of the affective states of others while undergoing fMRI. The results showed that in the adult eye-based mind-reading-related task, the pattern of activation of the right IFG (which is a brain region related to MNS) decreased with higher levels of depressive symptoms. They suggested that depressive symptoms negatively affect the neurocognitive function responsible for mind-reading, also known as the theory of mind, or the ability to predict others' mental state. Based on this research, the authors propose that MNS dysfunction may be the basis of impaired social skills in depression (Shimada et al., 2018).

The MNS is also involved in bipolar mania. However, the MNS activation pattern seems to work differently in these patients, as increased functional connectivity was observed between the amygdala, IFG, and the supplementary motor area (Goodin et al., 2019). A study using paired-pulse TMS showed that patients with mania had significantly greater putative MNS activity than healthy controls. Their findings suggest a higher mirroring response in mania, and a possible state-dependent effect of an exaggerated mirroring response during manic phases of bipolar disorder (Basavaraju et al., 2019).

Taken together, the findings available to date suggest the MNS has an important, but yet to be understood, role in emotional contagion and contagious depression. Although scarce, the studies show that mirror neurons in several areas are recruited during the observation of facial expressions and might support basic forms of facial mimicry or emotional contagion (Christov-Moore, 2014). The research of MNS impairments in

patients with autism may shed some light on the role of mirror neurons in social interactions, empathy, communication, and emotional contagion. Apparently, there is a connection between mood disorders and impairments in the pattern of MNS activation, linking a pattern of sub activation to depressive symptoms and a hyperactivation to bipolar mania symptoms (Basavaraju et al., 2019; Goodin et al., 2019; Shimada et al., 2018).

5. WHY DO WE SHARE EMOTIONS, EVEN BAD ONES? – AN EVOLUTIONARY PERSPECTIVE

According to what we have said so far, empathy and its related neurological mechanisms would be an innate characteristic (De Waal and Preston, 2017; Preston and Waal, 2002). Therefore, empathy would be in our genes, having been inherited over generations, and selected by natural selection (De Waal and Preston, 2017; Feldman et al., 2016; Gong et al., 2013; Walter, 2012; Warrier et al., 2018). This is a widely accepted hypothesis since empathy and emotional contagion have been observed in several species (Decety et al., 2016; Gonzalez-Liencres et al., 2013; Heyes, 2018; Panksepp and Panksepp, 2013). Evolution is not directed but is driven by natural selection, by which the best adapted organisms within an environment are selected. Applying this to empathy, it is believed that during early mammalian evolution, when parental care and cooperation between group members was increasingly important, natural selection would favor genes that promoted empathy. Therefore, those empathetic individuals reproduced more and kept the “empathy genes” in the environment. (De Waal and Preston, 2017).

We can say that empathy is a way to understand others' emotions when the feeling itself is not easily communicable, serving as an especially useful tool for parental care. De Waal (2017) suggested that offspring care probably strengthened the evolution of

empathy, as the connection between neonates and their caregivers received a positive selection pressure, being a trait rapidly selected in human evolution (De Waal and Preston, 2017). The signals emitted by their offspring do not merely induce an alert state in the parents but can equally cause distress. This negative effect provokes a natural motivation to act. In many species, including humans, the empathic response is increased by similarity, familiarity, and close social relationships where the individual is genetically related or has a reciprocal relation (De Waal and Preston, 2017). Parents who pay close attention to their children's emotional signals are considered to have increased fitness since the offspring has greater chances of survival and, therefore, reproducing their parents genes in the population. This is consistent with evolutionary theory, where the survival of the genes is prioritized (Dawkins, 1990).

Emotional contagion is also thought to be a way of learning environmental information from others. In this sense, the contagion of "bad" emotions, such as fear, could have evolved as a form of social learning (Nakahashi and Ohtsuki, 2015). In a situation where a real threat is presented, the contagion of fear can be used as an alert system to the entire group to evoke a reaction, in this case, all individuals will benefit from the emotional contagion. Nakahashi et al (2015) theorized a situation where an observer, not having perceived the source of danger, witnesses the behavior of a demonstrator who has already perceived the danger and taken an appropriate behavior. In this scenario, they showed that the observers who adopt emotional contagion spontaneously activate one of the two emotions, panic or fear, and react to those emotions automatically. The results suggested that emotional contagion works as an efficient social learning strategy when the sender and an receiver share the same environment or the same source of danger when compared to behavioral mimicry and independent reaction. Besides that, emotional contagion is a more efficient strategy in a noisy environment,

suggesting it could have evolved in species with low levels of cognitive ability (Nakahashi and Ohtsuki, 2015).

