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CLASSIFICAÇÃO DE TRANSTORNO BIPOLAR, ESQUIZOFRENIA e DEPRESSÃO UTILIZANDO REDES NEURAIS ARTIFICIAIS

Tese apresentada como requisito parcial para a obtenção do grau de Doutor em Saúde e Comportamento

Orientador: Prof. Dr. Jean Pierre Oses

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“Omnia mea mecum porto.”

— BIAS OF PRIENE

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RESUMO

O transtorno bipolar, a depressão maior e a esquizofrenia são transtornos de difícil diagnóstico e diferenciação. Estudos apontam que a alteração de níveis de biomarcadores inflamatórios e neurotróficos podem estar associados com o diagnóstico dessas doenças. Redes neurais artificiais (RNA) são ferramentas computacionais de inteligência artificial para modelagem baseadas em sistemas neurais biológicos, as quais utilizam fórmulas matemáticas mimetizando o comportamento neural. O objetivo deste trabalho é propor um modelo de RNA para auxiliar no diagnóstico de transtorno bipolar, da depressão maior e da esquizofrenia, utilizando biomarcadores e características simples da população amostrada. O método de análise para o primeiro artigo é o treinamento de RNA aplicada à um banco de dados de distribuição livre da *Stanley Neuropathology Consortium*, o qual consiste de biomarcadores inflamatórios e características da população com diagnósticos de esquizofrenia, transtorno bipolar e um grupo controle (sem transtornos); para o segundo artigo utilizou-se outro banco de dados, com variáveis bioquímicas, características da população e respostas de questionários com diagnósticos de depressão maior, transtorno bipolar e um grupo controle (sem transtornos). O programa de treinamento da RNA utilizado é o OpenNN, e também é de distribuição livre. Como resultado tem-se RNAs treinadas com mais de 80% de acurácia nas classificações dos diagnósticos.

Palavras-chave: Biomarcadores, redes neurais artificiais, transtorno bipolar, esquizofrenia, depressão, citocinas inflamatórias, neurotrofinas.

BIPOLAR DISORDER AND SCHIZOPHRENIA CLASSIFICATION USING ARTIFICIAL NEURAL NETWORK

ABSTRACT

Bipolar disorder and schizophrenia are disorders of difficult diagnosis and differentiation, and studies point to the alteration of levels of inflammatory biomarkers with the diagnosis of diseases. Artificial neural networks (ANNs) are computational tools of artificial intelligence for modeling based on biological neural systems, which use mathematical formulas mimicking neural behavior. The objective of this work is to propose a model of ANN to aid in the diagnosis of bipolar disorder and schizophrenia using biomarkers and simple characteristics of the sampled population. The method of analysis is ANN training applied to a free distribution database of the Stanley Neuropathology Consortium, which consists of inflammatory biomarkers and characteristics of the population with diagnoses of schizophrenia, bipolar disorder and a control (without mental disorders) group. The RNA training program used is OpenNN, and is also freely distributed. As a result, it is expected to train a ANN with more than 80% accuracy in the classification of bipolar disorder diagnoses, schizophrenia and control group.

Bipolar disorder, major depression and schizophrenia are disorders of difficult diagnosis and differentiation. Studies indicate that altered levels of inflammatory and neurotrophic biomarkers may be associated with the diagnosis of these diseases. Artificial neural networks (ANN) are computational tools of artificial intelligence for modeling based on biological neural systems, which use mathematical formulas mimicking neural behavior. The objective of this work is to propose an ANN model to aid in the diagnosis of bipolar disorder, major depression and schizophrenia, using biomarkers and simple characteristics of the population sampled. The method of analysis for the first article is ANN training applied to a free distribution database of the Stanley Neuropathology Consortium, which consists of inflammatory biomarkers and characteristics of the population with diagnoses of schizophrenia, bipolar disorder and one control group (without disorders); for the second article, another database was used, with biochemical variables, population characteristics and questionnaire responses with diagnoses of major depression, bipolar disorder and a control group (without disorders). The RNA training program used is OpenNN, and it is also freely distributed. As a result, trained RNAs with more than 80 % accuracy in diagnostic classifications.

Keywords: Biomarkers, artificial neural networks, bipolar disorder, schizophrenia, cytokines, neurotrophins.

LISTA DE ABREVIATURAS E SIGLAS

CTQ	Questionário de trauma infantil; *Childhood Trauma Questionnaire*
DDM	Distúrbio Depressivo Maior
DSM	Manual diagnóstico e estatístico de transtornos mentais; *Diagnostic and Statistical Manual of mental disorders*
FAST	Escala de Estadiamento funcional; *Functional Assessment Staging Test*
HDRS	Escala Hamilton de avaliação de depressão; *Hamilton Depression Rating Scale*
HPA	Hipotálamo-Pituitária-Adrenal
IA	Inteligência Artificial
MINI	Mini entrevista neuropsiquiátrica internacional; *Mini-International Neuropsychiatric Interview*
PPGSC	Programa de Pós Graduação em Saúde e Comportamento
RNAs	Redes Neurais Artificiais
SMRI	*Stanley Medical Research Institute*
SPSS	*Predictive Analytics Software and Solutions*
SZ	Esquizofrenia
TB	Transtorno Bipolar
UCPel	Universidade Católica de Pelotas
YMRS	Escala de Young de avaliação de Mania; *Young Mania Rating Scale*

BIOMARCADORES

BDNF	Fator Neurotrófico Derivado do Cérebro; *Brain-Derived Neurotrophic Factor*
GDNF	Fator Neurotrófico Derivado da Glia; *Glial cell-derived Neurotrophic Factor*
IgA	Anticorpo Imunoglobulina A
IgE	Anticorpo Imunoglobulina E

IgM	Anticorpo Imunoglobulina M
IL	Interleucina; *Interleukin*
IFN-γ	Interferon gama
NGF	Fator de Crescimento do Nervo; *Nerve Growth Factor*
NSE	Enolase específica para neurônios; *neuron-specific Enolase*
TGF-α	Fator de transformação do crescimento alfa; *Transforming Growth Factor alpha*
TNF-α	Fator de Necrose Tumoral alfa; *Tumor Necrosis Factor alpha*
TNF-β	Fator de Necrose Tumoral beta; *Tumor Necrosis Factor beta*

LISTA DE FIGURAS

LISTA DE TABELAS

SUMÁRIO

1 IDENTIFICAÇÃO

Mateus Beck Fonseca

1.1 Título

Classificação de transtorno bipolar, esquizofrenia e depressão utilizando redes neurais artificiais

1.2 Titulação em andamento que designa o autor do trabalho

Doutorando

1.3 Orientador

Prof. Dr. Jean Pierre Oses

1.4 Instituição

UCPel - Universidade Católica de Pelotas

1.5 Curso

PPGSC - Programa de Pós Graduação em Saúde e Comportamento

1.6 Linha de pesquisa

Neuroquímica

1.7 Data

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2 INTRODUÇÃO

O transtorno bipolar (TB), o distúrbio depressivo maior e a esquizofrenia (SZ) são transtornos psiquiátricos graves e crônicos que afetam 1% para o TB e 0,8% da população mundial para o SZ, apresentando diferenças para países, enquanto para o DDM afeta quase 5% da mundial, mas é estimado que 15% da população adulta vai vivenciar o distúrbio em algum momento da vida. No Brasil, a prevalência destes transtornos somados é em torno de 14%, e estudos epidemiológicos indicam que TB, DDM e SZ compartilham uma série de características, como sintomas psicóticos e disfunções cognitivas, sendo portanto de difícil diagnóstico e diferenciação (BAHN, 2002; PERÄLÄ et al., 2007; CLEMENTE et al., 2015). O TB caracteriza-se por apresentar episódios depressivos, (hipo)maníacos ou mistos (American Psychiatric Association, 2014). O DDM é definido como pelo menos duas semanas de humor deprimido ou perda de interesse ou prazer em quase todas as atividades, acompanhado de alguns dos sintomas de: problemas de sono, alterações no apetite e peso, fadiga, dificuldade de concentração, alterações psicomotoras e ideação suicida.(American Psychiatric Association, 2014). A SZ é caracterizada por disfunções executivas e sintomas desmotivadores, desorganizados, afetivos, delirantes, alucinatórios ou catatônicos (American Psychiatric Association, 2014). Ambos os transtornos foram associados a resultados negativos na saúde e comprometimentos progressivos (JANSEN et al., 2012; WEICKERT et al., 2015). Portanto, melhorar o diagnóstico pode estar associado a uma melhor definição do tratamento e menores danos ao indivíduo.

Várias evidências apontam que os transtornos psiquiátricos apresentam diversas alterações nos mecanismos moleculares e funcionais do neurônio, levando a alterações observáveis no cérebro (LOTAN et al., 2014). O TB, o DDM e a SZ foram associados a alterações nos níveis de citocinas inflamatórias, incluindo as interleucinas (IL-1, IL-6, IL-18 e IL-10), fator de necrose tumoral alfa (TNF-α) e beta (TNF-β), fator de crescimento tumoral beta (TGF-β) e interferon gama (IFNγ), quando comparados a controles saudáveis, bem como, têm sido associados a alterações nos níveis dos fatores neurotróficos (NGF - fator de crescimento do nervo, BDNF - fator neurotrófico derivado do Cérebro e GDNF - fator neurotrófico derivado da glia) em diversos trabalhos (MUNKHOLM et al., 2015; GHAFELEHBASHI et al., 2017; BAUER et al., 2014; PRATA et al., 2017; LUO et al., 2016). Esses biomarcadores são produzidas por uma variedade de tipos celulares, incluindo células imunes, gliais, musculares e neurônios, e medeiam a sinalização entre células imunes, sendo secretadas principalmente por monócitos (macrófagos, ou linfócitos) (DEMBIC, 2015). Além disso, as citocinas tem um papel fundamental no controle e modulação das respostas inflamatórias, com um equilíbrio constante entre

as citocinas pró-inflamatórias e anti-inflamatórias (MOREIRA et al., 2018). Já as neurotrofinas, são proteínas que induzem a sobrevivência, desenvolvimento e funções dos neurônios (ALLEN; DAWBARN, 2006).

Redes neurais artificiais (RNAs) são ferramentas computacionais de inteligência artificial (IA) para modelagem baseadas em sistemas neurais biológicos, as quais utilizam fórmulas matemáticas mimetizando o comportamento neural. O neurônio recebe entradas de múltiplos neurônios e fornece na saída um valor baseado na função de ativação (MEI et al., 2013). As entradas são multiplicadas por diferentes valores, simulando os pesos sinápticos, e gerando uma resposta preditiva. Este formato de resposta das RNAs é amplamente utilizado em diversas aplicações, como em classificação e reconhecimento de padrões (HASSOUN, 2003). A RNA como ferramenta é efetiva na modelagem de relacionamentos não lineares, que podem ser candidatos promissores para diferenciação em diversos processos biológicos (AMATO et al., 2013). Na literatura está descrita a utilização das RNAs no campo médico para análise de distúrbios do sono, citopatologia e histopatologia, bem como na classificação de imagens de câncer de mama e outras, na predição de doenças cardíacas, diferenciação de células T CD4+ e subgrupo de células imunes, combinando preditores clínicos de resposta antidepressiva em transtorno de humor e outras classificações (GANT; RODWAY; WYATT, 2001).

Nos últimos anos, tem havido um aumento de interesse dentro da comunidade de neurociência no uso de métodos de IA, incluindo RNA (AAKERLUND, 2000; ERGUZEL; TAS; CEBI, 2015). Análises de RNA estão ganhando força na pesquisa psiquiátrica, fornecendo modelos preditivos tanto para a prática clínica quanto para os sistemas de saúde pública (PINTO et al., 2017). Em comparação com métodos estatísticos tradicionais que fornecem principalmente resultados em nível de grupo, os algoritmos de aprendizado de máquina permitem previsões e estratificação de resultados clínicos no nível de uma amostra individual (PASSOS et al., 2016). No entanto, de acordo com o nosso conhecimento, não existe uma RNA usando um biomarcador periférico acessível (citocinas inflamatórias) para classificar o resultado em pacientes com TB, DDM e SZ. Dessa forma, o objetivo principal deste trabalho é propor o uso de RNA classificatória utilizando biomarcadores como preditores no desfecho de pacientes com transtornos.

3 OBJETIVOS E HIPÓTESES

3.1 Geral

Objetivo: Uso de rede neural artificial classificatória utilizando biomarcadores como preditores no desfecho de pacientes com transtornos.

Hipótese:

- RNAs irão contribuir para melhorar os diagnósticos e a orientação dos prognósticos nos pacientes com transtornos.
- Utilizar RNAs para a classificação de pacientes utilizando as informações das variáveis de entrada .

3.2 Específicos

Utilizar um banco de dados de livre acesso com marcadores inflamatórios e características da população de indivíduos saudáveis e com transtornos bipolar, esquizofrenia e depressão maior, para treinar uma RNA e gerar um modelo capaz de diferenciar cada indivíduo quanto ao seu transtorno.

3.2.1 Artigo 1

Objetivo: Para indivíduos saudáveis, pacientes com Transtorno Bipolar ou pacientes com esquizofrenia, espera-se classificar os pacientes quanto ao seu diagnóstico.

Hipótese: Espera-se conseguir um modelo que aplicada ao banco, classifique o indivíduos em saudável ou com transtorno, e qual o transtorno, bipolar ou esquizofrenia, com taxa de acerto maior que 80%, utilizando RNA.

