Universidad de Oviedo

Programa de Doctorado: Ciencias de la Salud

Determinación del flujo cerebral por medio de ultrasonido transcraneal en pacientes con esquizofrenia y controles sanos

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RESUMEN DEL CONTENIDO DE TESIS DOCTORAL

1.- Título de la Tesis	
Español: Determinación del flujo cerebral por medio de ultrasonido transcraneal en pacientes con esquizofrenia y controles sanos.	Inglés: Use of transcranial ultrasound to determine cerebral blood flow in patients with schizophrenia and healthy controls.

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RESUMEN (en español)

La esquizofrenia tiene peculiaridades neuroanatómicas y neurofisiológicas, las cuales están aparentemente relacionadas con la sintomatología, en especial con los déficits cognitivos. Este ultimo a su vez determina en el nivel de discapacidad y la calidad de vida de las personas afectadas. El flujo cerebral es un factor convergente entre el desempeño cognitivo, la actividad neuronal. El cual, a pesar de sus implicaciones clínicas y terapéuticas, ha sido poco estudiado. El ultrasonido transcraneal por su alta resolución temporal puede ser consideramdo un método de imagen idóneo para investigar los patrones de flujo sanguíneo cerebral. El presente estudio tiene como finalidad determinar por medio de ultrasonido transcraneal si en pacientes con esquizofrenia existe una relación entre los síntomas y déficits cognitivos, con diferentes patrones hemodinámicos en las arterias cerebrales medias.

Este trabajo de Tesis Doctoral se ha realizado mediante la ejecución de dos estudios complementarios. El primer estudio tiene un enfoque neurofisiológico, el segundo un enfoque psicométrico. Se diseñó un estudio neurofisiológico para determinar las características hemodinámicas de las arterias cerebrales medias durante una tarea neuropsicológica empleando ultrasonido transcraneal en pacientes con esquizofrenia y en controles sanos. El estudio psicométrico se diseño para determinar el desempeño de la escala psicopatológica “Escala Breve de Evaluación Psiquiátrica, BPRS” y la escala de funcionalidad- discapacidad “Mini-ICF-APP” en pacientes que requieren hospitalización por un trastorno mental, independientemente de la categoría diagnostica. Al emplear ambos estudios los métodos de evaluación psicométrica, se facilita la transferencia de los resultados del estudio neurofisiológico a la practica diaria de psiquiatría clínica.

Empleando ultrasonido transcraneal se pudo evaluar las características hemodinámicas de las arterias cerebrales medias durante una tare cognitiva en pacientes con esquizofrenia y controles sanos. Los pacientes con esquizofrenia tardaron más que los controles sanos en completar la tarea neuropsicológica, demostrando un desempeño cognitivo inferior; exponiendo adicionalmente un patrón de flujo cerebral distintivo entre pacientes con esquizofrenia y controles sanos. Los pacientes con esquizofrenia, una carga sintomática mayor se relaciona con una prolongación en el tiempo para completar la tarea neuropsicológica, a la vez que un patrón hemodinámico más distintivo.

En el análisis psicometrico se pudo demostrar que la sintomatología medida por medio de la Escala Breve de Evaluación Psiquiátrica, BPRS, y la discapacidad funcional y participación medida por la Mini-ICF-APP se solapan en un alto grado, pudiendo considerarse que miden la gravedad de un trastorno psiquiátrico desde dos ángulos distintos. Las consideramos aptas para evaluar la carga sintomática y el nivel de funcionalidad-discapacidad en pacientes con un trastorno mental, indistintamente del diagnostico. Por estos motivos consideramos que ambas escalas se complementan en la práctica clínica, siendo la una determinante para realizar el diagnóstico y orientar el tratamiento adecuado, mientras que la otra para establecer la mejoría funcional y, por ende, el efecto del tratamiento más allá de la reducción sintomática.

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RESUMEN (en Inglés)

Schizophrenia has neuroanatomic and neurophysiological peculiarities, which are related to symptoms, especially cognitive deficits. Cognitive performance largely determines the level of disability and the quality of life of those affected. Cognitive performance, neural activity, and blood flow are closely linked. However, there are few studies of cerebral flow, despite is convergent role in cognitive performance and the clinical and therapeutic implications. We consider transcranial ultrasound to be an ideal method to investigate cerebral blood flow patterns. The present study aims to determine in patients with schizophrenia a relationship between the disease, its symptoms and cognitive deficits, and different hemodynamic patterns in the middle cerebral arteries measured by transcranial ultrasound.