A good example supporting this theory involves food poisoning. When we observe someone eating something that tastes bad, we immediately realize that by their facial expression, we do not need to take a bite to feel repelled. We automatically infer that the food is terrible and cannot be eaten. Thus, it seems that to understand the facial expression the sender is presenting, we must elicit the same feeling. Wicker et al. (2003) show the observation of disgust induces the activation of neural substrates responsible for this feeling in the receiver, including the left anterior insula and right anterior cingulate cortex (Wicker et al., 2003). As can be imagined, this scenario of emotional contagion has an enormous evolutionary advantage and could have evolved as a primitive protection mechanism to avoid the digestion of suspicious food when means of communication were not as sophisticated as they are today (Wicker et al., 2003).

6. CONCLUDING REMARKS

In the 1970's, Coyne suggested the social environment could, somehow, interfere in a person's emotional content. After decades of research and the identification of a few "how's", this statement still stimulates further study. The social nature of humans has provided us with a few strategies that enable us to work in society, one of which seems to be the contagious aspect of emotions. We still have a lot to explore, but it seems that emotional contagion is a strategy that we developed to communicate our emotions when verbal communication was underdeveloped. It works so well that we still cannot describe in words a feeling with such detail that others will experience the same feeling. This precision is still exclusively the realm of emotional contagion. Several factors influence

emotional contagion, among them the individual's internal, social and external environmental factors.

As previously discussed in section 2.3, mimicry, considered a synonym of emotional empathy by some authors, is accepted as the main mechanism responsible for emotional contagion. Automatic mimicry occurs first through synchronization of facial and body expressions, followed by synchronization of emotional states, through elicitation of the corresponding neural activation. A few MRI studies have shown the MNS is activated in subjects during empathic tasks, suggesting this system plays an essential role in emotional contagion/empathy (Figure 4).

If emotions can be contagious, chronically dysfunctional emotional states, like depression, may also have a contagious aspect. Here, we have described a few studies that highlight the incidence of depressive behavior in people that coexist with depressive patients. Recent evidence has shown that depressive patients have difficulty recognizing a happy face, coping with their emotions, engaging socially, and being empathetic. All those alterations seem to be related to a defective MNS activation pattern, including the lateralization and hypoactivation of mirror areas. More research in this field is required to elucidate if a dysfunctional MNS might cause depressive symptoms. Perhaps, coexistence with a depressive individual can induce an inappropriate MNS activation pattern through emotional contagion, leading to the development of symptoms related to major depression in a contagious depression model. However, this hypothesis is yet to be tested.

Here we focused on different aspects of emotional contagion and how it relates to contagious depression. Although there still a lot to be understood, it seems the components acting on emotional contagion are also involved in the establishment of

contagious depression. Enhancing our knowledge regarding this phenomenon could lead to the development of new therapies and treatments and shape the way we treat mood disorder patients and their therapeutic prognosis.

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FIGURE CAPTIONS:

Figure 1: The two-stage model for emotional contagion and its path through mirror neurons. A) A social interaction starts with motor and autonomic mimicry, where both individuals can be acting as sender or receiver of the emotional cue. According to the two-stage model, the first stage is automatic mimicry, and the second stage is the afferent feedback where the receiver adopts the sender's expressions. The afferent feedback is thought to elicit corresponding areas in the receiver's brain, activating the mirror neuron system. Consequently, emotional contagion takes place, when both individuals experience emotional synchrony, also known as emotional empathy. This may or may not be followed by cognitive empathy, which is a conscious process involving numerous other factors. B) The emotional cues can vary from motor to autonomic reactions, including eye gaze, pupil diameter, blushing, heart rate, body posture, speech and facial expressions.

Figure 2: Factors affecting emotional contagion. Emotional contagion is most likely to happen under certain circumstances. **A)** When both individuals share a positive relationship, have an emotional connection, the social and environmental context is favorable, the chances of emotional contagion are higher. **B)** When the subjects have a negative valence relationship or share a feeling of disgust the emotional contagion may not be replicative but complementary. **C)** And finally, when there are no emotional ties or the social and environmental context are not favorable, emotional contagion may not take place.