3.2.2 Artigo 2

Objetivo: Utilizando outro banco de dados, com pacientes com depressão, transtorno bipolar e grupo controle (indivíduos sem transtorno), pretende-se repetir as análises discutidas no artigo 1, realizando treinamentos de RNAs para diferenciar três grupos: classificar em

indivíduos sem transtorno, pacientes com Transtorno Bipolar ou pacientes com depressão.

Hipótese: Será trabalhado com três tipos distintos de classificação, por divisão de amostra: análise de distinção entre grupo controle e grupo com diagnóstico de depressão, classificação de grupo controle com transtorno bipolar, e separação de indivíduos com transtorno bipolar e com depressão. Espera-se conseguir uma diferenciação entre os grupos, utilizando RNA, maior que 80%.

4 REVISÃO DE LITERATURA

4.1 Estratégias de busca

A revisão de literatura foi realizada principalmente no site de buscas Pubmed[1] utilizando como filtro estudos com humanos, sem restrição por ano e linguagem. Os descritores utilizados estão descritos abaixo juntamente com o número de artigos encontrados de acordo com cada descritor. As pesquisas foram realizadas em Agosto de 2018.

- *Artificial Neural Network AND Bipolar Disorder* – 6 artigos
- *Artificial Neural Network AND Schizophrenia* – 54 artigos
- *Artificial Neural Network AND Major Depression* - 18 artigos
- *Artificial Neural Network AND Major depression AND Bipolar Disorder* - 3 artigos
- *Artificial Neural Network AND Bipolar Disorder AND Schizophrenia* – 1 artigo
- *Artificial Neural Network AND Biomarker* – 336 artigos

4.2 Transtornos psiquiátricos e biomarcadores

O Transtorno Bipolar (TB) tem sido foco de inúmeros estudos, manifestados por questões que partem de sua noologia e de características fisiopatológicas à apuração epidemiológica (BAHN, 2002; MOREIRA et al., 2018; METIN et al., 2017). A prevalência do transtorno bipolar tipo 1, o mais grave e clássico, encontra-se em torno de 1%, considerando que quase todo o "espectro" chegue a mais de 4% (KAPCZINSKI, 2016). No Brasil, estudos de base populacional estimam que o transtorno possa atingir até 8,3% dos adultos entre todas as suas expressões (MORENO; ANDRADE, 2005). Além disso, quando verificada a presença de episódio maníaco e hipomaníaco entre jovens brasileiros, esta proporção é apresentada como 7,5% e 5,3%, respectivamente (JANSEN et al., 2011). Ainda, o TB também causa substancial impacto econômico (KESSLER; MERIKANGAS; WANG, 2007) e sobrecarga a seus familiares (SILVA, 2011). Essa carga está associada a um grande prejuízo na funcionalidade (JANSEN et al., 2012) e pior qualidade de vida (JANSEN et al., 2011), consequentemente, as alterações de humor no TB estão associadas a maior probabilidade de ideação e risco de suicídio (ORES, 2011).

[1] PubMed é um site de buscas grátis e acessa primeiramente a base de dados MEDLINE, composta de revistas e livros de ciências da saúde e tópicos biomédicos, cobrindo partes das ciências da vida, comportamentais, química e bioengenharia. (https://www.ncbi.nlm.nih.gov/pubmed/)

Nos transtornos psiquiátricos graves, como o TB, DDM e a esquizofrenia, a progressão da doença ocorre frequentemente (BERK et al., 2011). O entendimento da fisiopatologia em amostras clínicas tardias (com muitos anos de doença e episódios prévios) fica prejudicado pela dificuldade em separar alterações causais consequentes da psicopatologia. Assim, estudos em indivíduos jovens apresentam vantagens, por serem menos afetados pela carga, tanto do transtorno, quanto do uso crônico de medicações (GOLDSTEIN et al., 2009). Estudos com indivíduos jovens oferecem a vantagem de terem uma apresentação fenotípica próxima a de adultos e menos controversa que em crianças. Não obstante, um desenho longitudinal de base populacional em uma população de adultos jovens, permite avaliar não apenas a fisiopatologia do TB, mas possíveis cadeias causais entre variáveis psicossociais e vias biológicas de importância para a progressão e a resiliência aos efeitos da doença. Uma vez que é indubitável a confluência de dados recentes em apontar um envolvimento multissistêmico no TB.

Diversas evidências apontam que o TB possui diversas alterações nos mecanismos moleculares e funcionais do neurônio, levando a mudanças observáveis no humor (LOTAN et al., 2014). Estudos sugerem que eventos estressores são importantes nos estágios iniciais da doença (POST; KALIVAS, 2013), assim, a manifestação fenotípica dos transtornos de humor são, presumivelmente, o resultado da interação entre os efeitos do estresse ambiental e alterações neuroquímicas. Estes eventos estressores iniciais vão desencadear um estado de inflamação crônica, promovendo um aumento nos níveis de radicais livres, e assim, alterar mediadores do metabolismo energético e plasticidade sináptica, causando um dano celular (WALKER et al., 2014). Estudos na literatura demonstram que a ativação exacerbada do sistema imunológico e, consequentemente, um aumento nas concentrações extracelulares de proteínas pró-inflamatórias têm surgido como um dos fatores que contribui para a etiologia dos transtornos de humor, incluindo o TB (KUNZ et al., 2011; MAGALHÃES et al., 2011). Existem evidências clínicas de que os transtornos de humor são desordens imuno-inflamatórias caracterizadas, entre outras coisas, pelo aumento de citocinas pró-inflamatórias (MAES et al., 2012). Estas evidências têm estimulado a busca por marcadores periféricos relevantes, e há diversas indicações de relações entre sistemas metabólicos, pró e anti-inflamatórios, pró-oxidantes e antioxidantes, entre outros.

Outro sistema envolvido no TB é a sinalização através dos fatores neurotróficos. Estes fatores são proteínas com funções importantes durante o desenvolvimento do sistema nervoso e da plasticidade neuronal (FERNANDES et al., 2011). Dentre estes podemos citar o fator neurotrófico derivado do cérebro (BNDF), o fator de crescimento do nervo (NGF) e o fator neurotrófico derivado da glia (GDNF). O BDNF tem a expressão mais abundante e difundida no sistema nervoso central (PRUUNSILD et al., 2007), e este fator neurotrófico é liberado de neurônios

tanto constitutivamente, como de forma dependente de atividade (LESSMANN; BRIGADSKI, 2009); interagindo com seus receptores específicos [receptor de neurotrofina p75 (p75NTR) e receptor de cinase relacionadas com a tropomiosina B (TrkB)]. A redução na expressão ou secreção do BDNF tem sido associada a uma série de transtornos psiquiátricos e neurológicos (BALARATNASINGAM; JANCA, 2012). Neste contexto, tem sido demonstrado um aumento dos níveis séricos de BDNF em pacientes tratados com antidepressivos (DWIVEDI, 2009), uma vez que os medicamentos antidepressivos aumentam os níveis séricos de BDNF (POST, 2007). Outro fator neurotrófico envolvido no TB é o NGF, este fator neurotrófico tem recebido muita atenção ultimamente, uma vez que este possui um efeito neuroprotetor em neurônios colinérgicos e seus níveis apresentaram-se aumentados em pacientes com TB (LIU et al., 2014). Ainda, os níveis séricos desta proteína foram significantemente correlacionados com a duração da doença e o número de episódios de mania anteriores (LIU et al., 2014; ZHANG et al., 2014). Em relação ao GDNF, os níveis plasmáticos desta neurotrofina foram significativamente aumentados em pacientes bipolares eutímicos em comparação com controles saudáveis e pacientes com TB em mania. E nestes pacientes, os níveis plasmáticos de GDNF foram negativamente correlacionados com a gravidade da mania e positivamente correlacionada com a idade do sujeito (BARBOSA et al., 2011).

Após pouco mais de 100 anos das primeiras definições, a esquizofrenia continua sendo um transtorno de difícil diagnóstico, sendo definida por apresentar um ou mais das seguintes anormalidades: delírios, alucinações, pensamento (discurso) desorganizado, comportamento motor grosseiramente desorganizado ou anormal (incluindo catatonia) e sintomas negativos (expressão emocional diminuída e desmotivação) (American Psychiatric Association, 2014). A esquizofrenia também apresenta alterações da estrutura cerebral e mudanças dos neurotransmissores dopamínicos, tardiamente é associada à alucinações e ilusões. Seu tratamento é mais basado no controle que na cura (OS; KAPUR, 2009).

Embora alguns trabalhos relacionem a esquizofrenia com alterações nos níveis de fatores neurotróficos como o BDNF e TNF e biomarcadores (HARRIS et al., 2012; NIETO; KUKULJAN; SILVA, 2013; JAROS et al., 2012), o trabalho de (SABHERWAL et al., 2016) apresenta diversas interleucinas (IL-5 e IL-10 e outras citocinas) relacionando as alterações de biomarcadores com a esquizofrenia.

Pesquisas apontam o fator neurotrófico derivado do cérebro (BNDF) como relacionado ao DDM (FERNANDES et al., 2011), também há indícios da associação do DDM com alterações em fatores de crescimento neuronal (NGF) (DUMAN; AGHAJANIAN, 2012) e marcadores inflamatórios - interleucinas e citocinas - (ANISMAN; HAYLEY, 2012).

Além disso, indivíduos com diagnóstico de depressão maior ou transtorno bipolar, especialmente durante os episódios depressivos, são mais propensos a ter um estilo de vida sedentário e uma dieta rica em calorias, aumentando o risco de doenças cardiovasculares e síndrome metabólica (KILBOURNE et al., 2007; TEYCHENNE; BALL; SALMON, 2010). Estudos que avaliem a síndrome metabólica e seus componentes individuais com foco em episódios depressivos ainda são limitados.

4.3 Ferramenta de inteligência artificial

Os avanços nas tecnologias e aquisição de dados simplificaram a coleta e o armazenamento de grandes conjuntos de dados com séries temporais longas, encontrando campos de aplicação cada vez mais frequentes e variados, incluindo as áreas biomédicas e *data-mining*.

Desta maneira, o processo de avaliação de grandes volumes de dados é um processo de valor inestimável e os recentes estudos sublinham o uso de métodos de *machine learning* com resultados promissores (ERGUZEL; TAS; CEBI, 2015; YUAN; CHU, 2007; ZHANG; CHEN; HE, 2010; CHEN; TANG; CHEN, 2013; HUANG; HU; YANG, 2011). Uma vez que grandes conjuntos de dados e alta dimensionalidade de recursos podem sofrer na precisão, sobrepondo dados de classificação e desempenho sem usar métodos de validação adequados, técnicas de *nested cross-validation* são utilizadas para superar a estimativa de erro tendenciosa e remover ruídos que venham a interferir no diagnóstico precoce e o processo de tratamento eficaz. Nesta técnica, um *loop* de validação entre cruzamentos é usado para a seleção do modelo, enquanto uma validação cruzada externa é usada para calcular uma estimativa do erro com um conjunto de dados completamente novo (ERGUZEL; TAS; CEBI, 2015).

Na última década, houve um aumento de interesse no uso de métodos de Inteligência Artificial (IA) nas neurociências. Um desses métodos é o *machine learning* (ML) (ou aprendizado de máquina) supervisionado, podendo detectar automaticamente os padrões nos dados de treinamento existentes e então usar os padrões detectados para prever os dados futuros (MURPHY, 2012). Métodos supervisionados de ML abordam diferenças individuais, em vez de considerar as diferenças entre os grupos, como fazem as comparações estatísticas mais tradicionais, e classificar os indivíduos de modo a contribuir para o processo de decisão clínica. Esses métodos geram um modelo usando um conjunto de treinamento que inclui dados de entrada e de saída. Após o processo de classificação, o modelo é testado usando dados de teste externos para estimar a capacidade de previsão do modelo. Esses métodos também são sensíveis a efeitos espacialmente distribuídos e sutis que, de outra forma, seriam indistinguíveis aplicando méto-

dos estatísticos univariados tradicionais que focalizam as diferenças brutas no nível do grupo (ORRÙ et al., 2012; ERGUZEL; TAS; CEBI, 2015).

4.3.1 Redes Neurais Artificiais

Redes neurais artificiais (RNAs) são um tipo específico de IA ou ML supervisionado. RNA supervisionada significa que a saída já é conhecida em um banco de dados de treinamento. As RNAs supervisionadas calculam uma função de erro entre a saída fixa desejada (alvo) e sua própria saída, e ajustam as forças de conexão (pesos) durante o processo de treinamento para minimizar o resultado da função de erro. A RNA treinada pode ser vista como uma equação que traduz as entradas da RNA em saídas, e regras pelas quais os pesos são modificados para minimizar o erro da equação (LUO et al., 2016). RNAs são capazes de relacionar as informações das variáveis de entrada de forma não linear, e gerar uma fórmula que classifique o desfecho para cada indivíduo.