This Doctoral Thesis work has been carried out through the execution of two complementary studies. The first study has a neurophysiological approach, the second a psychometric approach. We designed the neurophysiological study to determine with transcranial ultrasound the hemodynamic characteristics of the middle cerebral arteries during a neuropsychological task; in patients with schizophrenia and healthy controls. We designed the psychometric study to determine the performance of the psychopathological scale "Brief Psychiatric Assessment Scale, BPRS" and the functionality-disability scale "Mini-ICF-APP" in patients requiring hospitalization for a mental disorder, regardless of the diagnoses. By using both studies the psychometric evaluation methods, we facilitate the transfer of the results of the neurophysiological study to the psychiatric practice.

Using transcranial ultrasound, we evaluated the hemodynamic characteristics of the middle cerebral arteries during a cognitive task in patients with schizophrenia and healthy controls. Patients with schizophrenia took longer than healthy controls to complete the neuropsychological task, demonstrating lower cognitive performance. In parallel, transcranial ultrasound measurement of blood flow in the middle cerebral arteries revealed a distinctive flow pattern between patients with schizophrenia and healthy controls. Furthermore, in patients with schizophrenia, a higher symptom burden is related to a longer time to complete the task and a more distinctive hemodynamic pattern.

In the psychometric analysis, it was possible to demonstrate that the symptoms measured by the Brief Psychiatric Assessment Scale (BPRS) and the functional disability measured by the Mini-ICF-APP overlap to a high degree. We considered that both measure severity of a psychiatric disorder from two different angles. We consider them suitable for evaluating the symptomatic burden and the level of functionality-disability in patients with a mental disorder. Thus, they can be used in patients with different diagnoses and to document the evolution of clinical pictures. For these reasons, we consider that both scales complement each other in clinical practice, the one being decisive for making the diagnosis and guiding the appropriate treatment, while the other is determining for establishing functional improvement and, therefore, the effect of treatment beyond symptomatic reduction.

SR. PRESIDENTE DE LA COMISIÓN ACADÉMICA DEL PROGRAMA DE DOCTORADO EN CIENCIAS DE LA SALUD

a mis padres, mis suegros…

a Yolanda y Nicolás.

Índice de Contenidos

1. Introducción

Los trastornos psicóticos en general y la esquizofrenia en particular son trastornos mentales graves. Tienen como rasgo común los síntomas psicóticos, los cuales implican el impedimento del individuo de verificar la realidad, es decir una disrupción de la capacidad de distinguir entre la experiencia interior y la realidad externa del entorno (1). La esquizofrenia, presenta en adición a los síntomas psicóticos, una combinación heterogénea de síntomas, involucrando el estado de ánimo, la volición y la cognición (2-4). La esquizofrenia afecta aproximadamente al uno por ciento de la población. Las personas afectadas presentan un primer episodio psicótico durante la adolescencia tardía o en la edad adulta temprana; síntomas tempranos, incluyendo un distanciamiento social, experiencias psicóticas y un declive cognitivo son comunes (4, 5).

La esquizofrenia está asociada con una marcada discapacidad funcional y laboral, una baja calidad de vida y una muerte anticipada (4-6). Aproximadamente el cinco por ciento de las personas con esquizofrenia mueren por suicidio (7). Aparte del suicidio, los pacientes con esquizofrenia tienen una tasa de morbilidad y mortalidad elevada, con una expectativa de vida reducida de 15 a 28 años (8, 9). Adicionalmente, tienen una tasa de comorbilidad psiquiátrica elevada, en especial con el consumo y abuso de alcohol y sustancias (2, 3).

El origen de la esquizofrenia no es conocido con certeza, existe una amplia evidencia que apunta a un origen multifactorial. En base a la evidencia de estudios en gemelos, se estima que la esquizofrenia puede tener un componente heredable de hasta el 80%, con un bagaje genético complejo (10, 11). Además del riesgo y la vulnerabilidad genética, factores ambientales juegan un papel relevante en el desarrollo del

trastorno. La interacción entre los factores genéticos y ambientales, en periodos claves del neurodesarrollo, puede alterar la estructura neuronal, con la consiguiente alteración de su funcionalidad (12, 13). Esto puede representar la base patofisiológica de los trastornos psicóticos en general, y la esquizofrenia en particular (6).