Figure 3: Traits influencing direction of contagion. The direction of contagion is defined by several components, personality traits, self-construal, genetic heritance and early experiences being some examples. Externalizers, extroverts, people that see themselves

as independent and unique are more likely to be the sender of emotional cues. Whereas people who see themselves as interrelated with others, pay close attention to others, internalize feelings, and have introvert personalities are more likely to be receivers of emotional cues, tending to be affected by other's emotions.

Figure 4: Contagious depression: Physiological, environmental and behavioral components. Some environmental aspects such as living with a depressed person or developing a negative attachment cognition may contribute to contagious depression, as may some impaired behavior responses, such as difficulty being empathetic, coping with emotions or developing social skills. A third important component that seems to be related is an impaired MNS, probably due to the lateralization of activity or hypoactivity in some MNS areas.

FIGURE 1.

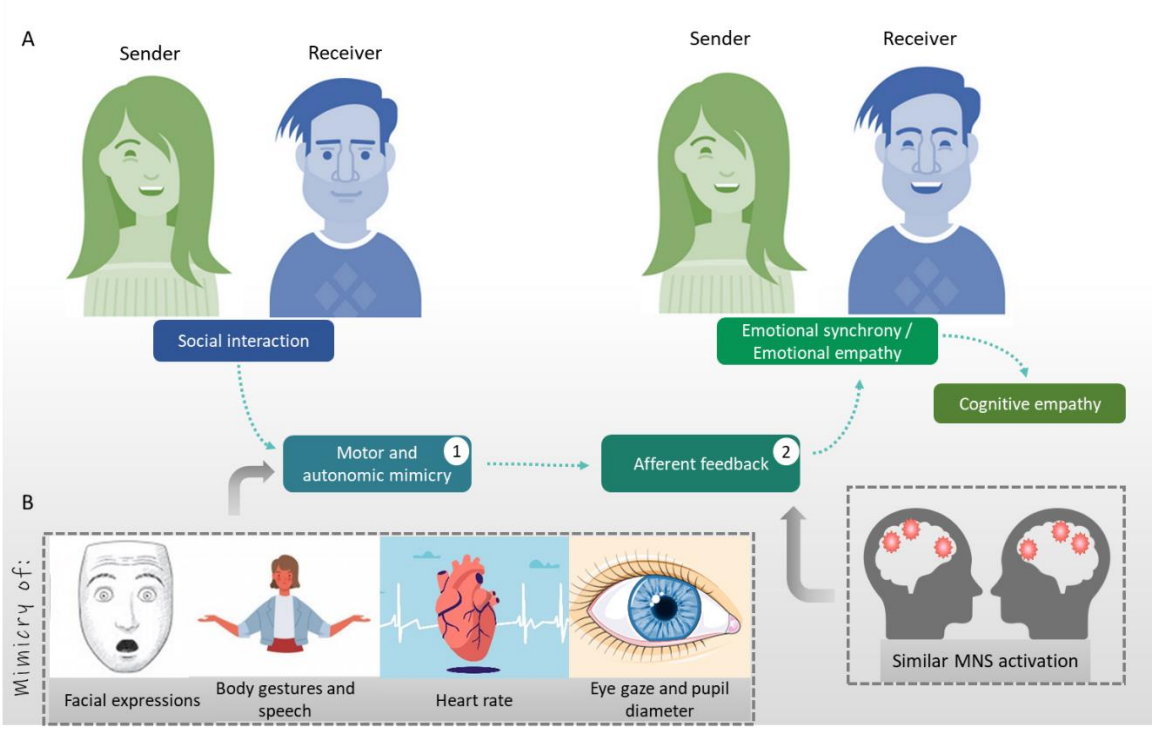

A
Sender
Receiver
Social interaction
Motor and autonomic mimicry
1
Afferent feedback
2
Sender
Receiver
Emotional synchrony / Emotional empathy
Cognitive empathy
B
Mimicry of:
Facial expressions
Body gestures and speech
Heart rate
Eye gaze and pupil diameter
Similar MNS activation

FIGURE 2.