O trabalho com RNAs envolve treinamento da RNA e validação ou teste. Tipicamente, usa-se a distribuição pelo princípio de PARETO (PARETO, 1971) de 80% das amostras do banco de dados disponíveis para treinamento, e 20% para testes, distribuídas aleatoriamente, e novamente distribui-se o treinamento inicial em treinamento e validação pelo mesmo princípio (validação cruzada) (REITERMANOVÁ, 2010). As RNAs, como ferramentas de classificação binária, fornecem como resultado após a etapa de testes, uma matriz de confusão, exibida na matriz 4.1, composta pelo somatório dos resultados de verdadeiros positivos, falsos positivos, falsos negativos e verdadeiros negativos. A qualidade do treinamento pode então ser avaliada a partir das análises estatísticas da matriz de confusão, Observando valores de acurácia, sensitividade, especificidade, F1-Score, entre outros (SAMMUT; WEBB, 2007; STEHMAN, 1997; EGMONT-PETERSEN et al., 1994).

$$\begin{bmatrix} \text{Verdadeiro Positivo} & \text{Falso Negativo} \\ \text{Falso Positivo} & \text{Verdadeiro Negativo} \end{bmatrix} \tag{4.1}$$

A RNA que se pretende usar é de distribuição livre (OpenNN..., 2009), foi desenvolvida em uma tese de doutorado (GONZÁLEZ, 2008), publicada (LOPEZ; BALSA-CANTO; OÑATE, 2008), possui manuais e página na internet com ajuda (LOPEZ, 2008), e possui exemplo com banco de dados para prover diagnóstico (predizer o aparecimento de diabetes com base em medidas de diagnóstico utilizando o banco de dados público dos índios americanos Pima (KAHN, 1994)). Desenvolvida em linguagem C++, pode ser compilada em qualquer compu-

tador, e por gerar o próprio programa de execução (não depender de outros programas) possui desempenho otimizado.

Uma RNA é composta de neurônios e ligações entre neurônios. O modelo matemático de um Neurônio pode ser dado pelo somatório das entradas multiplicadas por pesos, ligados à uma função de ativação (HASSOUN, 2003). Uma representação de uma RNA genérica pode ser vista na Figura 4.1 e na Equação 4.2, esta topologia tem *p* entradas, um peso *w* conectado em cada entrada, *k* neurônios em paralelo em uma camada Oculta (ou média), um valor constante (bias) somado em conjunto em cada neurônio, com uma função de ativação não linear (representada pela tangente hiperbólica, neste caso), e um neurônio na camada de saída, com função de ativação linear, para uma variável de saída. Este modelo de RNA pode aproximar a saída de qualquer função contínua (HASSOUN, 2003, p. 35).

$$Output = \sum_{j}^{k} w_j.tanh\left(\sum_{i}^{p} w_{ij}.p_i + bias\right) + bias \tag{4.2}$$

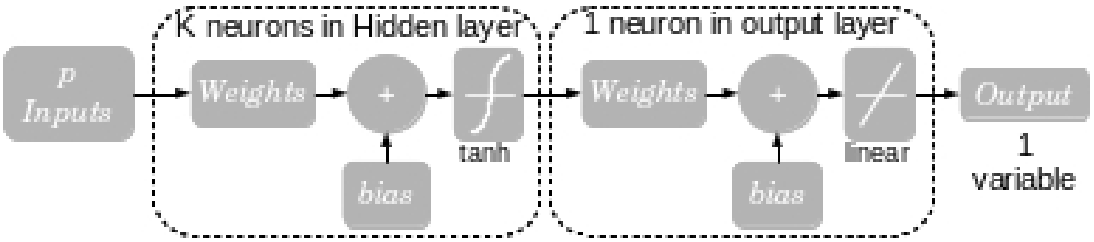

Figura 4.1 – Representação da rede neural com *p* entradas, *k* neurônios na camada oculta (intermediária) e um neurônio de saída para uma variável de saída. Note que é possível ter $p \neq k$, desde que cada entrada tenha seu pesos.

As aplicações das RNAs envolvem problemas complexos, em que extensas massas de dados devem ser analisadas em contexto multidisciplinar, envolvendo, simultaneamente, tanto os aspectos estatísticos e computacionais como os dinâmicos e de otimização, como por exemplo em problemas de classificação e reconhecimento de padrões.

4.4 RNA como ferramenta de classificação dos transtornos psiquiátricos

Alguns distúrbios psiquiátricos são sub-diagnosticados, o que acaba acarretando em uma intervenção tardia ou inadequada. Diferenciar a esquizofrenia do TB em fases iniciais da doença poderia, portanto, ajudar a facilitar o tratamento eficiente e específico. Estudos recentes utilizaram métodos de neuroimagem entre distúrbio depressivo maior (DDM) e TB para revelar

padrões discretos de anormalidades funcionais e estruturais em sistemas neurais e encontraram algum potencial (KALATZIS et al., 2004; CHEN et al., 2014; DUKART et al., 2013). Em alguns outros estudos, técnicas estatísticas convencionais foram usadas e esses métodos se baseiam na suposição básica de combinações lineares que podem ter sido bem conhecidas em adequações para discriminar diagnósticos psiquiátricos heterogêneos baseados em sintomas (TAS et al., 2015; ERGUZEL; TAS; CEBI, 2015). Na última década, os métodos de ML têm sido usados cada vez mais nos estudos de transtornos afetivos para diferenciar estes pacientes em relação a outros transtornos psiquiátricos (ALMEIDA et al., 2009). Na Tabela 4.1, são apresentados estudos utilizando biomarcadores e as ferramentas de ML utilizadas na separação do transtorno bipolar de outras doenças.

Como pode ser analisado na Tabela 4.1, a técnica de RNA não foi utilizada em nenhum dos métodos citados, tampouco com TB, contudo as revisões presentes neste capítulo tornam atrativa a utilização deste método para classificação destes transtornos.

Tabela 4.1 – Estudos desenvolvidos utilizando aprendizado de máquina e biomarcadores para classificar transtorno bipolar e outros diagnósticos

Autor, ano	Dados utilizados	Tamanho da amostra e diagnósticos	Modelo de ML	Acurácia	outras medidas
(BESGA et al., 2015)	Observações clínicas, testes neuropsicológicos e biomarcadores plasmáticos específicos.	95 indivíduos: -37 com DA; -32 com TB tardio; -26 GC.	SVM RF CART	95,76% (GC x TB); 90,26% (DA x TB).	- -
(HAENISCH et al., 2016)	Proteômicas para avaliação sanguínea dos biomarcadores de TB.	907 indivíduos: - 249 com TB; -122 com pre-diag. TB; - 75 com pre-diag. SZ - 90 início DDM; - 371 GC.	LASSO	NA	AUC: 0,79 (TB x GC) 0,91 (TB x SZ)
(PINTO et al., 2017)	Biomarcadores periféricos: IBDNF, IL-6, IL10, CCL11, glutationa S-transferase, glutationa peroxidase	60 indivíduos: - 20 GC - 20 com TB - 20 com SZ	SVM	72,5% (TB vs. GC) 77,5% (SZ vs. GC)	TB x GC: Especif. = 73,68% Sensit. = 71,42% PPV = 75% NPV = 70%

DA, Doença de Alzheimer; AUC, Área sob a curva; BDNF, brain-derived neurotrophic factor; CART, Classification and Regression trees; CL11, eotaxin-1; GC, grupo controle; IL-6, interleukin-6; IL-10, interleukin-10; LASSO, Least Absolute Shrinkage and Selectin Operator; DDM, Distúrbio depressivo maior; RF, Random Forest; SZ, Esquizofrenia; SVM, Support Vector Machine.

Fonte: (LIBRENZA-GARCIA et al., 2017)

5 MÉTODO

A metodologia utilizada é a classificação de indivíduos (amostras) de um banco de dados utilizando redes neurais artificiais.

5.1 Delineamento

Estudo de análise de diagnósticos caso-controle, aplicado em um banco de dados com três coortes.

5.2 Amostra – tamanho e tipo

5.2.1 Primeiro artigo

Para facilitar o número e a qualidade dos estudos de neuropatologia para os principais distúrbios psiquiátricos e identificar possíveis alvos para o desenvolvimento de medicamentos, o *Stanley Medical Research Institute* (SMRI) (Stanley Medical Research Institute, 2009) fornece tecido cerebral *post-mortem* para pesquisa desde 1994 (TORREY et al., 2000). O SMRI fornece amostras com 35 casos em cada um dos três grupos: SZ, TB e controles não afetados. Os grupos diagnósticos em coleções são pareados pelas variáveis descritivas, idade, sexo, raça, intervalo pós-morte, qualidade do RNAm (NIR), pH cerebral e hemisfério (TORREY et al., 2000; KIM; WEBSTER, 2010; KIM et al., 2015).

Os dados foram obtidos de amostras de tecido cerebral descritas por (MIMMACK et al., 2002). As amostras de córtex pré-frontal foram obtidas do consórcio de coleção de cérebros e neuropatologia da Stanley Foundation, EUA. Além desta coleção, foram utilizadas coleções de tecido cerebral de pacientes esquizofrênicos e de um grupo controle japonês (*Department of Psychiatry, Tokyo Metropolitan Matsuzawa Hospital*) e neozelandês (*New Zealand Neurological Foundation Human Brain Bank, University of Auckland, School of Medicine*). A coleção de cérebros da Fundação Stanley consiste em tecido do córtex pré-frontal, derivado de 15 cérebros de esquizofrênicos, 15 cérebros de sujeitos com transtorno bipolar, 15 cérebros de sujeitos com depressão maior e 15 indivíduos controle. A coleção da Japão/Nova Zelândia consiste em tecido do córtex pré-frontal correspondente de 20 esquizofrênicos, 20 com transtorno bipolar e 20 controles pareados. O tecido foi coletado de pacientes que haviam sido previamente

diagnosticados de acordo com o DSM-IIIR[1] (American Psychiatric Association, 1987) ou o DSM-IV(American Psychiatric Association, 1994), feitos por dois psiquiatras seniores, com base em registros médicos, e quando necessário por entrevistas telefônicas com os membros da família. A avaliação dos controles foi baseada em entrevistas estruturadas por um psiquiatra sênior com membro(s) da família para descartar diagnósticos do Eixo I[2].

Tipo de amostra: Os dados que constituem o consórcio neuropatológico foram realizados sem custos por grupos de pesquisa ao redor do mundo. Todas as amostras foram coletadas entre setembro de 1994 e fevereiro de 1997 de tecido cerebral póstumo.

5.2.2 Segundo artigo

Este é um estudo aninhado em um corte transversal de base populacional de pessoas de 18 a 24 anos desenvolvido inicialmente por (JANSEN et al., 2011). Após uma triagem inicial de psicopatologia, toda a população foi avaliada com a versão brasileira do *Mini-International Neuropsychiatric Interview* - MINI (AMORIM, 2000). A fim de melhorar a confiabilidade do diagnóstico, nesta subamostra, o diagnóstico foi fornecido por psicólogos usando a versão brasileira da Entrevista Clínica Estruturada para o DSM-IV (SCID) (DEL-BEN et al., 2001). Para os fins do presente estudo, foram recrutados todos os indivíduos livres de drogas com TB do estudo de base populacional. Além disso, dois grupos de controles foram recrutados. Indivíduos sem histórico de transtornos de humor foram selecionados aleatoriamente e pareados por sexo, idade e anos de estudo - ou seja, uma amostra de controle saudável. Também foi recrutado um segundo grupo de controle, com transtorno depressivo maior. Todos os sujeitos foram informados sobre o estudo e concordaram em participar fornecendo seu consentimento livre e esclarecido, responderam aos questionários e às entrevistas de diagnóstico estruturado. O projeto foi aprovado pelo Comitê de Ética da Universidade Católica de Pelotas (UCPel), Brasil. (JANSEN et al., 2011). Usando esta estratégia, 144 pacientes em três grupos (48 controles saudáveis, 48 TB e 48 MDD) foram pareados.

O banco de dados original era maior, com 231 indivíduos, mas algumas amostras foram retiradas devido a valores ausentes e outras foram sorteadas aleatoriamente para corresponder aos grupos.

Tipo de amostra: Os dados que constituem o banco foram realizados sem custos pela

[1] DSM - *Diagnostic and statistical manual of mental disorders*

[2] Diagnóstico multiaxial Eixo I: Transtornos psiquiátricos clínicos, incluindo transtornos do desenvolvimento e aprendizado (American Psychiatric Association, 2014)

UCPel. Todas as amostras foram coletadas entre 2008 e 2010 de plasma sanguíneo de pacientes vivos.

5.3 Definição das variáveis

5.3.1 Primeiro artigo

A variável dependente (desfecho) é o diagnóstico, o qual pode ser grupo controle, transtorno bipolar ou esquizofrenia.

Variáveis de entrada (independentes) presentes no banco são características da população, biomarcadores neurotróficos e inflamatórios coletados a partir de tecido cerebral póstumo. As variáveis de entrada são: Idade, Sexo, BDNF, IFN-γ, IgA, IgE, IgM, IL-1α, IL-1β, IL-1ra, IL-2, IL-3, IL-5, IL-6, IL-6 Receptor, IL-7, IL-8, IL-10, IL-11, IL-12p40, IL-12p70, IL-13, IL-15, IL-16, IL-17, IL-17E, IL-18, IL-23, NGF-β, RANTES, TGF-α, TNF RII, TNF-α, TNF-β.

As dosagens dos níveis dos biomarcadores foram realizadas pelo laboratório da Prof^a. Sabine Bahn (*Department of Chemical Engineering and Biotechnology, University of Cambridge, Cambridge, UK*) por meio da técnica de multiplex e disponibilizados no site da Stanley Foundation (Stanley Medical Research Institute, 2009). As amostras foram randomizadas e processadas cegamente usando a plataforma de imunoensaio multiplex de acordo com as normas do fabricante (*Myriad Rules Based Medicine - Myriad RBM, Austin, Texas, EUA*). A plataforma de ensaio *Human Discovery MAPTM* foi utilizada para medir diferentes concentrações das diferentes proteínas, peptídeos e moléculas pequenas (coletivamente referidas como 'analitos') (BERTENSHAW et al., 2008).