1.1. Diagnóstico de la Esquizofrenia

El diagnóstico de la esquizofrenia es realizado de manera clínica, sin existir una prueba o examen de laboratorio o imagen confirmatorios (4). Antes del primer episodio psicótico, existe un pródromo de meses o inclusive años de duración que se caracteriza por cambios sutiles en el comportamiento y un deterioro funcional (4, 14). El diagnóstico de la esquizofrenia se realiza por medio de la exploración psicopatológica. El diagnóstico formal de la esquizofrenia requiere que los pacientes cumplan con ciertos criterios diagnósticos, los cuales incluyen las características de los síntomas, su duración y su nivel de discapacidad funcional; a la vez que se descarten condiciones capaces de imitar el trastorno (3, 4). En la actualidad los criterios están definidos ya sea en la quinta edición Manual de Diagnóstico y Estadístico de la Asociación Americana de Psiquiatría (15) o en la décima edición de la Clasificación Internacional de Enfermedades de la Organización Mundial de la Salud (16). Ambas clasificaciones presentan un gran solapamiento de los criterios diagnósticos, siendo actualmente la mayor diferencia la eliminación de los subtipos de esquizofrenia en la quinta edición del Manual de Diagnóstico y Estadístico de la Asociación Americana de Psiquiatría (17).

1.1.1. Síntomas de la Esquizofrenia

La esquizofrenia tiene una presentación sintomática heterogénea, con una combinación de síntomas que afecta el pensamiento, la percepción y experiencia de la realidad, y el comportamiento (2-4, 18). Adicionalmente, los síntomas pueden variar, tanto en presencia como en intensidad, en el curso de la enfermedad; motivo por el cual son agrupados en diferentes dimensiones (19, 20). De esta manera, la sintomatología de la esquizofrenia es clasificada en síntomas negativos, síntomas positivos y déficit cognitivo (21, 22).

Los síntomas positivos de la esquizofrenia pueden ser definidos sucintamente, como experiencias, o vivencias anómalas de la realidad (21). Estas comprenden la experiencia alucinatoria, las ideas delirantes y los trastornos del pensamiento. Las alucinaciones, comprenden la percepción sensorial, sin existir un estímulo externo. Las alucinaciones pueden involucrar cualquier sentido, como el tacto, el gusto, el olfato o la visión; sin embargo, las alucinaciones auditivas (generalmente en la forma de oír voces) son las más frecuentes. Las ideas delirantes implican una noción falsa o errónea de la realidad, la cual no es compartida por otros y no es corregible a pesar de evidencia clara, objetiva y razonable de lo contrario. Los trastornos del pensamiento se manifiestan con una desorganización del habla, con un discurso errático, con cambios de tema, sin un hilo u objetivo reconocible (23). Los síntomas positivos tienden a recaer y remitir en el transcurso de la enfermedad (21).

Los síntomas negativos implican la ausencia en la capacidad de experimentar, sentir, pensar y actuar. Estos incluyen el afecto plano, empobrecimiento del habla y del

pensamiento, anhedonia, distanciamiento social, falta de motivación e intereses. El afecto plano, comprende la falta de expresión emocional. Generalmente conlleva la ausencia de mímica y contacto visual. La pobreza del habla y del pensamiento se hace evidente en el diálogo, con la imposibilidad de expresar ideas o pensamientos. La abulia, se caracteriza por una falta de motivación e interés, que conlleva a pasividad, con una falta de propósito y de objetivos. La falta de sociabilidad conlleva al auto- aislamiento, en el que el contacto cercano o íntimo es evitado activamente (23). En contraste con los síntomas positivos, los síntomas negativos son crónicos y se relacionan con los efectos a largo plazo en el funcionamiento psicosocial de las personas afectadas (21).

1.1.1.1. Evaluación de los Síntomas de la Esquizofrenia

La evaluación psicopatológica estandarizada de la esquizofrenia se puede realizar empleando una serie de instrumentos psicométricos precisamente diseñados y evaluados para este cometido (24). Uno de los primeros instrumentos constituye la Escala Breve de Evaluación Psiquiátrica (BPRS) (25). La BPRS fue diseñada para evaluar la gravedad de los síntomas en varios trastornos psiquiátricos graves, como son la esquizofrenia, el trastorno bipolar y la depresión con síntomas psicóticos (24, 25), siendo en la actualidad una de las escalas de referencia para evaluar la sintomatología y gravedad en personas con esquizofrenia (26, 27). Otros de los primeros instrumentos desarrollados fueron la Escala de Evaluación de Síntomas Positivos (SAPS) (28) y la Escale de Evaluación de Síntomas Negativos (SANS) (29) en las que se incorporaron las diferentes dimensiones psicopatológicas de la esquizofrenia (19, 20). A partir de estas escalas varios instrumentos psicométricos

han sido progresivamente desarrollados, destacando la Escala para el Síndrome Positivo y Negativo de la Esquizofrenia (PANSS) (30) que incorpora aspectos importantes de las tres escalas (24).

La BPRS es una escala de uso simple, por el hecho de no ser especifica para un síndrome en concreto es mucho más versátil, capaz de ser empleada para evaluar la psicopatología en otros trastornos mentales graves (24). Ha sido utilizada reiteradamente en estudios clínicos en los que se reclutan a pacientes con distintos trastornos psiquiátrica (31-33). Adicionalmente los valores de la BPRS (obtenidos en pacientes con esquizofrenia) pueden ser convertidos a sus valores equivalentes en la PANSS, permitiendo una comparación directa de los ensayos clínicos que emplean ambas escalas (34, 35).