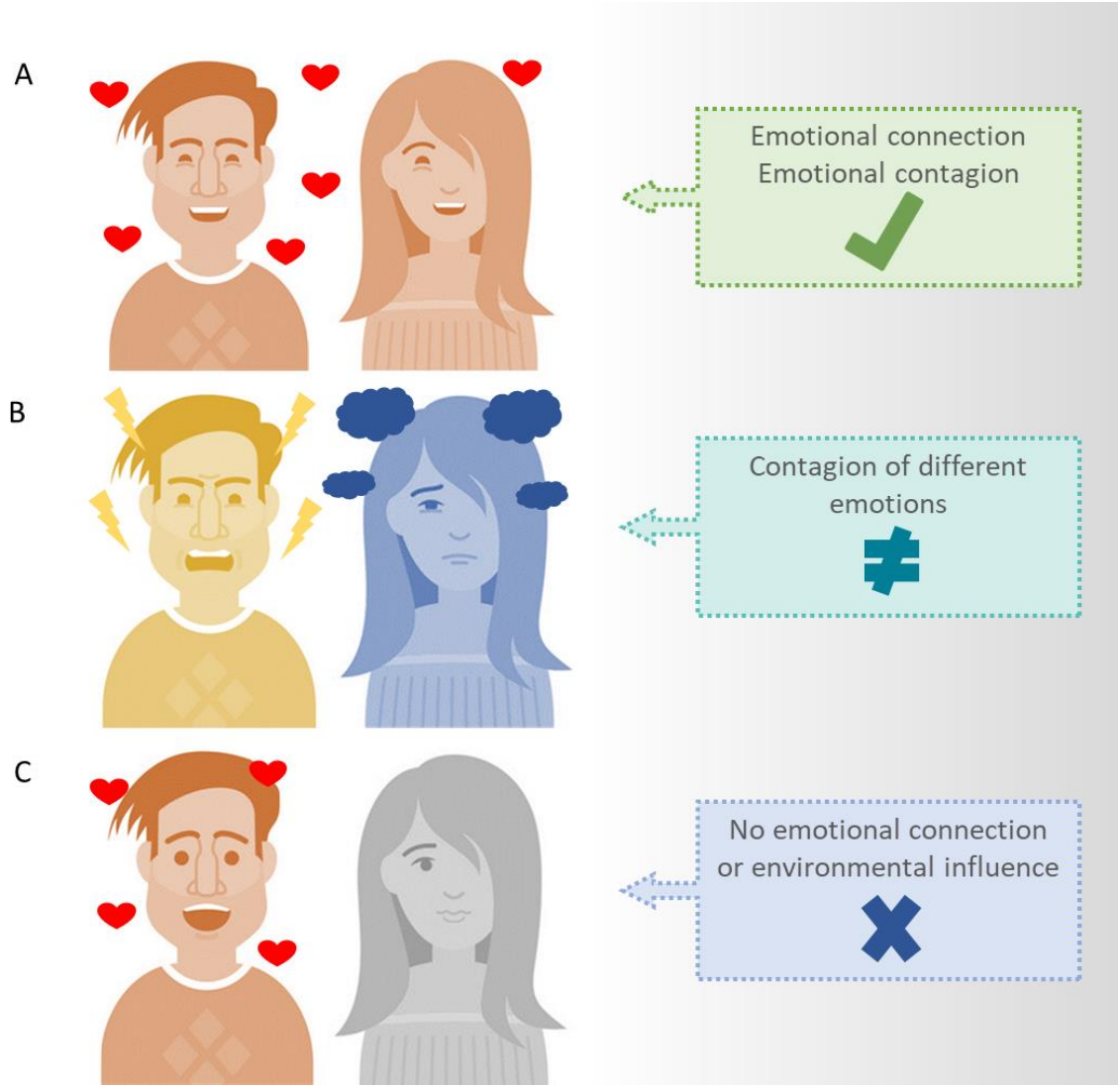

A
Emotional connection
Emotional contagion
B
Contagion of different
emotions
C
No emotional connection
or environmental influence

FIGURE 3.