5.3.2 Segundo artigo

A variável dependente (desfecho) é o diagnóstico, o qual pode ser grupo controle, transtorno bipolar ou depressão maior.

Variáveis de entrada (independentes) presentes no banco são características da população, bioquímicas analisadas de plasma sanguíneo de pacientes vivos e respostas de questionários avaliando a severidade dos transtornos. As variáveis de entrada são: Sexo, idade, cor da pele, classe social, IL-6, IL-10, TNF-α, BDNF, NSE, ácido tiobarbitúrico (medida de estresse oxidativo), ácido úrico, glutationa, abuso de cigarro, abuso de álcool, use de drogas psicotró-

picas, tratamento clínico prévio, CTQ (questionário de trauma infantil) total, escala Hamilton de avaliação de depressão (HDRS) total, escala de Young de avaliação de Mania (YMRS) total, propensão à brigas, problemas de sono, escala Brian total e os seis itens do test FAST.

5.4 Processamento e análise de dados

5.4.1 Análise estatística

A análise estatística dos dados será realizada no programa SPSS 22.0, e no programa GraphPad Prism 6.0. As características sociodemográficas e clínicas serão comparadas utilizando os testes χ^2 para variáveis categóricas e teste t ou análise de variância (ANOVA) para variáveis contínuas. Se a distribuição for Gaussiana os dados serão apresentados por média e desvio padrão e a análise será processada através do teste t, ANOVA e correlação de Pearson. Caso não-Gaussiana, as variáveis serão apresentados por medianas e intervalos interquartis, enquanto os testes de associações serão realizados através dos testes Wilcoxon rank-sum, Kruskal-Wallis e correlação de Spearman.

5.4.2 Análise classificatória por RNA

O método para a análise de classificação será a utilização de redes neurais artificiais.

O programa é o OpenNN, a interface é a linguagem de programação C (C++) em código fonte ou em interface gráfica (através do programa *Neural Designer*), logo, é multiplataforma e de excelente performance, também é um software livre, adaptável e com literatura disponível. Para este trabalho pretende-se utilizar a interface em código fonte.

Para treinamento da RNA, aleatoriamente 80% dos dados disponíveis são utilizados para treinamento da rede, e 20% para teste. Na etapa de treinamento, a rede neural é ajustada, e obtém-se uma fórmula de classificação para o desfecho, em que cada indivíduo pode ser classificado quanto ao seu transtorno. Na etapa de testes, resultados da matriz de confusão (equação 4.1) podem ser apresentados em termos de acurácia, F1-Score, sensitividade e especificidade, por exemplo.

5.5 Cronograma

Na Tabela 5.1 são apresentadas as atividades realizadas até o momento. Nos primeiros anos as atividades preponderantes foram o curso de disciplinas e o estudo do tema 1: "Sistema de auxilio de escuta Binaural para portadores de deficiência auditiva". Contudo o tema 1 se mostrou inviável devido à necessidade de laboratórios com modelos auditivos humanos e passou-se para o estudo do tema 2: "Análise de qualidade de pêssegos por imagem e ultrassom", o qual chegou a ser apresentado no Salão universitário 2015 e que rapidamente mudou para "Avaliação de fenóis em morangos", devido aos morangos apresentarem uma quantidade significativamente maior de fenóis. Pretendia-se construir uma máquina para detectar os fenóis presentes em morangos por meio de luz infra vermelha e ultrassom, mas a dificuldade do trabalho com lentes e espelhos inviabilizou o projeto. O estudo do tema 3, que é o título deste projeto, iniciou no final de 2016.

Tabela 5.1 – Cronograma de atividades passadas. Resumo das atividades desenvolvidas do início do curso até o momento.

Atividades	2015\1	2015\2	2016\1	2016\2	2017\1	2017\2	2018\1
Curso de disciplinas	x	x	x	x	x		
Estudo de tema 1	x	x					
Estudo de tema 2		x	x	x			
Estudo de tema 3				x	x	x	x

Na Tabela 5.2 é apresentado um cronograma resumindo as principais atividades restantes do trabalho.

Tabela 5.2 – Cronograma de atividades futuras

Atividades	*Out*	*Nov*	*Dez*	*Jan*	*Fev*
Revisão de literatura	x	x	x	x	
Processamento dos dados	x				
Qualificação e projeto	x				
Redação de artigos	x	x	x	x	x
Redação da tese	x	x	x	x	
Defesa					x

5.6 Orçamento

Não se aplica. O banco de dados utilizado é livre, assim como o programa para RNA, que é executado em máquina pessoal, os programas estatísticos foram adquiridos com verbas de outros projetos do PPGSC e rodam em máquinas da universidade.

5.7 Aspectos éticos

Este estudo foi aprovado (A2012-117) pelo comitê de ética do Centro Nacional de Neurologia e Psiquiatria do Japão. As amostras foram coletadas, com consentimento informado dos parentes próximos, pelos examinadores médicos participantes. Todos os dados foram retiradas de um banco de dados público disponível em (Stanley Medical Research Institute, 2009).

6 CONSIDERAÇÕES FINAIS

Esta tese buscou atender aos objetivos propostos e hipóteses formuladas em seu projeto. Dois artigos foram originados deste trabalho, um já publicado e outro a ser submetido, conforme anexos. Ambos artigos utilizam a técnica de treinamento de uma rede neural artificial para conseguir classificar o diagnóstico por indivíduo e não por grupo, como nas análises estatísticas convencionais.

O uso de RNA's em banco de dados da saúde não é uma novidade, mas a aplicação nos transtornos apresentados com a utilização de biomarcadores e características da população é, de acordo com as revisões apresentadas no Capítulo 4.

O primeiro artigo trata da classificação de pacientes com transtornos Bipolar e esquizofrenia, bem como de um grupo controle de indivíduos sem transtornos, utilizando RNA. E apresenta-se resultados de mais de 90% de acerto no diagnóstico dos pacientes. Para este artigo, são apresentadas ao final como anexos as fórmulas decorrentes dos modelos de treinamento das RNAs.

O segundo artigo aborda a classificação de indivíduos com depressão maior, transtorno bipolar e um grupo controle de indivíduos sem transtornos, utilizando RNA. São apresentados resultados de interpretação da matriz de confusão dos resultados de testes dos treinamentos, com mais de 80% de acerto nas classificações dos diagnósticos.

Nota-se para os dois artigos como é mais fácil diagnosticar um indivíduo entre com ou sem transtorno do que predizer qual o seu transtorno.

É importante destacar que os dados do primeiro artigo foram coletados de tecido cerebral *post mortem*, enquanto que para o segundo artigo os dados foram coletados de pacientes vivos por meio de análises do plasma sanguíneo.

6.1 PERSPECTIVAS FUTURAS

A principal ideia deste trabalho é o auxílio do diagnóstico de transtornos mentais por meio de uma amostra de sangue e características simples do individuo como idade e sexo. Contudo o diagnóstico dos transtornos mentais por meio de uma amostra de sangue ainda é uma ideia distante, dado que os biomarcadores utilizados para realizar as classificações deste trabalho ainda não são consenso na comunidade como indicadores dos transtornos aqui relacionados. Outro fato interessante é a própria definição dos transtornos, embora sejam consolidados, sofreram modificações para melhor diagnosticar ao longo dos anos, como podem

ser observados nas variações dos manuais de diagnóstico e estatística de transtornos mentais DSM-IIIR(American Psychiatric Association, 1987), DSM-IV(American Psychiatric Association, 1994) e DSM-5(American Psychiatric Association, 2014).

Biomarcadores específicos para transtornos mentais ainda são perspectivas, mas este trabalho, através do uso de RNA, não aborda um marcador específico, e sim o envolvimento em conjunto de todas as variáveis aplicadas nas entradas das RNAs. Esta técnica inter-relaciona as variáveis com o desfecho, criando uma interpretação a partir de todas as entradas com o diagnóstico do indivíduo.

Espera-se que esta tese ajude a difundir a técnica de RNA e outras ferramentas de inteligencia artificial ou aprendizado de máquina no campo da saúde, aplicando-a em outros bancos de dados e gerando auxilio nos diagnósticos, com diagnósticos mais precisos, o que pode levar a tratamentos mais eficazes, aprofundando as análises do estado de saúde e bem-estar para a saúde pública.

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APÊNDICE A — ARTIGO PUBLICADO

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Bipolar and Schizophrenia Disorders Diagnosis Using Artificial Neural Network

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Abstract

Motivation: Bipolar disorder (BD) and schizophrenia (SZ) has a difficult diagnosis, so the main objective of this article is to propose the use of Artificial Neural Networks (ANNs) to classify (diagnose) groups of patients with BD or SZ from a control group using sociodemographic and biochemical variables. **Methods:** Artificial neural networks are used as classifying tool. The data from this study were obtained from the array collection from Stanley Neuropathology Consortium databank. Inflammatory markers and characteristics of the sampled population were the inputs variables. **Results:** Our findings suggest that an artificial neural network could be trained with more than 90% accuracy, aiming the classification and diagnosis of bipolar, schizophrenia and control healthy group. **Conclusion:** Trained ANNs could be used to improve diagnosis in Schizophrenia and Bipolar disorders.

Keywords

Bipolar Disorder, Schizophrenia Disorder, Biomarkers, Artificial Neural Network

1. Introduction

Artificial neural network (ANN) attempts to use multiple layers of calculations to emulate the neuronal circuitry in the human brain by interpreting and drawing conclusions from several information. ANN algorithms are mathematical models based on biological neural systems that simulate the behavior of neurons. The neuron receives inputs from multiple neurons and outputs a value based

upon the activation function [1]. The ANN inputs are multiplied by different weights to generate a predictive response. So, these responses in ANN are widely used for several applications such as classification and pattern recognition [2]. This tool is effective modeling non-linear relationships that may be a promising candidate for differentiation for several biological processes [3]. ANN are used in medical field to analysis of sleep disorders, cytopathology and histopathology such as classification of breast cancer images and others, in prediction of heart disease, CD4+ T cell differentiation and immune cell subset classification, combining clinical predictors of antidepressant response in mood disorder, and other classifications [4] [5].

Bipolar disorder (BD) and schizophrenia (SZ) are complex mental disorders with high genetic load, and are the largest global contributors to years with functional disability [6]. These disorders are among the most severe psychiatric disorders that affects around 1% and 0.8% of the general population, respectively [7] [8] [9]. BD is characterized by depressive, (hypo)manic, or mixed episodes [10]. SZ is characterized by amotivational, disorganized, affective, delusional, hallucinatory, or catatonic symptoms [10]. Both have been associated with negative health outcomes and progressive impairments [11] [12]. Therefore improve the diagnosis may be associated with a better definition of the treatment and lower damages to subject. Several evidences point out that psychiatric disorders have several changes in the molecular and functional mechanisms of the neuron, leading to observable changes in the brain [13]. Studies suggest that stressful events are important in the early stages of the disease [14], so the phenotypic manifestation of mood disorders is presumably the result of the interaction between the effects of environmental stress and genetic predisposition.

BD and SZ have been associated with alteration in inflammatory cytokine levels, including Interleukin (IL-1, IL-6, IL-18, and IL-10), tumor necrosis factor alpha (TNF-α) and beta (TNF-β), transforming growth factor beta (TGF-β), and interferon gamma (IFNγ), when compared to healthy controls, and has been associated to neurotrophic factors changes [15] [16] [17] [18] [19]. These cytokines are produced by a variety of cell types including immune cells, muscular cells, glial cells and neurons; they mediate signaling between immune cells, and are mainly secreted from monocytes, macrophages or lymphocytes [20]. Moreover, cytokines play a central role in the control and modulation of inflammatory responses, and modulate the neurotrophins, with a constant balance between proinflammatory and anti-inflammatory cytokines [21].

In the last years, there has been an upsurge of interest within the neuroscience community in the use of artificial intelligence (AI) methods, including ANN [22] [23]. Moreover, ANN analyses are gaining traction in psychiatric research, providing predictive models for both clinical practice and public health systems. Compared with traditional statistical methods that provide primarily average group-level results, machine-learning algorithms provide predictions and stratification of clinical outcomes at the level of an individual subject [24]. However, for the best of our knowledge there is no ANN using an accessible peripheral

biomarker (inflammatory interleukins) to classify the outcome in BP and SZ patients. In this way, the main objective of this article is to propose the use of ANN to classify (diagnose) groups of patients with BP or SZ from a control group.

2. Methods

2.1. Participants

The data from this study were obtained from the Array collection from Stanley Neuropathology Consortium databank (SNC) [25] [26]. The databank consists of 105 brains samples (35 schizophrenia brains, 35 bipolar disorder brains, and 35 health control brains). For one trainingscenario, schizophrenia and bipolar disorder were grouped as outcome to perform the analysis, so 35 samples were randomly drawn to match the control group. As input variables, 34 sociodemographic and biochemical variables were applied to train an ANN. The ANN training data input variables were: age, sex, smoking, BDNF, IFN-gamma, IgA, IgE, IgM, IL-1alpha, IL-1beta, IL-1ra, IL-2, IL-3, IL-5, IL-6, IL-6 Receptor, IL-7, IL-8, IL-10, IL-11, IL-12p40, IL-12p70, IL-13, IL-15, IL-16, IL-17, IL-17E, IL-18, IL-23, NGFb, RANTES, TGF-alpha, TNF RII, TNF-alpha, TNF-beta.