1.1.2. Déficit Cognitivo en la Esquizofrenia

Sin ser parte formal de los criterios diagnósticos, el déficit cognitivo es un rasgo particular en pacientes afectados por esquizofrenia (18), pudiendo estar presente antes del primer episodio psicótico y permaneciendo constante en el transcurso de la enfermedad (36, 37). El déficit cognitivo abarca un impedimento, en mayor o menor medida, en las siguientes áreas: atención, velocidad de procesamiento, memoria de trabajo o declarativa, pensamiento abstracto, resolución de problemas, así como la comprensión de relaciones e interacciones sociales (4, 21). El déficit cognitivo es uno de los determinantes del bienestar y la calidad de vida de las personas afectadas (38, 39).

1.1.2.1. Evaluación de los Déficits Cognitivos en la Esquizofrenia

En pacientes con esquizofrenia, los déficits de la cognición y de las funciones ejecutivas pueden ser evaluados con un sin fin de instrumentos de diagnóstico y evaluación neuropsicológica (40, 41). El estándar para evaluar las funciones cognitivas en personas con esquizofrenia es la Batería Cognitiva de Consenso Matrics (MCCB) (42). En esta batería cognitiva se evalúan de manera rápida y concisa los dominios cognitivos, relevantes en personas con trastornos psicóticos, en particular la esquizofrenia. La batería cognitiva incluye diez pruebas neuropsicológicas diferentes, que evalúan siete dominios cognitivos. Las pruebas psicológicas han sido profundamente evaluadas y validadas. La administración de la batería cognitiva sigue un orden predeterminado, para facilitar la interpretación y comparación de los resultados obtenidos, existen valores estandarizados para la población adulta (43, 44). Por medio de esta batería se estudian y comparan los diferentes aspectos de la cognición y funciones ejecutivas afectadas con frecuencia en personas con esquizofrenia (42, 43, 45).

1.1.3. Pronóstico, Déficit Funcional-Discapacidad en la Esquizofrenia

Para determinar el pronóstico de la esquizofrenia, generalmente se han considerado la presencia de los criterios diagnósticos en relación con el efecto del tratamiento, la

necesidad de tratamiento (hospitalario) y variables sociales (46). En general las personas que padecen una esquizofrenia, afrontan discapacidades en la mayoría de los ámbitos (47). La trayectoria de la esquizofrenia, sin embargo es heterogénea con una diferente evolución de la enfermedad (48). En la mayoría de los casos (aproximadamente tres cuartos), se intercalan periodos de remisión con recidivas, con tan solo una minoría de los pacientes alcanzando la recuperación (49, 50). Las tasas de recuperación y remisión de la esquizofrenia publicadas desde las primeras descripciones del trastorno son estables en el trascurso de los años, con tan solo una mejoría relacionada con avances en el tratamiento (introducción de los medicamentos antipsicóticos) y cambios en los criterios diagnósticos permaneciendo nuevamente estables desde entonces (50, 51).

La interacción entre estados psicopatológicos y funcionalidad psicosocial, marca el curso de la enfermedad y la recuperación en las personas con esquizofrenia (52). La funcionalidad psicosocial en pacientes con esquizofrenia está relacionada más con la presencia y expresión de los déficits cognitivos y volitivos de la enfermedad, que con la sintomatología de esta (52-54). Para determinar la necesidad de tratamiento, así como la efectividad de este, la evaluación de la funcionalidad psicosocial en un contexto individual es fundamental (55, 56). De hecho, la recuperación de la funcionalidad parece ser posible, aun en presencia de síntomas psicopatológicos de la enfermedad (57).

1.2. Neuroanatomía y Neurofisiología de la Esquizofrenia

Los pacientes con esquizofrenia presentan varias peculiaridades neuroanatómicas. El hallazgo más frecuentemente reportado es un alargamiento del sistema ventricular, particularmente de los ventrículos laterales y del tercer ventrículo (58). El alargamiento ventricular, aparentemente ocurre a expensas del volumen cerebral y de la sustancia gris (59). Los lóbulos frontales, la amígdala, el hipocampo, el tálamo, el lóbulo medial temporal, el cíngulo y el giro temporal superior muestran un menor volumen en pacientes con esquizofrenia (58, 60-62). Tanto el alargamiento ventricular, como la disminución de volumen no pueden ser atribuidos solamente a la cronicidad o al efecto de los medicamentos, puesto que estos cambios pueden ser observados en pacientes recién diagnosticados (63), así como en familiares en riesgo de padecer la enfermedad (64).