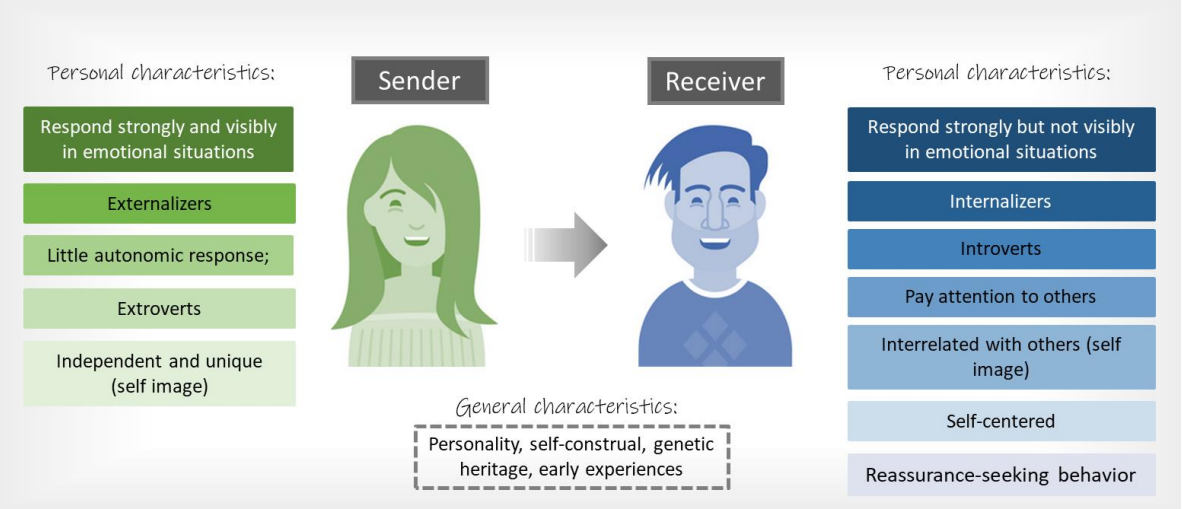
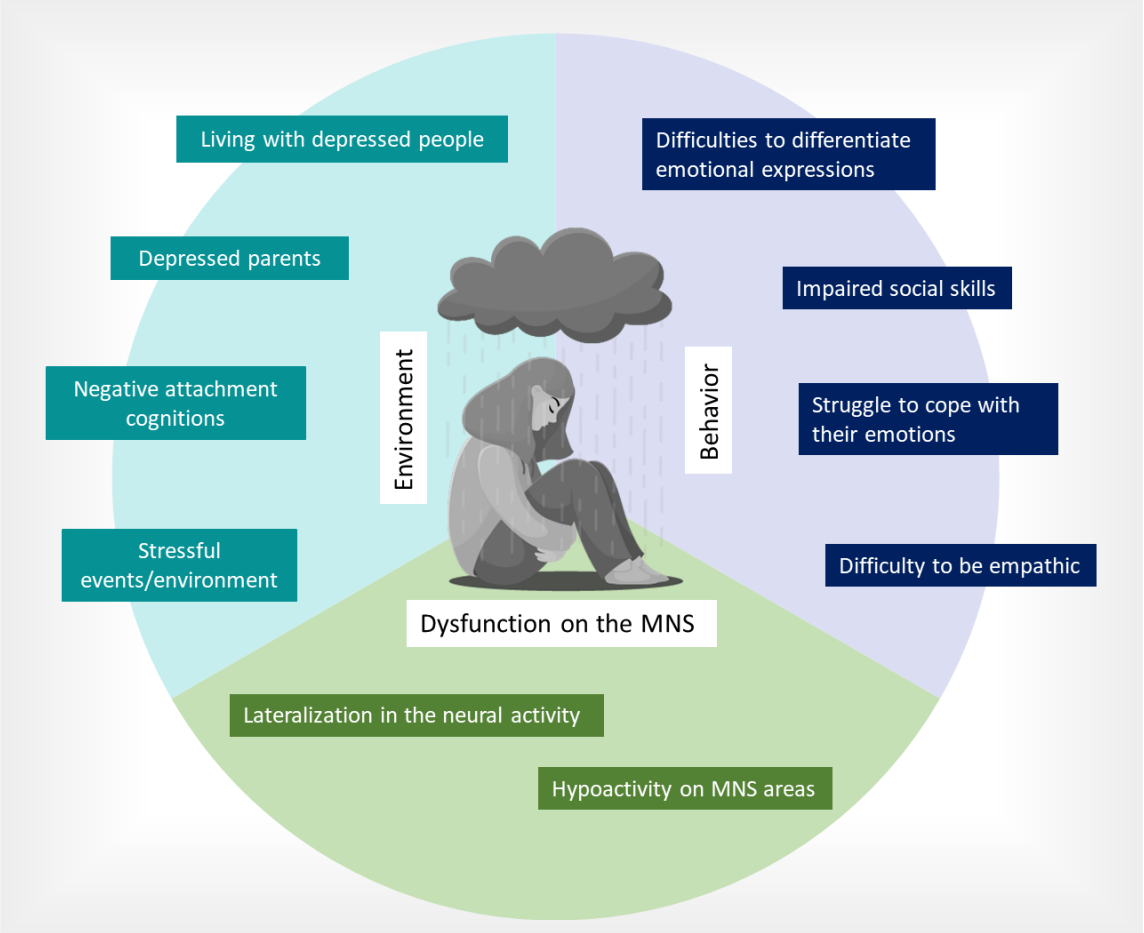