2.1.1. Selection, Clinical Information, and Diagnosis

Briefly, donors for the brain collection are identified by investigators in original study. Individuals over age 65 are excluded because of the increased likelihood of comorbid neurological disorders. A preliminary diagnosis and requests permission for donation of the brain and for release of the deceased's medical records was solicited. Data regarding the sociodemographic, clinical and psychiatric history, substances use was collected. Medical and psychiatric records are requested for known hospitalizations and outpatient treatments to be made until sufficient information has been collected to make a clear diagnosis. All records was reviewed by one psychiatrist and the information is entered into a computerized database (demographic data, family history, education, age of onset, total duration of hospitalizations, psychiatric diagnosis, cause of death, medical diagnoses, medications at time of death, brain weight, interval between death and refrigeration of body, and interval between death and freezing of brain tissue [*postmortem* interval (PMI)]) by identifying number only (more details see [25]). After all information was collected, the DSM-IV [10] psychiatric diagnosis was made independently by two senior psychiatrists. If there was disagreement between them, the records were made by a third senior psychiatrist.

2.1.2. Processing of Brain Tissue

Trained medical examiners collected and processed the brain tissue. Half of brain was fixed in formalin while the other is cut into 1.5 cm thick coronal slices and frozen in a mixture of isopentane and dry ice. The frozen half was stored at −70˚C until analysis.

2.1.3. Neuropathology Consortium

The Stanley Medical Research Institute (SMRI) [25] provides postmortem brain

tissue for research since 1994 facilitating the number and quality of neuropathology studies for the major psychiatric disorders and to identify possible targets for drug development. In this context, the arraycollection [26] provides samples with 35 cases in each of three groups: SZ, BD and unaffected controls. The diagnostic groups in collections are matched for the descriptive variables, age, gender, race, postmortem interval, mRNA quality (RIN), brain pH and hemisphere [25] [27]. All samples were collected between September 1994 and February 1997. The specimens that constitute the Neuropathology Consortium are made available without charge to research groups around the world.

2.1.4. Multiplex Immunoassay Analysis

All analytes were measured by multiplex immunoassay. Extracts (200 μL) were analyzed using the Discovery MAP™ multiplexed immunoassay panel at Myriad-RBM (Austin, TX, USA). Each assay was calibrated using duplicate 8-point standard curves, and raw intensity measurements were interpreted into final protein concentrations using proprietary software. Machine performance was verified using quality control samples at low, medium, and high levels for each analyte [28].

2.2. ANN Training and Statistical Analyses

In this study the inputs to the first layer of the neural network consist of 34 sociodemographic and biochemical variables while the target output consist of the following outputs trainings classifications: 1) control or case group; 2) control or BD group; 3) control or SZ group; and 4) BD or SZ group. The network is then trained to attempt to predict response from the set of variables. Supervised ANNs were applied in this work. Supervised ANNs means that the output is already know, in a training data bank. Supervised ANNs calculate an error function between the desired fixed output (target) and their own output, and adjust the connection strengths (weights) during the training process to minimize the result of the error function. The trained ANN can be seen as an equation, which translate the ANNs inputs into outputs, and rules by which the weights are modified to minimize the error of the equation [29]. A general ANN can be identified in **Figure 1**, this topology has p inputs, one weight connected in each input, k neurons in parallel in a Hidden (or middle) layer, with a non-linear activation function, and one neuron in output layer, with linear activation function, for one output variable. This model of ANN can approximate the output of any continuous function [2], and was used in this work to classify the diagnosis.

To perform ANN training analyses, the OpenNN software was used. It is a multiplatform and open source software, for artificial neural networks [30]. In this work, the weights were randomized at the start of each training, and trained until the performance increase was above 1e-6 with the quasi-newton method. Also, the data bank was divided for training and testing, being 80% for training and 20% of the bank for test. The ANN training gives as result a confusion matrix. The accuracy, sensitivity, specificity and F1 score (harmonic mean between

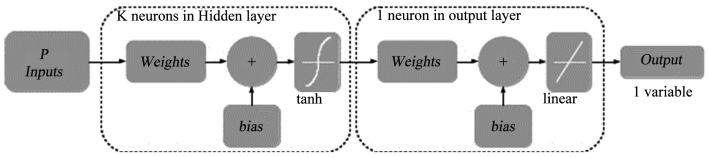

Figure 1. Neural network representation with p inputs, k neurons in hidden (middle) layer and one output neuron for one output variable. Note that is possible to have $p \neq k$, provided that each input has its weights. In this work we used 35 inputs (brain inflammatory markers and characteristics of the sampled population) and the output is binary as a classification of control group or BD or SZ disease. We vary the neurons in hidden layer to compare results and found the best suitable network.

precision and sensitivity) were obtained from confusion matrix calculation. Some related works also show classification functions to analyze the ANN training [31] [32]. In this work, we performed ten trainings for each number of neurons in hidden layer. They are show as mean and standard deviation (mean ± S.D.) and the best achieved result of these trainings is also presented.

Statistical analyzes were performed by the Statistical Program for Social Sciences (SPSS) 22.0. The Chi Square and Analysis of Variance (ANOVA) test were used to check the consistency of match between groups.

3. Results

The analysis was conducted with 104 data samples. The original data bank was composed of 105 individuals, 35 in bipolar disorder, 35 in schizophrenia and 35 in control group. One case of bipolar disorder has no data available, so training and analysis with BD were matched to 34 individuals.

The characteristics of patients are shown in **Table 1**. In BD group, most subjects were female (67%) while in SZ and control groups were male (74% in both groups) ($p = 0.025$). 44% of BD patients and 20% of SZ patients are suicide victims, although there are no cases in control group ($p \leq 0.001$). The mean age was 45.4 ± 10.67, 42.57 ± 8.47, and 44.2 ± 7.58 years for BD, SZ and control respectively. The duration of illness was 20.00 ± 9.62 and 21.29 ± 10.14 years for BD and SZ, respectively. In addition, the lifetime antipsychotics were 1.13 ± 2.62 and 9.70 ± 11.45 years for BD and SZ, respectively. Smoking data was also available, but due to the more than forty percent of missing values, these data was not take intoaccount at the training or in **Table 1**. For the duration of illness, lifetime antipsychotics and suicide status, there were no event in control group, so these variables were not used in ANN training. Demographic data and complementary information were provided in Stanley Foundation research site [33].

ANN training results changing the comparisons groups can be analyzed in **Tables 2-5**. They present the best result of ten different training and the mean and ±standard deviation of these trainings. The classification training results can be seen as accuracy, F1 score, sensitivity and specificity in these tables. For the best results, the displayed data stands for the best accuracy case, taking the F1

score, sensitivity and specificity of this best case, using F1 score as tiebreaker when needed. ANN middle layer neurons were also compared from three to nine neurons. For less than three and more than nine neurons in ANN hidden layer, the accuracy results was below 50% (data not show).

A classification with cases and controls were performed. BD and SZ were grouped, (samples were randomly drawn to match the control group), in one patient cases group. An ANN training was done to classify cases and control groups. Results of these training can be seen in Table 2. Results in Table 2 show the best achieved accuracy, F1 score, sensitivity and specificity; they were respectively 0.93, 0.95, 1.00 and 0.80 for three neurons.

For differentiation of BD from healthy people, ANN training results can be seen in Table 3. One sample from control group was randomly drawn to match the BD group data sample. In Table 3 best training result is for six neurons, using F1 score as tiebreaker. This gives 0.92 of accuracy, 0.95 of F1 score, 1.00 for sensitivity and 0.75 for specificity. So with six neurons in ANN hidden layer, 92% of accuracy diagnosis can be achieved, recognizing all BD patients.

Schizophrenia patients group is differentiated from healthy group in Table 4. Table 4 best results for accuracy, F1 score, sensitivity and specificity, were respectively 0.93, 0.93, 1.00, 0.86 for seven neurons in ANN hidden layer. So, one can classify with 93 of accuracy a SZ patient from healthy people, correctly identifying all SZ patients.

Table 5 shows BD and SZ ANN training classification results. One sample from SZ group was randomly drawn to match the BD group data sample. It exemplifies classifications where the BD and SZ diagnosis is not clear. With three neurons in ANN hidden layer, the best result of training is achieved, and is 0.92 of accuracy, 0.93 of F1 score, 0.88 of sensitivity and 1.00 of specificity. This leads to a diagnosis of 92% of accuracy, with all SZ patients correctly identified.

Table 1. Characteristics of the sampled population for cases and control group.

Variables	BD	SZ	CTRL	p-value
	(n = 34)	(n = 35)	(n = 35)	
Gender[a]				0.025
Male	16 (39)	26 (74)	26 (74)	
Female	18 (67)	9 (26)	9 (26)	
Suicide Status[a]	15 (44)	7 (20)	-	≤0.001
Age[b]	45.40 ± 10.67	42.57 ± 8.47	44.20 ± 7.58	0.422
PMI Pos Morten Interval (h)[b]	37.90 ± 18.62	31.40 ± 15.54	29.37 ± 12.87	0.071
Brain PH[b]	6.43 ± 0.30	6.47 ± 0.24	6.60 ± 0.27	0.018
Duration of Illness (years)[b]	20.00 ± 9.62	21.29 ± 10.14	-	≤0.001
Lifetime Antipsychotics (years)[b,c]	1.13 ± 2.62	9.70 ± 11.45	-	≤0.001

BD = Bipolar disorder, SZ = schizophrenia, and CTRL = control. [a]Simple and relative frequencies (%), [b]Mean and standard deviation, [c]12 cases in BD with no use of Antipsychotics, while all cases in SZ used.

Table 2. Cases (BD and SZ grouped) and control groups ANN classification training results.

	Accuracy		F1 Score		Sensitivity		Specificity	
#Neurons	Best result	Mean ± S.D.	Best result	Mean ± S.D.	Best result	Mean ± S.D.	Best result	Mean ± S.D.
3	0.93	0.66 ± 0.12	0.95	0.64 ± 0.16	1.00	0.68 ± 0.21	0.80	0.62 ± 0.26
4	0.79	0.62 ± 0.08	0.80	0.59 ± 0.16	0.75	0.58 ± 0.20	0.83	0.62 ± 0.23
5	0.71	0.63 ± 0.08	0.78	0.63 ± 0.12	0.91	0.63 ± 0.20	1.00	0.60 ± 0.19
6	0.79	0.64 ± 0.07	0.80	0.58 ± 0.12	0.86	0.57 ± 0.18	0.71	0.71 ± 0.11
7	0.93	0.68 ± 0.12	0.94	0.67 ± 0.14	1.00	0.67 ± 0.19	0.83	0.65 ± 0.18
8	0.86	0.65 ± 0.10	0.80	0.63 ± 0.14	0.86	0.63 ± 0.14	0.89	0.60 ± 0.33
9	0.79	0.63 ± 0.09	0.77	0.58 ± 0.22	0.83	0.57 ± 0.23	0.75	0.65 ± 0.20

Result for each number of Neurons and results shown for 10 different ANN training for each number of neurons in hidden layer (70 different trainings). Accuracy, F1 Score, Sensitivity and Specificity, are presented as mean and standard deviation (S.D.).

Table 3. Bipolar disorder and control groups ANN classification training results.

		Accuracy		F1 Score		Sensitivity		Specificity
#Neurons	Best result	Mean ± S.D.	Best result	Mean ± S.D.	Best result	Mean ± S.D.	Best result	Mean ± S.D.
3	0.77	0.55 ± 0.05	0.82	0.57 ± 0.08	0.78	0.59 ± 0.16	0.75	0.56 ± 0.19
4	0.69	0.56 ± 0.05	0.75	0.58 ± 0.10	1.00	0.62 ± 0.19	0.43	0.48 ± 0.20
5	0.92	0.65 ± 0.12	0.94	0.64 ± 0.11	0.89	0.67 ± 0.15	1.00	0.65 ± 0.25
6	0.92	0.60 ± 0.12	0.95	0.58 ± 0.22	1.00	0.64 ± 0.28	0.75	0.51 ± 0.23
7	0.85	0.59 ± 0.09	0.80	0.58 ± 0.09	0.67	0.59 ± 0.13	1.00	0.61 ± 0.15
8	0.77	0.55 ± 0.09	0.80	0.58 ± 0.11	0.86	0.69 ± 0.19	0.67	0.43 ± 0.15
9	0.77	0.56 ± 0.10	0.77	0.56 ± 0.15	0.83	0.58 ± 0.17	0.71	0.54 ± 0.19

Results shown for 10 different ANN training for each number of neurons in hidden layer (70 different trainings). Accuracy, F1 Score, Sensitivity and Specificity, are presented as mean and standard deviation (S.D.), and the best result for each number of Neurons.

Table 4. Schizophrenia and control groups ANN classification training results.

	Accuracy		F1 Score		Sensitivity		Specificity	
#Neurons	Best result	Mean ± S.D.	Best result	Mean ± S.D.	Best result	Mean ± S.D.	Best result	Mean ± S.D.
3	0.79	0.57 ± 0.09	0.82	0.57 ± 0.14	1.00	0.59 ± 0.21	0.57	0.57 ± 0.20
4	0.71	0.55 ± 0.07	0.71	0.56 ± 0.09	0.63	0.54 ± 0.14	0.83	0.58 ± 0.16
5	0.71	0.51 ± 0.08	0.71	0.54 ± 0.15	0.71	0.57 ± 0.21	0.71	0.43 ± 0.25
6	0.71	0.51 ± 0.08	0.67	0.50 ± 0.09	0.67	0.52 ± 0.16	0.75	0.52 ± 0.17
7	0.93	0.56 ± 0.13	0.93	0.52 ± 0.17	1.00	0.48 ± 0.22	0.86	0.66 ± 0.15
8	0.86	0.55 ± 0.14	0.86	0.49 ± 0.20	0.75	0.51 ± 0.27	1.00	0.60 ± 0.13
9	0.79	0.54 ± 0.11	0.77	0.54 ± 0.12	0.83	0.60 ± 0.24	0.75	0.51 ± 0.20

Results shown for 10 different ANN training for each number of neurons in hidden layer (70 different trainings). Accuracy, F1 Score, Sensitivity and Specificity, are presented as mean and standard deviation (S.D.), and the best result for each number of Neurons.