En personas con esquizofrenia se ha podido determinar anormalidades en el flujo cerebral en las regiones frontales, tálamo y cerebelo durante tareas que involucran las funciones ejecutivas, memoria y atención sostenida (65, 66). Asimismo, se ha observado también una disminución del flujo sanguíneo en el lóbulo dorsolateral prefrontal, un fenómeno conocido como hipofrontalidad (67, 68), que conlleva a un entorpecimiento de circuitos neuronales, y no a la disfunción aislada de áreas concretas del cerebro (13, 69).

En la fisiopatología de la psicosis en general y la esquizofrenia en particular están involucradas varias redes neuronales, con varios sistemas de neurotransmisores implicados (70, 71). Durante muchos años se consideró al sistema de la dopamina esencial en la psicopatología de las psicosis en general y de la esquizofrenia en particular: Esto fue debido a que la liberación excesiva de dopamina produce síntomas parecidos a la psicosis, y los antipsicóticos bloquean los receptores de dopamina, principalmente en el sistema dopaminérgico en el estriado ventral, el área ventral tegmental y en la vía mesolímbica (70, 72). Sin embargo, en la psicosis y por ende en la esquizofrenia, están implicados múltiples neurotransmisores en múltiples circuitos neuronales los cuales interactúan entre si (70, 71).

A parte de la dopamina, en la fisiopatología de las psicosis se ha involucrado a los sistemas del glutamato y de la serotonina (70, 71). En estados psicóticos se ha podido observar una hipofunción del glutamato, específicamente del receptor N-metil-D-aspartato (NMDA) en el córtex prefrontal, sistema límbico y el tálamo. La desregulación del sistema del glutamato afecta a otros sistemas neuronales especialmente la dopamina, a la vez que involucra a sistemas de regulación como el gabérgico (70, 71). Medicamentos antagonistas del glutamato pueden producir alucinaciones, ideas delirantes paranoides y estados disociativos (73).

Una hiperfunción del sistema de la serotonina/5-hidroxitriptamina es capaz de producir por si síntomas psicóticos como en el caso de substancias alucinógenas (73-75) o el de la enfermedad de Parkinson (76). El sistema de la serotonina parece regular parcialmente al sistema del glutamato. La interacción y el balance entre los

sistemas de la dopamina, glutamato y serotonina juegan un papel importante en la fisiopatología de los trastornos psicóticos (71, 76-78).

1.3. Métodos de Neuroimagen en la Esquizofrenia

Las técnicas de neuroimagen estructural y funcional han permitido avanzar en la comprensión de la esquizofrenia (79). Estudios de neuroimagen han sido capaces de identificar regiones y circuitos cerebrales involucrados en los diferentes síntomas y déficits presentes la esquizofrenia (80). Los estudios de imagen estructural, como la tomografía axial computarizada y la imagen por resonancia magnética, han contribuido a comprender mejor la anatomía cerebral en personas con esquizofrenia (80). Las técnicas de neuroimagen funcional, como la imagen por resonancia magnética funcional, la espectroscopia por resonancia magnética, la tomografía por emisión de positrones, permiten una evaluación de la funcionalidad cerebral, y su correlación con las anomalías anatómicas y genéticas (80).