Personal characteristics:
Respond strongly and visibly in emotional situations
Externalizers
Little autonomic response;
Extroverts
Independent and unique (self image)
Sender
Receiver
General characteristics:
Personality, self-construal, genetic heritage, early experiences
Personal characteristics:
Respond strongly but not visibly in emotional situations
Internalizers
Introverts
Pay attention to others
Interrelated with others (self image)
Self-centered
Reassurance-seeking behavior

FIGURE 4.


Living with depressed people
Difficulties to differentiate emotional expressions
Depressed parents
Impaired social skills
Environment
Behavior
Negative attachment cognitions
Struggle to cope with their emotions
Stressful events/environment
Difficulty to be empathic
Dysfunction on the MNS
Lateralization in the neural activity
Hypoactivity on MNS areas

6 CONSIDERAÇÕES FINAIS

O transtorno depressivo maior parece ter um aspecto de contágio social envolvido e diversas linhas de pesquisa apontam para essa possibilidade. Os mecanismos responsáveis podem ser os mesmos que permitem o contágio emocional, onde tanto emoções positivas quanto negativas podem ser transmitidas. Dentre estes mecanismos, exploramos o mimetismo automático, baseado na imitação automática de expressões faciais, corporais, fala, gestos, e parâmetros autonômicos. E do sistema de neurônios espelhos, uma rede neural distribuída em diversas regiões do encéfalo capaz de ativar-se na realização uma ação e ao observar essa ação ser efetuada por outra pessoa. Segundo V. S. Ramachandran, em seu livro 'O que o cérebro tem para contar' (2014), esse conjunto de células que não sabe a diferença entre o "eu" e o "outro" pode ser a base biológica do que hoje entendemos por empatia.

O contágio emocional parece ter se desenvolvido como uma forma de comunicação não verbal, selecionada durante a evolução de diversas espécies. A depressão contagiante como uma resultante desse tipo de comunicação não parece trazer nenhuma vantagem para os indivíduos que a partilham. Porém, conforme citado anteriormente, o contágio de emoções positivas também ocorre e ademais foi observado que efeitos positivos do tratamento para depressão também podem ser contagiosos, sendo observados em indivíduos com até 3 graus de separação (84).

Embora tenhamos diversas linhas de evidência apontando para a existência de depressão por meio do contágio social, é necessário salientar que a depressão é uma doença multifatorial. Dessa forma é improvável que apenas um fator de risco, como o convívio com outro individuo depressivo, seja o suficiente para, por si só, explicar o estabelecimento da comorbidade ou prevenir o desenvolvimento da mesma (85). Além disso, diversos fatores parecem estar envolvidos na determinação da direção do contágio, entre eles o tipo e grau de relação existente entre os indivíduos envolvidos, o ambiente em que estão inseridos e as personalidades e características individuais de cada um. Essa linha de pesquisa, embora fascinante tem recebido pouca atenção da comunidade científica. É necessário ampliar o conhecimento nesse campo e investir em pesquisas que ajudem a esclarecer os diversos aspectos da depressão contagiante que permanecem apenas no campo das hipóteses.

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8 ANEXOS

8.1 Participação em Artigos Científicos Durante o Mestrado

- Artigo científico publicado no periódico "*Brain Structure and Function*", FI: 3,622, em 22 de agosto de 2019.

Brain Structure and Function
https://doi.org/10.1007/s00429-019-01943-4

ORIGINAL ARTICLE

Increases in dendritic spine density in BLA without metabolic changes in a rodent model of PTSD