Table 5. Bipolar disorder and Schizophrenia ANN classification training results.

	Accuracy		F1 Score		Sensitivity		Specificity	
#Neurons	Best result	Mean ± S.D.	Best result	Mean ± S.D.	Best result	Mean ± S.D.	Best result	Mean ± S.D.
3	0.92	0.53 ± 0.12	0.93	0.81 ± 0.30	0.88	0.58 ± 0.17	1.00	0.56 ± 0.23
4	0.77	0.57 ± 0.08	0.80	0.59 ± 0.12	0.86	0.64 ± 0.16	0.67	0.48 ± 0.10
5	0.92	0.57 ± 0.11	0.91	0.59 ± 0.12	1.00	0.62 ± 0.17	0.88	0.59 ± 0.12
6	0.77	0.54 ± 0.10	0.84	0.53 ± 0.15	0.89	0.55 ± 0.19	0.50	0.50 ± 0.14
7	0.62	0.52 ± 0.04	0.74	0.52 ± 0.10	1.00	0.61 ± 0.23	0.17	0.45 ± 0.31
8	0.77	0.58 ± 0.09	0.80	0.60 ± 0.09	1.00	0.65 ± 0.13	0.57	0.50 ± 0.17
9	0.77	0.57 ± 0.09	0.84	0.60 ± 0.08	0.80	0.62 ± 0.12	0.67	0.53 ± 0.16

Results shown for 10 different ANN training for each number of neurons in hidden layer (70 different trainings). Accuracy, F1 Score, Sensitivity and Specificity, are presented as mean and standard deviation (S.D.), and the best result for each number of Neurons.

4. Discussion

In present study was applied an ANN to discriminate two mental disorders and health subjects in clinical and inflammatory-based data. The ANN model was able to identify correctly a high percentage of subjects with a psychiatric disorder in a sample with sick and healthy individuals. Moreover, the ANN model shows very specific and sensitive, in confusion matrix interpretation. In our knowledge, this is the first study that proposes an ANN model to improve the use of markers and clinical data in diagnoses of BD and SZ. Our analyses suggest that an ANN function could properly classify the cases and control groups of these disorders.

Studies investigating the impact of a variety of inflammatory stimuli on the brain and behavior have reported evidence that inflammation and the release of inflammatory cytokines affect the relevant circuits for BD and SZ [16] [28]. Inflammatory cytokines reach the brain and are associated with increased expression of pro-inflammatory eicosanoids, nitric oxide, TNF-α, IL-1β, reactive oxygen species, as well as monocytes and macrophages in the brain [17]. Several studies have suggested an imbalance in pro and anti-inflammatory responses in the pathogenesis of SZ and BD. However, the mechanisms involved in these processes remain unknown. Thus, the results found in our study agree with previous studies where there is an involvement of the immune system in these disorders. There is clinical evidence that mood disorders are immunoinflammatory disorders characterized, among other things, by the increase of proinflammatory cytokines [16] [17]. These evidences have stimulated the search for relevant peripheral markers, and there are several indications of relationships between metabolic, pro and anti-inflammatory, pro-oxidant and antioxidant systems, among others.

Advances in technology and data acquisition have simplified the collection and storage of large datasets with long time series, finding increasingly frequent and varied fields of application, including biomedical and data mining areas. In this way, the process of evaluating large volumes of data is an invaluable process

and the recent studies emphasize the use of AI methods with promising results [23] [24]. Supervised ANN methods address individual differences, rather than considering differences between groups, as do more traditional statistical comparisons, and classifying individuals in order to contribute to the clinical decision making process. These methods generate a model using a training set that includes input and output data. After the classification process, the model is tested using external test data to estimate the predictive capacity of the model. These methods are also sensitive to spatially distributed and subtle brain effects that would otherwise be indistinguishable by applying traditional univariate methods that focus on gross differences at the group level [23]. Although ANN methods are used in biomedical studies, AI techniques in psychiatric disorders are still incipient. Several neuroimaging studies of [34] use AI techniques and neural networks to look for possible changes in BD patients. In addition, these authors have described, from the clinical point of view, findings relevant to the pathophysiological understanding of bipolar disorder. In this sense, our study has demonstrated that there is an interaction between several neurochemical and inflammatory factors that may be directly involved in BP and SZ.

Regarding peripheral markers, there are still few studies that used AI techniques to identify biomarkers in patients with bipolar disorder or schizophrenia. A study by [35] was highlighted. The Space Vector Machine (SVM) algorithm differentiated patients with bipolar disorder from healthy controls with a predictive accuracy of 72.5%, and patients with schizophrenia from healthy subjects with a prediction accuracy of 77.5%. However, the algorithm was not able to differentiate patients with bipolar disorder from patients with schizophrenia (REF). In our study, although using a different technique, it found an accuracy of 92% when comparing patients with BD with healthy individuals, and 93% when we compared SZ with healthy individuals. Moreover, our findings differentiate patients with bipolar disorder from patients with schizophrenia; it was found an accuracy of 92%. It is necessary to point out that in the study of [35]; the evaluations were carried out on blood samples, whereas the sample of this study was brain tissue.

This is a study to evaluate the feasibility of using a biomarker tool developed with ANN algorithms to identify a patient with bipolar disorder or schizophrenia when compared to healthy controls. However, the present work has some limitations: 1) Our sample was small as we used a brain from post-mortem tissue; 2) the majority of individuals were taking medication, a factor that influences the results obtained. Despite these limitations, future studies should assess larger samples from multiple centers; use advanced mathematical techniques combined with other biological and clinical variables to improve our knowledge about schizophrenia and bipolar disorder. Moreover, in the last years the use of ANNs has been growing as to a promise approach in basic and clinical studies. Here, our findings suggest that artificial neural network could be valid to detect the role of markers in the involvement of inflammatory mechanisms in the pathophysiology of bipolar disorder and schizophrenia.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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APÊNDICE B — ARTIGO ORIGINAL NÃO PUBLICADO

Bipolar and Depression Disorders Diagnosis Using Artificial Neural Network

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Abstract

Motivation: Bipolar and major depression disorders have a difficult diagnosis, so this work is a proposal for diagnosis improvement, using an Artificial Neural network to classify the individuals.

Methods: Artificial neural network as classifying tool, brain inflammatory markers and characteristics of the sampled population as well as diagnostic questionnaires for bipolar disorder and major depression as inputs variables from a case-control data bank study of of 48 healthy control subjects, 48 with diagnosis of bipolar disorder (BD) and 48 with major depressive disorder (MDD).

Results: Trained artificial neural network with 95% accuracy diagnosis, aiming the classification of BD and MD from a control group.

Conclusion: ANN can be trained and used to improve diagnosis in Bipolar and depression disorders.

Keywords

Bipolar disorder; Major depressive disorder; Artificial Neural Network; Biomarkers;

1. Introduction

Artificial neural network (ANN) attempt to use multiple layers of calculations to mimetize the neuronal circuitry in the human brain interpreting and draws conclusions from several information. The algorithms from ANN are mathematical models based on biological neural systems that simulate neuron behavior. The neuron receives inputs from multiple neurons and outputs one value based upon the activation function (Mei et al., 2013). The ANN inputs are multiplied by different weights to generate a predictive response. These responses in ANN are widely used for several applications like as classification and pattern recognition (Hassoun, 2009). This tool is effective modeling non-linear relationships, that can be promissory candidates for differentiation for several biological processes (Amato et al., 2013). ANN are used in medical field to analysis of sleep disorders, for cytopathology and histopathology such as classification of breast cancer images and others, in prediction of heart disease, CD4+ T cell differentiation and immune cell subset classification, for combining clinical predictors of antidepressant response in mood disorder, and other classifications (Gant et al, 2001; Singh et al, 2018).

Bipolar disorder (BD) and major depressive disorder (MDD) are complex mental disorders with high genetic charge, and are the largest global contributors to years lived with functional disability (Doan et al., 2017). Bipolar disorder (BD) is a severe neuropsychiatric disorder characterized by recurrent episodes of mania/hypomania and depression in alternation with euthymic periods (Jakobsson et al., 2014; Mesman et al., 2014). Approximately 8% of the population is affected by BD (Moreno and Andrade, 2005), implying high social costs associated with personal suffering, functional impairment, premature mortality, and higher risk for other psychiatric and medical disorders (Jakobsson et al., 2014). Depression is a common mental disorder that often starts at a young age, reduces people's functioning, it is often recurring, and can lead to suicide (WHO, 2012). The World Federation for Mental Health states that Depression is estimated to affect 350 million people and lifetime prevalence rates range from approximately 3 percent in Japan to 16.9 percent in the United States, with most countries falling somewhere between 8 and 12 percent. Moreover, unipolar depressive disorders will be the leading cause of the global burden of disease by 2030 (WHO, 2012). Population-based studies in Brazil found a general prevalence of depression of 17 and 20% (Andrade and Wang, 2014; Munhoz et. al., 2016), while the prevalence found in clinical samples ranges from 22% to 47% (Fleck et al., 2004).

In the last years, there has been an upsurge of interest within the neuroscience community in the use of artificial intelligence (AI) methods, including ANN (Aakerlund, 2000; Erguzel, et. al., 2015). Moreover, ANN analyses are gaining traction in psychiatric research, providing predictive models for both clinical practice and public health systems. Compared with traditional statistical methods that provide primarily average group-level results, machine-learning algorithms provide predictions and stratification of clinical outcomes at the level of an individual subject (Passos, I. C., 2016). Several evidences point out that psychiatric disorders have several changes in the molecular and functional mechanisms of the neuron, leading to observable changes in brain (Lotan et al., 2014). Studies suggest that stressful events are important in the early stages of the disease (Post and Kalivas, 2013), so the phenotypic manifestation of mood disorders is presumably the result of the interaction between the effects of environmental stress and neurochemical changes. Thus, this work aims to classify (diagnose) groups of patients with BP or MD from a control group, using artificial neural networks.

2. Methods

2.1 Participants

This is a case-control study nested in a population-based cross-section of people aged 18 to 24 (Jansen, K. et al., 2011). After an initial psychopathology screen, the whole population was assessed with the Brazilian version of the Mini-International Neuropsychiatric Interview-MINI for diagnostic of bipolar disorder and major depressive disorder (Amorim et al., 1998). In order to improve diagnosis reliability, in this subsample, the diagnosis was provided by psychologists using the Brazilian version of Structured Clinical Interview for DSM-IV (SCID) (Del-Ben et al., 1996). For the purposes of the current study, we recruited all the drug-free subjects with BD from the population-based study. Additionally, two groups of control subjects were recruited. Subjects without any history of mood disorder were randomly selected and matched for sex, age and years of education — i.e. a healthy control sample. We also recruited a second control group, those with major depression disorder. Using this strategy, we were able to obtain data from 144 subjects (48 population controls, 48 subjects with MDD and 48 subjects with BD). The original data bank was larger, with 231 individuals, but some samples were draw due to missing values and others randomly draw to match the groups. All subjects were informed about the study and agreed to participate by providing their free and informed consent, answered the questionnaires and the structured diagnostic interviews. The project was approved by the Ethics Committee of the Catholic University of Pelotas (UCPel), Brazil (Jansen, K. et al., 2012).

2.2 Input variables

Twenty seven (27) variables were used to train the ANN. They are sociodemographic, biochemical and diagnostic questionnaire answers variables. The ANN training data input variables were: sex, age, skin color, social class, IL-6, IL-10, TNF-α, BDNF, NSE (neuron-specific Enolase), thiobarbituric acid (oxidative stress measure), uric rate, glutathione, tobacco abuse, alcohol abuse, use of psychotropic drugs, previous clinical treatment, CTQ (Childhood Trauma Questionnaire) total, Hamilton Depression Rating Scale (HDRS) total, Young Mania Rating Scale (YMRS) total, propensity to fight, sleep problems, Brian scale total and the six items of Functional Assessment Staging Test (FAST) (autonomy, occupation functioning, Cognitive functioning, financial issues, interpersonal relationships and leisure time).

2.3 Analyses

2.3.1 Statistical Analyses

For the characteristics of the population, the numerical variables were expressed as mean and standard deviation (mean ± S.D.), and the categorical variables were added and the percentage was calculated.

The ANN training give as result a confusion matrix. The accuracy, sensitivity, specificity and F1 score (harmonic mean between precision and sensitivity) were obtained from confusion matrix calculation. Some related works also show classification functions to analyze the ANN training (Serretti et al. 2007; Metin et al, 2017). In this work we performed ten trainings for each number of neurons in hidden layer. They are show as mean and standard deviation (mean ± S.D.) and the best achieved result of these trainings is also presented.

All statistical analyses were performed in free LibreOffice spreadsheets and IBM-SPSS 22.