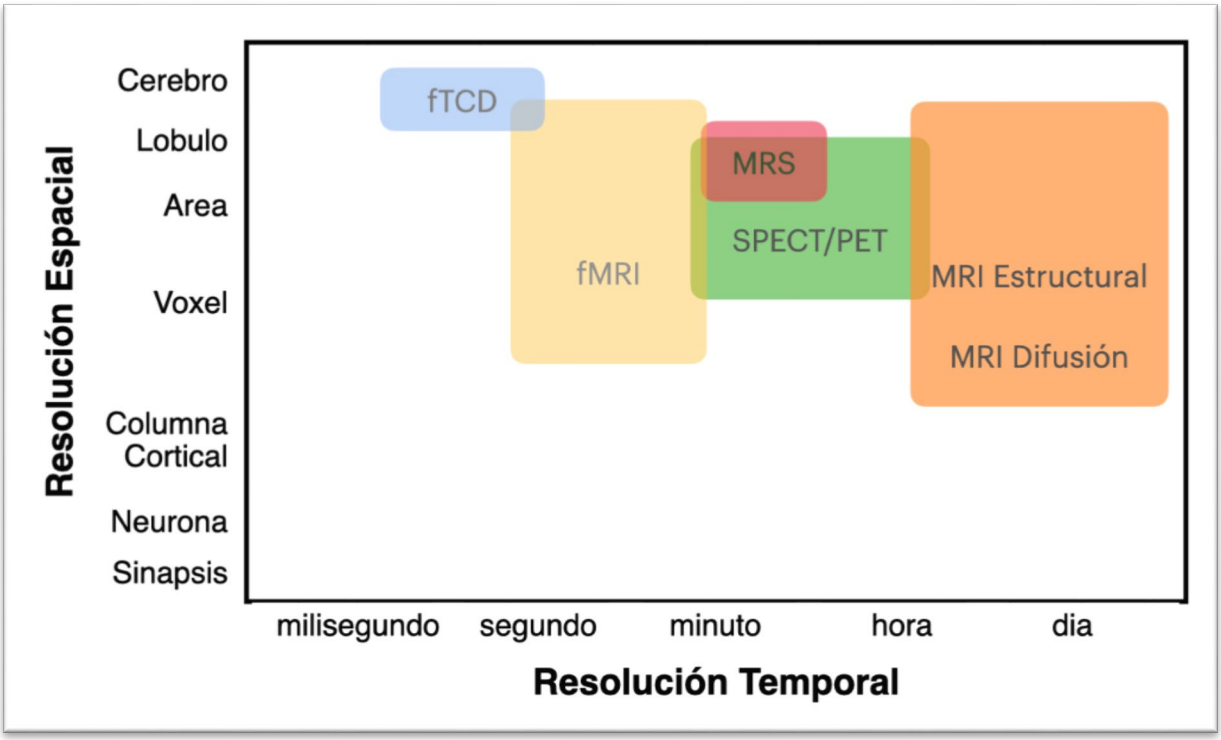

Figura 1: Relación entra la resolución temporal y la resolución espacial para diferentes exámenes de neuroimagen. fTCD Ultrasonido Transcraneal funcional; fMRI Imagen por Resonancia Magnética funcional; MRS Espectroscopia por Resonancia Magnética; SPECT/PET Tomografía por Emisión de Positrones; MRI Imagen por Resonancia Magnética. Modificado de Kraguljac NV et al (79).

Por medio de las técnicas de neuroimagen se ha podido determinar un menor volumen de sustancia gris en diversas regiones neuroanatómicas, en los lóbulos prefrontal y temporal principalmente, pero también en los lóbulos occipitales y parietales (81). Los análisis funcionales, han permitido visualizar las interacciones entre diferentes regiones cerebrales, a la vez que el nivel actividad de estas durante tareas cognitivas. Las relaciones entre la estructura y la función son consideradas un potencial biomarcador de imagen (82). Las técnicas empleadas en neuroimagen, sin embargo, tienen en el mejor de los casos una resolución temporal de varios segundos,

por lo cual no pueden captar procesos neuronales que ocurren en centésimas de segundo (79).

1.3.1. Ultrasonido Transcraneal en la Esquizofrenia

El ultrasonido transcraneal es un método de neuroimagen no invasivo, con una alta resolución temporal. El ultrasonido transcraneal utiliza el efecto doppler para visualizar las arterias cerebrales a través de la ventana acústica del hueso temporal (83, 84). Es una técnica robusta para determinar el flujo sanguíneo cerebral, que en comparación con otros métodos y técnicas tiene un bajo coste, a la vez que es de fácil uso y acceso (85, 86).

En el trascurso de las últimas décadas el ultrasonido transcraneal se ha instaurado como un método de neuroimagen válido y aceptado para determinar las características hemodinámicas de las arterias cerebrales (85, 87). Un inconveniente del ultrasonido transcraneal es su baja resolución espacial, sin proporcionar una imagen neuroanatómica (85, 86). A pesar de este inconveniente, el ultrasonido transcraneal se usa en la rutina clínica y de investigación para determinar las características hemodinámicas de varias enfermedades neurológicas y trastornos mentales, contribuyendo enormemente a la comprensión de estos trastornos (85, 88-90).