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Abstract
Imaging studies have shown abnormal amygdala function in patients with posttraumatic stress disorder (PTSD). In addition, alterations in synaptic plasticity have been associated with psychiatric disorders and previous reports have indicated alterations in the amygdala morphology, especially in basolateral (BLA) neurons, are associated with stress-related disorders. Since, some individuals exposed to a traumatic event develop PTSD, the goals of this study were to evaluate the early effects of PTSD on amygdala glucose metabolism and analyze the possible BLA dendritic spine plasticity in animals with different levels of behavioral response. We employed the inescapable footshock protocol as an experimental model of PTSD and the animals were classified according to the duration of their freezing behavior into distinct groups: "extreme behavioral response" (EBR) and "minimal behavioral response". We evaluated the amygdala glucose metabolism at baseline (before the stress protocol) and immediately after the situational reminder using the microPET and the radiopharmaceutical ^{18}F-FDG. The BLA dendritic spines were analyzed according to their number, density, shape and morphometric parameters. Our results show the EBR animals exhibited longer freezing behavior and increased proximal dendritic spines density in the BLA neurons. Neither the amygdaloid glucose metabolism, the types of dendritic spines nor their morphometric parameters showed statistically significant differences. The extreme behavior response induced by this PTSD protocol produces an early increase in BLA spine density, which is unassociated with either additional changes in the shape of spines or metabolic changes in the whole amygdala of Wistar rats.

Keywords PTSD · Amygdaloid complex · Dendritic spines · ^{18}F-FDG · MicroPET

Introduction

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), Posttraumatic stress disorder (PTSD) is a psychiatric condition classified in the "Trauma and Stressor-Related Disorders" category (American Psychiatric Association 2013). PTSD is a debilitating disorder that develops after exposure to a traumatic event which involves threatened death, serious injury or sexual violence. The psychophysiological symptoms of PTSD are associated with the traumatic event and include avoidance, negative thoughts and mood and alterations in arousal and reactivity. These symptoms persist more than a month and cause significant impairment in patients' lives (American Psychiatric Association 2013; Shalev et al. 2017). In addition, DSM-5 recognizes a dissociative subtype of PTSD, where patients present

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Selective brain neuronal and glial losses without changes in GFAP immunoreactivity: Young versus mature adult Wistar rats

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ABSTRACT

Normal ageing results in brain selective neuronal and glial losses. In the present study we analyze neuronal and glial changes in Wistar rats at two different ages, 45 days (young) and 420 days (mature adult), using Nissl staining and glial fibrillary acidic protein (GFAP) immunohistochemistry associated to the Sholl analysis. Comparing mature adults with young rats we noted the former present a decrease in neuronal density in the cerebral cortex, corpus callosum, pyriform cortex, L.D.D.M., L.D.V.L., central medial thalamic nucleus and *zona incerta*. A decrease in glial density was found in the dorsomedial and ventromedial hypothalamic nuclei. Additionally, the neuron/glia ratio was reduced in the central medial thalamic nucleus and increased in the habenula. No changes were found in the neuronal and glial densities or neuron/glia ratio in the other studied regions. The number of astrocytic primary processes and the number of intersections counted in the Sholl analysis presented no significant difference in any of the studied regions. Overall, neither GFAP positive astrocytic density nor GFAP immunoreactivity showed alteration.

1. Introduction

In humans and rodents, cognitive decline, memory loss and reduced learning ability are associated with brain ageing and losses of neuronal and glial cells throughout life, although in most cases there is no apparent major pathological component, in part, due to the action of healthy glial cells in protecting neurons and repairing damaged tissue in the central nervous system (CNS) (Chung et al., 2009; Tansey and Goldberg, 2010; Fabricius et al., 2013; Chinta et al., 2014; Lopez-Leon et al., 2014; Kalia and Lang, 2015; Ojo et al., 2015; Rodríguez-Arellano et al., 2016; Bellaver et al., 2016).

Among the glial cells, astrocytes are the most numerous in the brain (Pekny and Pekna, 2004), comprising as much as 25% of the cells and 35% of the total mass of the CNS (Eng et al., 1992). They perform key roles in normal brain physiology, including blood flow regulation, providing glucose and lactate to neurons, participating in synaptic function and plasticity, and maintaining the extracellular balance of ions and fluids (Giaume et al., 2007; Rodríguez et al., 2009; Verkhratsky et al., 2012; Sofroniew and Vinters, 2010; Gomes et al., 2013). During the ageing process, astrocytes may react differently (through hyperplasia and/or reactive astrogliosis) in different brain regions, such as the striatum and the frontal cortex (Mythri et al., 2011; Eddleston and Mucke, 1993). Whilst there is no consensus regarding astrocytic density in humans, one study showed the number of astrocytes remains unchanged even in centenarian individuals (Fabricius et al., 2013).