2.3.2 ANN Training

Supervised ANNs were applied in this work. Supervised ANNs means that the output is already know, in a training data bank. Supervised ANNs calculate an error function between the desired fixed output (target) and their own output, and adjust the connection strengths (weights) during the training process to minimize the result of the error function. The trained ANN can be seen as a equation which translate the ANNs inputs into outputs, and rules by which the weights are modified to minimize the error of the equation (Luca et al, 2005).

A general ANN can be identified in Fig 1, this topology has *p* inputs, one weight connected in each input, *k* neurons in parallel in a Hidden (or middle) layer, with a non linear activation function, and one neuron in output layer, with linear activation function, for one output variable. This model of ANN can approximate the output of any continuous function (Hassoun, 2009, pag. 35), and is used in this work to classify disorders diagnosis.

In this work were used 27 inputs, one neuron on the output for one variable (negative diagnosis /positive diagnosis) and three neurons in middle layer.

To perform ANN training analyses, the OpenNN software was used. It is an multi platform and open source software, for artificial neural networks (OpenNN). In this work, the weights were randomized at the start of each training, and trained until the performance increase was above 1e-6 with the quasi-newton method. Also, the data bank was divided for training and testing, being 80% for training and 20% of the bank for test.

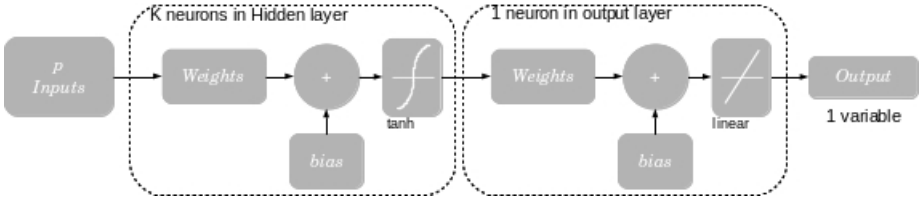

Fig. 1. Neural network representation with *p* inputs, *k* neurons in hidden (middle) layer and one output neuron for one output variable. Note that is possible to have *p ≠ k, provided that each input has its weights. In this work we used 35 inputs* (brain inflammatory markers and characteristics of the sampled population), *the output is binary as a classification of control group or BD and SZ disease.*

3. Results

The analysis was conducted with 144 data samples. Table 1 shows the characteristics of the sampled population, with 5 categorical variables (sex, skin color, Social Class, Tobacco and Alcohol abuse), and 1 continuous variables (age). It is possible to note how all variables are well distributed in cases and control groups.

In this work, is presented four indicators of the ANN training performance as a binary classification test: accuracy, F1 score, sensitivity and specificity. Accuracy is the how well a binary classification test correctly identifies or excludes a condition. F1 score is a measure of a test's accuracy, it is the harmonic average of Precision and Recall, and so this score takes both false positives and false negatives into account. Sensitivity measures the proportion of positives results that are correctly identified as such. Specificity identifies the proportion of negatives outcomes that are correctly identified.

ANN training results changing the comparisons groups can be analyzed in Table 2. This present the best result of ten different training and the mean and standard deviation of these trainings. The classification training results are accuracy, sensitivity, specificity and F1 score.

A classification with controls and MDD were performed, it exemplifies classifications intended to sort healthy people from depressive ones. Results of these training can be seen in Table 2. Results in Table 2 show the best achieved accuracy, sensitivity, specificity and F1 score, they were respectively 0.95, 0.91, 1.00 and 0.95 for three neurons in hidden layer, using F1 score as tiebreaker, as well as the mean and standard deviation for ten tests. So, one can get with three neurons, 95% of accuracy diagnosis with this trained ANN, in a test with all cases correctly identified.

For a differentiation of BD patients from healthy people, ANN training results for three neurons in the middle layer can be seen in Table 2. CTRL x BD in Table 2 best training result gives 0.95 of accuracy, 0.92 for sensitivity, 1.00 for specificity and 0.96 of F1 score. So, 95% of accuracy diagnosis can be achieved, recognizing all BD patients.

Bipolar Disorders can be differentiated from Major depressive individuals in Table 2, BD x MDD line. Table 2 best results for best results for accuracy, sensitivity, specificity and F1 score, were respectively 0.89, 0.93, 0.75, 0.93. So, one can differentiate with 89% of accuracy a BD from MDD patient.

4. Discussion

In this study was applied an ANN to discriminate two mental disorders and health subjects in clinical and inflammatory-based data. In our knowledgment, this is the first study that proposes an ANN model to improve the use of markers and clinical data in diagnoses of BD and MDD. Our analyses suggest that an ANN function can properly classify the cases and control groups of the disorders.

The ANN model with three neurons was able to identify correctly 95% of the cases. Moreover, the ANN model shows very specific and sensitive, in confusion matrix interpretation.

The clinical data and empirical evidences suggest a molecular, neurochemical, and structural brain abnormalities in BD (van Os and Kapur, 2009). In line with the clinical and pathophysiological heterogeneity evident in these disorders, the brain underpinnings are multidimensional, reflecting a myriad of complex pathological processes and environmental effects.

Although we could not find works classifying BD and MDD using clinical and inflammatory-based data with ANN, the work of (Metin et al, 2017) presents a 87% classification accuracy, but it uses different input variables (clinical magnetic resonance imaging scan and electroencephalography recording) and uses an ANN to classify as BD and FTD (Frontotemporal Dementia), thus (Metin et al, 2017) shows how difficult is to achieve high accuracy ratios for this disorders classifications. A work to improve the 21-item Hamilton Rating Scale for Depression (Hamilton, 1967) using ANN was done by Serreti (2007), but it do not clearly shows the ANN

accuracy classifications, presenting only the training goals and aiming the main results at others statistical analysis (Serreti et al, 2007). A work to predict the depression after mania in BD patients was done by (Pendleton et. al., 1998), but it do not use biomarkers, only age, sex, episodes information and medication treatment, and it differs from our paper, since our goal is to separate BD patients from healthy and MDD patients.

We were able to found one review work (Siekmeier, 2015) relating ANN and BD disorder (MDD not included), but the review work was in the idea of computational modeling of psychiatric illnesses, not the use of ANN as a classification tool to aid in diagnosis. We also found one meta-analysis (Lee et. al., 2018), relating machine learning techniques and depression outcomes, were the only cited paper using ANN and depression is the paper previously commented of Serreti (2007).

ANN has been used in others ways in BD patients, as in the work of Mariani, S., et. al. (2012), to compute the sleep profile of patients with BD and use the Heart Rate Variability signal that correlate to the clinical state in patients affected by bipolar disorder. The work of Fonseca et al, (2018) uses ANN for BD classification and differentiation from control group and the schizophrenia, also, the biochemical analysis was done from dead brain tissue and here we show results for blood serum biochemical markers collected from living people.

Specific biomarkers for mental disorders are still perspectives, but this work, through the use of ANN, does not address a specific marker, but rather the involvement together of all the variables used in the ANN entries. This technique interrelates as one of the variables with the objective of obtaining an interpretation from all the inputs with the diagnosis of the individual..

This work presents four indicators of the ANN training performance as a binary classification test, they were selected to provide different interpretation of the classification, showing that in some cases the best specificity not leads to the best accuracy.

This study has a limitation, the size of the database. Ideally, the larger the database size, the better ANN training (Hassoun, 2009). This limitation impacts in the confusion matrix size and statistics results, were only nineteen cases (20% of the data) left for the independent test bank and matrix confusion construction. This lead to each test case can means up to 5.26% in statistical results. But is important to highlight that this work is the first (for the best of our knowledgment) relating BD and MDD from a control group using ANN and biomarkers.

5. Conclusion

In the last years the use of ANNs has been growing as to a promise approach in basic and clinical studies. Here, our findings suggest that artificial neural network could be valid to detect the role of markers in the involvement of inflammatory mechanisms in the pathophysiology of bipolar disorder and major depression. Thus, the model that presented better performance could be eventually applied at clinical and research settings, in order to facilitate and assist in diagnosis.

As future work we intend to use different variables inputs to perform the ANN training to aid in disorders diagnosis.

Table 1: Characteristics of the sampled population for cases and control group

Variables	CONTROL	MDD	BD
	N(%)	N(%)	N(%)
Sex			
Male	12(25)	12(25)	12(25)
Female	36(75)	36(75)	36(75)
Skin Color *			
I - Light, pale white	35(73)	30(63)	34(71)
II - White, fair	6(13)	7(15)	8(17)
III - Medium, white to light brown	6(13)	11(23)	5(10)
IV - Olive, moderate brown	0(0)	0(0)	0(0)
V - Brown, dark brown	1(2)	0(0)	1(2)
VI - Very dark brown to black	0(0)	0(0)	0(0)
Social Class			
A	3(6)	1(2)	1(2)
B	16(33)	14()	12(25)
C	21(44)	22(46)	28(58)
D	7(15)	9(19)	5(10)

E		1(2)	2(4)	2(4)
Tobacco abuse		11(23)	19(40)	22(46)
Alcohol abuse		10(21)	24(50)	20(42)
		Mean ± S.D.	Mean ± S.D.	Mean ± S.D.
Age		22 ± 2.31	22 ± 2.14	22 ± 2.32
	Total	**48(100)**	**48(100)**	**48(100)**

* Fitzpatrick scale, auto declared
MDD: Major Depression Disorder; BD: Bipolar Disorder

Table 2: ANN classification training results for the classifications groups. Results shown for 10 different ANN training for three neurons in hidden layer. Accuracy, Sensitivity, Specificity, and F1 Score are presented as mean (X) and standard deviation (S.D.) and the best training result.

	Accuracy		Sensitivity		Specificity		F1 Score	
	Best result	X ± SD	Best result	X ± SD	Best result	X ± SD	Best result	X ± SD
CTRL x MDD	0.95	0.78 ± 0.08	0.91	0.73 ± 0.17	1.00	0.85 ± 0.05	0.95	0.76 ± 0.12
CTRL x BD	0.95	0.77 ± 0.07	0.92	0.74 ± 0.09	1.00	0.82 ± 0.11	0.96	0.75 ± 0.10
BD x MDD	0.89	0.53 ± 0.15	0.93	0.54 ± 0.25	0.75	0.51 ± 0.13	0.93	0.51 ± 0.20

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ANEXO A — MODELOS DE RESULTADO DE TREINAMENTO DAS RNAS

Abaixo são apresentadas as fórmulas que representam os modelos treinados pelas RNAs apresentadas no primeiro artigo.

Definição das variáveis utilizadas nas fórmulas:

a= BDNF

b= IFN-gamma

c= IgA

d= IgE

e= IgM

f= IL-10

g= IL-11

h= IL-12p40

i= IL-12p70

j= IL-13

k= IL-15

l= IL-16

m= IL-17

n= IL-17E

o= IL-18

p= IL-1alpha

q= IL-1beta

r= IL-1ra

s= IL-2

t= IL-23

u= IL-3

v= IL-5

x= IL-6

w= IL-6 Receptor

y= IL-7

z= IL-8

aa= NGFb

bb= RANTES

cc= TGF-alpha

dd= TNF RII

ee= TNF-alpha

ff= TNF-beta

gg= Age

Sex-number

kk= duration of illness

mm= SuicideStatus

BD x SZ melhor resultado com 3 neurônios na camada oculta:

$y_{11} = tanh(-26.9921 - 11.5519 * a + 42.7322 * b - 18.3889 * c + 90.3138 * d - 134.68 * e + 56.3438 * f - 107.735 * g + 87.9865 * h + 34.3724 * i - 101.152 * j + 66.7322 * k + 10.5135 * l - 38.9398 * m - 7.35241 * n + 59.6302 * o + 69.6616 * p + 52.7997 * q + 32.3923 * r - 51.6814 * s - 0.0607762 * t + 133.124 * u - 12.1253 * v - 19.4963 * x + 27.8949 * w - 134.773 * y - 69.4307 * z + 84.8686 * aa + 8.5326 * bb - 115.799 * cc - 58.2428 * dd + 37.4543 * ee + 52.1094 * ff - 22.0948 * gg + 47.4803 * hh - 76.0853 * kk - 17.5931 * mm);$

$y_{12} = tanh(-13.2923 - 36.8475 * a + 58.2135 * b - 14.8435 * c + 43.8834 * d - 42.8881 * e + 23.8549 * f - 89.8261 * g - 33.6554 * h - 16.029 * i + 48.6591 * j + 49.7178 * k - 38.1239 * l - 102.033 * m - 19.27 * n + 44.7704 * o - 33.2027 * p + 16.5615 * q - 42.0923 * r - 84.1143 * s + 3.54916 * t - 21.9063 * u + 67.231 * v + 3.87588 * x + 8.00375 * w + 53.7774 * y + 30.3049 * z - 31.9535 * aa + 18.0695 * bb - 19.6731 * cc + 29.1308 * dd - 47.5557 * ee + 64.9502 * ff - 16.2647 * gg - 81.3652 * hh + 23.8321 * kk + 6.69805 * mm);$

$y_{13} = tanh(48.739 + 54.2214 * a - 80.891 * b - 19.0876 * c + 22.7473 * d + 106.221 * e + 49.2966 * f - 27.4682 * g - 94.5916 * h - 18.0698 * i - 119.213 * j + 48.3611 * k + 32.3086 * l - 19.3831 * m - 25.5053 * n - 41.069 * o + 2.47722 * p + 0.326723 * q + 26.0158 * r + 81.4606 * s - 5.99244 * t + 7.58509 * u - 80.9647 * v - 20.0631 * x - 50.6451 * w - 52.5796 * y - 16.3226 * z - 15.7361 * aa - 35.8898 * bb + 52.4339 * cc + 37.4954 * dd + 45.3899 * ee + 21.2879 * ff - 62.0852 * gg + 12.7419 * hh - 93.5716 * kk - 71.9756 * mm);$

bdxSZ=(0.0845654-0.323222*$y_{11} + 0.133189 * y_{12} + 0.407787 * y_{13}$);