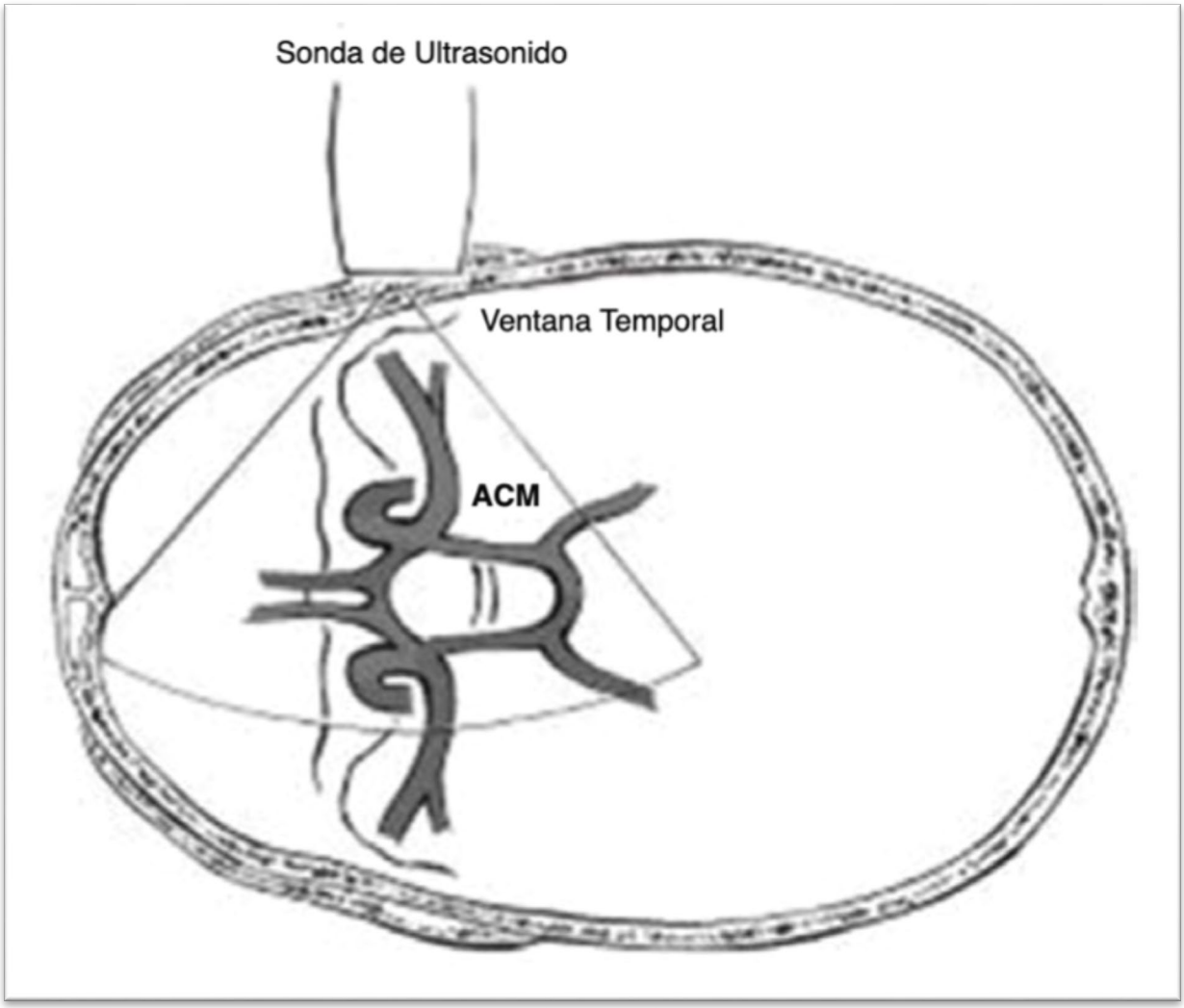

Figura 2. Esquema del empleo de ultrasonido. ACM Arteria Cerebral Media. Modificado de D'Andrea A et al (83).

1.4. Marco Teórico y Conceptual del Estudio

El desempeño cognitivo está parcialmente determinado por la habilidad del cerebro de incrementar inmediatamente el flujo sanguíneo a las áreas activadas durante una tarea cognitiva. Debido a las condiciones anatómicas del cráneo, el incremento en el diámetro de las arterias es limitado. Por lo cual incrementos en el flujo sanguíneo cerebral se consiguen mediante un incremento en la velocidad de flujo en las arterias

cerebrales. Por lo expuesto, podemos considerar a la velocidad de flujo sanguíneo en las arterias cerebrales un indicador de activad cerebral (85, 89, 90).

El déficit cognitivo en la esquizofrenia está relacionado con la alteración en el flujo sanguíneo a varias áreas del cerebro, inclusive el córtex dorsolateral prefrontal (91-94). Las arterias cerebrales medias irrigan los hemisferios laterales del cerebro, incluyendo el córtex dorsolateral prefrontal, estructuras subcorticales, los ganglios basales y el estriado (95). Una parte de estas estructuras, principalmente el córtex dorsolateral prefrontal, el estriado y el tálamo, se activan durante el Test del Trazado (TMT) (93). Por ello, el uso de ultrasonido transcraneal es un método valido para evaluar continuamente la actividad cerebral a través de los cambios hemodinámicos de la arteria cerebral media durante esta actividad cognitiva en pacientes con esquizofrenia (85, 89, 96, 97) .