By contrast, a previous study in rats showed the number of astrocytes and pericytes tends to increase by 20% in the cerebral cortex and other brain regions during ageing, while the number of oligodendrocytes and microglia remains unchanged (Cotrina and Nedergaard, 2002).

Ageing is also associated with increased glial fibrillary acidic protein (GFAP) expression. GFAP is a reliable astrocytic marker and increased GFAP immunoreaction is generally accepted as a sign of

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Research article

Adaption of microbial communities to the hostile environment in the Doce River after the collapse of two iron ore tailing dams

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ABSTRACT

In November 2015, two iron ore tailing dams collapsed in the city of Mariana, Brazil. The dams' collapse generated a wave of approximately 50 million m^3 of a mixture of mining waste and water. It was a major environmental tragedy in Brazilian history, which damaged rivers, and cities 660 km away in the Doce River basin until it reached the ocean coast. Shortly after the incident, several reports informed that the concentration of metals in the water was above acceptable legal limits under Brazilian laws. Here the microbial communities in samples of water, mud, foam, and rhizosphere of *Eichhornia* from Doce River were analyzed for 16S and 18S rRNA-based amplicon sequencing, along with microbial isolation, chemical and mineralogical analyses. Samples were collected one month and thirteen months after the collapse. Prokaryotic communities from mud shifted drastically over time (33% Bray-Curtis similarity), while water samples were more similar (63% Bray-Curtis similarity) in the same period. After 12 months, mud samples remained with high levels of heavy metals and a reduction in the diversity of microeukaryotes was detected. Amoebozoans increased in mud samples, reaching 49% of microeukaryote abundance, with Discosea and Lobosa groups being the most abundant. The microbial communities' structure in mud samples changed adapting to the new environment condition. The characterization of microbial communities and metal-tolerant organisms from such impacted environments is essential for understanding the ecological consequences of massive anthropogenic impacts and strategies for the restoration of contaminated sites such as the Doce River.

1. Introduction

In November 2015, two iron ore waste dams collapsed in Mariana, Minas Gerais state, Brazil. The waste buried Bento Rodrigues sub-district with approximately 50 million m^3 of water and mining tailings (Escobar, 2015). The accident had a substantial impact on rivers and cities along the Doce River basin, reaching the marine environment 16 days later (IBAMA, 2015; Segura et al., 2016; Hatje et al., 2017). The Doce River's

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Does Angiotensin II Peak in Response to SARS-CoV-2?

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Human infection by the SARS-CoV-2 is causing the current COVID-19 pandemic. With the growing numbers of cases and deaths, there is an urgent need to explore pathophysiological hypotheses in an attempt to better understand the factors determining the course of the disease. Here, we hypothesize that COVID-19 severity and its symptoms could be related to transmembrane and soluble Angiotensin-converting enzyme 2 (tACE2 and sACE2); Angiotensin II (ANG II); Angiotensin 1-7 (ANG 1-7) and angiotensin receptor 1 (AT1R) activation levels. Additionally, we hypothesize that an early peak in ANG II and ADAM-17 might represent a physiological attempt to reduce viral infection *via* tACE2. This viewpoint presents: (1) a brief introduction regarding the renin-angiotensin-aldosterone system (RAAS), detailing its receptors, molecular synthesis, and degradation routes; (2) a description of the proposed early changes in the RAAS in response to SARS-CoV-2 infection, including biological scenarios for the best and worst prognoses; and (3) the physiological pathways and reasoning for changes in the RAAS following SARS-CoV-2 infection.

Keywords: COVID-19, SARS-CoV-2, Angiotensin-converting enzyme 2, angiotensin-II, immune activation, immune response

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INTRODUCTION

The current COVID-19 pandemic, caused by SARS-CoV-2 infection, has affected virtually all the countries in the world (1). With new cases and deaths being reported daily, there is an urgent need to understand the pathophysiological basis of the disease's progression, especially in the most severe cases. This may accelerate the discovery of effective treatments, thus increasing survival rates and consequently alleviating the disease's social impact. There is considerable biochemical, physiological and pathological evidence to show that the renin-angiotensin-aldosterone system (RAAS) plays a pivotal role in COVID-19. Here, we propose two hypotheses regarding the RAAS, its related receptors, enzymatic synthesis and degradation routes to address Angiotensin II (ANG II) involvement in the range of clinical prognoses of COVID-19.

This study is divided into three main parts. The first provides a description of the RAAS, detailing its receptors, molecular synthesis and degradation routes. The second deals with changes in the RAAS

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