BD x CTRL melhor resultado com 5 neurônios na camada oculta:

$y_{11} = tanh(0.601711 + 2.95601 * a - 4.20399 * b + 4.55678 * c - 4.14815 * d + 17.0677 * e + 12.4619 * f - 0.788119 * g - 0.171052 * h + 5.84537 * i + 3.01358 * j - 17.5196 * k - 4.01518 * l + 0.595329 * m - 1.03891 * n - 1.48717 * o + 0.543458 * p + 5.37597 * q - 3.0755 * r - 6.17053 * s + 2.11584 * t - 0.886673 * u + 3.68455 * v + 0.680507 * x - 3.15738 * w +$

$2.6882 * y + 1.32862 * z - 1.82151 * aa + 0.874971 * bb + 1.74701 * cc + 1.06716 * dd - 0.585148 * ee + 9.78409 * ff + 9.65384 * gg + 3.80926 * hh)$;

$y_{12} = tanh(-0.389171 + 2.06233 * a + 4.79133 * b - 0.695448 * c + 2.28539 * d + 0.538443 * e - 2.64898 * f - 3.30366 * g + 4.41553 * h - 0.270496 * i - 7.90867 * j - 1.32661 * k + 0.443377 * l - 4.97284 * m - 8.48098 * n + 1.66242 * o + 3.06228 * p - 1.29034 * q - 2.35934 * r - 1.25362 * s + 0.00192076 * t + 1.44875 * u + 0.25248 * v - 2.82909 * x - 0.67102 * w - 6.5175 * y - 2.16132 * z + 3.91371 * aa - 6.01636 * bb - 2.92118 * cc - 1.56157 * dd - 2.70278 * ee - 0.900805 * ff + 3.32439 * gg + 0.647855 * hh)$;

$y_{13} = tanh(-0.223582 - 2.88463 * a - 17.1354 * b + 5.28444 * c - 3.75147 * d + 6.49981 * e + 6.69891 * f - 0.167878 * g - 3.81258 * h - 1.52445 * i - 11.2878 * j + 2.8706 * k - 4.01769 * l + 0.147154 * m + 17.6021 * n - 1.12307 * o - 6.15301 * p + 0.788037 * q + 3.19992 * r + 2.95348 * s - 0.948685 * t - 3.91321 * u - 8.47504 * v + 1.28457 * x + 3.8325 * w - 6.81035 * y + 0.444558 * z - 1.42124 * aa + 0.601535 * bb + 5.12052 * cc + 2.76091 * dd + 1.95814 * ee + 0.296755 * ff + 6.74806 * gg - 10.2293 * hh)$;

$y_{14} = tanh(-0.969169 + 2.94225 * a - 3.6999 * b + 4.18745 * c - 0.141768 * d + 3.53244 * e + 4.10388 * f + 2.81099 * g - 0.0787229 * h + 1.08865 * i - 5.57598 * j + 1.52585 * k - 1.25298 * l - 0.173232 * m - 2.03493 * n - 3.60535 * o - 5.26975 * p - 0.380447 * q + 0.874918 * r + 2.46228 * s - 3.24483 * t - 2.8082 * u + 2.34722 * v + 1.34901 * x + 1.80905 * w + 3.93747 * y + 0.958627 * z - 0.472141 * aa + 4.70681 * bb + 0.914276 * cc + 0.29379 * dd - 0.648462 * ee + 1.07244 * ff - 5.92244 * gg + 1.62879 * hh)$;

$y_{15} = tanh(-3.96246 + 2.34956 * a + 0.00387748 * b + 1.57885 * c + 1.89761 * d + 4.12962 * e - 1.53997 * f + 1.59936 * g + 0.310261 * h + 0.512897 * i - 1.43999 * j - 3.82324 * k - 5.37764 * l - 3.10255 * m - 1.94248 * n + 2.36903 * o - 3.10432 * p + 1.62801 * q + 0.186826 * r + 5.24738 * s + 5.25314 * t + 3.57323 * u - 8.50012 * v + 1.66127 * x + 3.27672 * w - 3.76123 * y + 1.49868 * z - 1.42652 * aa + 0.913802 * bb - 0.457412 * cc + 0.543548 * dd - 1.44724 * ee + 1.04171 * ff + 2.32465 * gg - 7.12327 * hh)$;

bdxCTRL=(-0.271507-4.03688*$y_{11} - 3.76557 * y_{12} + 0.44446 * y_{13} + 4.53691 * y_{14} - 4.98155 * y_{15})$;

SZ x CTRL melhor resultado com 7 neurônios na camada oculta:

$y_{11} = tanh(5.97473 + 14.0281 * a - 15.0305 * b + 61.2056 * c + 18.2735 * d - 44.7563 * e + 75.3938 * f + 2.22096 * g - 24.8436 * h + 49.7698 * i - 5.49981 * j + 29.7501 * k - 6.91853 * l + 0.780259 * m - 19.6927 * n + 3.51948 * o + 15.5725 * p + 65.5402 * q + 31.7367 * r + 15.9173 * s - 4.8633 * t + 1.06415 * u + 25.8261 * v - 2.29559 * x - 22.1544 * w + 7.08213 *$

$y + 19.7967 * z + 10.7407 * aa + 150.964 * bb - 28.2685 * cc + 9.11538 * dd + 3.43346 * ee + 15.3771 * ff - 59.9996 * gg + 2.86881 * hh)$;

$\mathrm{y}_{12} = tanh(-7.40655 + 372.045 * a + 239.306 * b + 200.574 * c - 94.1038 * d - 9.20087 * e - 75.3484 * f - 0.0166116 * g + 8.04279 * h + 107.084 * i + 246.47 * j + 39.2091 * k - 87.8264 * l - 325.334 * m - 397.706 * n - 12.5674 * o - 50.7297 * p + 98.8486 * q - 107.379 * r - 19.9565 * s + 35.8178 * t + 23.4634 * u - 168.936 * v + 10.902 * x - 187.981 * w + 115.157 * y + 21.4246 * z + 105.55 * aa + 10.6418 * bb + 221.638 * cc + 82.2515 * dd + 49.0326 * ee + 246.274 * ff + 129.031 * gg - 242.115 * hh)$;

$\mathrm{y}_{13} = tanh(-14.3973 + 29.9069 * a + 15.1646 * b + 13.881 * c + 12.5191 * d + 17.562 * e + 11.8753 * f + 29.5687 * g + 10.7112 * h + 22.5239 * i + 30.7344 * j + 9.96891 * k - 4.1492 * l + 3.13411 * m + 24.2072 * n + 9.23327 * o + 15.9343 * p + 16.4928 * q + 16.5389 * r + 2.56941 * s + 17.6892 * t - 2.60986 * u + 6.68602 * v + 15.4819 * x - 10.8261 * w + 14.1056 * y + 14.0052 * z - 5.62176 * aa + 12.9302 * bb - 0.262352 * cc + 7.64223 * dd + 13.9087 * ee + 8.75885 * ff - 10.7504 * gg + 27.2247 * hh)$;

$\mathrm{y}_{14} = tanh(0.628095 + 396.255 * a - 119.717 * b + 137.593 * c - 157.331 * d + 69.0356 * e - 140.212 * f + 1.66977 * g - 146.528 * h + 274.47 * i + 294.518 * j - 14.7454 * k + 66.2401 * l - 19.8858 * m - 78.5238 * n - 1.58551 * o - 200.883 * p - 15.1633 * q + 132.645 * r + 80.0191 * s - 128.486 * t - 163.056 * u - 128.342 * v + 0.601441 * x - 113.525 * w - 59.5902 * y + 0.893094 * z + 75.9665 * aa - 64.4648 * bb - 187.476 * cc - 43.5016 * dd - 31.1347 * ee - 22.1935 * ff - 52.5576 * gg - 58.3301 * hh)$;

$\mathrm{y}_{15} = tanh(-12.242 + 1.21727 * a + 6.97988 * b + 9.54841 * c + 0.758721 * d - 2.61613 * e - 6.16335 * f - 30.271 * g - 14.2623 * h + 1.57018 * i + 7.64073 * j + 0.634762 * k - 2.02006 * l - 5.05277 * m + 4.78243 * n - 5.06 * o + 9.37939 * p - 17.7253 * q - 3.93843 * r + 11.6977 * s - 1.1336 * t + 4.19742 * u - 2.58193 * v + 10.301 * x + 12.0729 * w + 4.50275 * y + 4.00024 * z + 7.84728 * aa + 15.7142 * bb + 5.51698 * cc + 0.655325 * dd + 11.2381 * ee - 23.1375 * ff + 3.23524 * gg + 7.70489 * hh)$;

$\mathrm{y}_{16} = tanh(21.9644 + 37.3054 * a - 105.806 * b + 207.939 * c + 52.0451 * d - 39.4515 * e - 26.9571 * f - 4.12156 * g + 61.7871 * h + 120.595 * i + 25.5781 * j + 23.1076 * k - 59.3922 * l + 33.1234 * m + 6.53732 * n + 13.6167 * o - 172.217 * p - 32.1743 * q + 78.778 * r - 13.1283 * s - 13.5412 * t - 27.5819 * u + 48.4565 * v - 23.064 * x + 120.143 * w - 23.9925 * y - 16.744 * z + 107.903 * aa + 86.7801 * bb - 28.9473 * cc - 36.701 * dd - 8.4383 * ee - 34.3447 * ff - 21.3121 * gg + 224.377 * hh)$;

$\mathrm{y}_{17} = tanh(-33.9141 + 14.286 * a + 28.4019 * b - 15.2668 * c + 11.3824 * d + 37.5401 * e + 17.6568 * f + 24.8563 * g - 0.794573 * h - 19.6004 * i + 16.981 * j + 20.1068 * k + 18.8781 *$

$l - 15.3997 * m - 0.261984 * n + 24.948 * o - 0.152185 * p + 33.6943 * q + 26.6611 * r - 10.0917 * s + 24.7044 * t + 18.6878 * u - 3.90851 * v + 32.5195 * x + 1.99669 * w - 0.920824 * y + 33.3315 * z - 7.2577 * aa + 33.1603 * bb + 1.64159 * cc + 7.04887 * dd + 32.449 * ee + 20.3462 * ff + 13.641 * gg + 27.6396 * hh)$;

szxCTRL=$(28.0773+22.8754 * y_{11} - 0.499999 * y_{12} - 31.9783 * y_{13} + 0.499999 * y_{14} - 23.3754 * y_{15} + 0.499999 * y_{16} + 60.0556 * y_{17})$;

BD e SZ agrupados x CTRL melhor resultado com 3 neurônios na camada oculta:

$y_{11} = tanh(7.6083 - 3.69313 * a - 7.26659 * b + 3.1841 * c - 1.61428 * d - 4.74619 * e + 0.58701 * f - 7.41916 * g + 5.54706 * h + 5.66824 * i + 4.70704 * j + 3.65931 * k - 1.49906 * l - 4.96013 * m - 4.11823 * n + 3.35471 * o - 0.756756 * p - 2.92916 * q - 5.10558 * r + 3.60379 * s - 6.95965 * t + 3.22585 * u + 5.63452 * v - 6.22828 * x + 3.31748 * w + 1.32004 * y - 7.16618 * z + 3.52686 * aa - 7.69514 * bb - 1.2336 * cc - 3.09199 * dd - 6.84623 * ee + 4.04764 * ff + 2.28537 * gg - 5.74741 * hh)$;

$y_{12} = tanh(54.5819 - 235.669 * a + 582.07 * b - 101.138 * c + 121.609 * d - 240.001 * e + 109.218 * f + 34.3213 * g + 82.34 * h + 0.685508 * i + 183.156 * j - 22.431 * k - 128.98 * l - 34.1366 * m - 720.34 * n + 68.1971 * o + 305.637 * p + 53.0324 * q - 114.733 * r - 41.923 * s - 19.9776 * t - 0.512944 * u + 12.0747 * v - 53.5871 * x - 54.2798 * w - 148.171 * y - 42.6387 * z - 8.89494 * aa + 57.5235 * bb + 164.992 * cc - 32.022 * dd - 18.6992 * ee - 32.5085 * ff + 47.0397 * gg - 146.965 * hh)$;

$y_{13} = tanh(-15.8548 - 37.8282 * a - 114.427 * b + 157.88 * c + 18.129 * d + 20.5454 * e + 9.43948 * f + 41.5264 * g - 41.5181 * h - 101.424 * i - 101.641 * j - 74.6204 * k - 56.1189 * l + 221.276 * m + 78.2086 * n + 46.6026 * o + 33.9276 * p - 30.6727 * q + 0.75831 * r + 9.04905 * s - 33.021 * t - 90.0291 * u + 113.727 * v + 14.4918 * x + 19.2119 * w + 32.278 * y + 13.258 * z - 19.4418 * aa - 16.4661 * bb - 75.1486 * cc - 41.2918 * dd + 12.1595 * ee - 126.114 * ff + 24.1109 * gg - 107.109 * hh)$;

Group=$(1.17994-0.688769 * y_{11} + 0.350288 * y_{12} - 0.121184 * y_{13})$;