1.4.1. Justificación del Estudio

La esquizofrenia tiene peculiaridades neuroanatómicas y neurofisiológicas, las cuales están aparentemente relacionadas con la sintomatología, en especial con los déficits cognitivos. El desempeño cognitivo, la actividad neuronal y el flujo sanguíneo están estrechamente vinculados. El desempeño cognitivo a su vez determina en gran medida el nivel de discapacidad y la calidad de vida de las personas afectadas. El flujo cerebral es un factor convergente que, a pesar de su importancia y las profundas implicaciones clínicas y terapéuticas que tiene, ha sido poco estudiado. El conocimiento actual se basa principalmente en métodos no idóneos para investigar el flujo cerebral, sobre todo por su baja resolución temporal. Esto implica un doble

sesgo puesto que el flujo cerebral es altamente dinámico, con cambios de volumen o velocidad capaces de ocurrir y desaparecer en fracciones de segundo. Tomando en consideración lo expuesto, consideramos al ultrasonido transcraneal como un método idóneo para investigar los patrones de flujo sanguíneo cerebral.

El presente estudio tiene como finalidad determinar en pacientes con esquizofrenia si existe una relación entre la enfermedad, sus síntomas y déficits cognitivos, y diferentes patrones hemodinámicos en las arterias cerebrales medias medidos por medio de ultrasonido transcraneal. Los resultados obtenidos ayudarán a mejorar la comprensión de la esquizofrenia desde un punto de vista neurofisiológico. Adicionalmente, contribuirán al empleo del ultrasonido transcraneal como un método de neuroimagen y diagnóstico válido y útil para la evaluación de los trastornos neuropsiquiátricos, como es el caso de la esquizofrenia.

2. Objetivos e Hipótesis

2.1. Objetivos

1. Determinar si existen diferencias en el desempeño neurocognitivo entre pacientes con esquizofrenia y controles sanos, por medio de una tarea neuropsicológica.

2. Identificar diferencias en el patrón hemodinámico en las arterias cerebrales medias, por medio de ultrasonido transcraneal durante una actividad neuropsicológica, entre controles sanos y pacientes con esquizofrenia, así como en función de la presencia y el nivel de carga de sintomática.

3. Evaluar y determinar los métodos de análisis estadísticos idóneos para el análisis y comprensión de los parámetros hemodinámicos en las arterias cerebrales medias determinados por medio de ultrasonido transcraneal, durante una actividad visomotora de control.

4. Establecer si el nivel de funcionalidad-discapacidad de un trastorno mental, evaluado mediante la escala Mini-ICF-APP, depende de su diagnóstico psiquiátrica.

5. Identificar si la escala de evaluación psicopatológica “Escala Breve de Evaluación Psiquiátrica (BPRS)” puede emplearse de manera genérica en diferentes trastornos mentales, y si existe una relación entre la carga sintomática y el nivel de funcionalidad-discapacidad a lo largo del espectro diagnóstico.

6. Determinar si el empleo de instrumentos de evaluación psicopatológica (Escala Breve de Evaluación Psiquiátrica, BPRS) y de funcionalidad-discapacidad (Mini-ICF-APP) pueden utilizarse de forma complementaria en pacientes con distintos trastornos mentales; permitiendo comparar por medio de estos instrumentos los resultados de ultrasonido transcraneal obtenidos en diferentes diagnósticos psiquiátricos.

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2.2. Hipótesis

1. El desempeño neurocognitivo durante una tarea neuropsicológica de los pacientes con esquizofrenia es inferior al desempeño de los controles sanos.

2. El patrón hemodinámico, determinado por ultrasonido transcraneal en las arterias cerebrales medias durante una actividad neuropsicológica, varía en controles sanos y pacientes con esquizofrenia, así como en relación con la presencia y el nivel de carga sintomática.

3. Existen diferencias entre los métodos estadísticos empleados para el análisis y comprensión de los parámetros hemodinámicos en las arterias cerebrales medias determinados por medio de ultrasonido transcraneal, durante una actividad visomotora de control.

4. El nivel de funcionalidad-discapacidad de un paciente evaluado con la escala Mini-ICF-APP es independiente del diagnóstico psiquiátrico.

5. La Escala Breve de Evaluación Psiquiátrica (BPRS) puede emplearse de manera genérica en diferentes trastornos mentales, existiendo síntomas psicopatológicos determinantes del nivel de funcionalidad-discapacidad presentes a lo largo del espectro diagnóstico.

6. La Escala Breve de Evaluación Psiquiátrica (BPRS), para la evaluación de la psicopatología, y la escala Mini-ICF-APP, para la evaluación de funcionalidad-

discapacidad, pueden usarse de manera complementaria. Utilizadas conjuntamente permiten la comparación de los resultados obtenidos por medio del ultrasonido transcraneal en diferentes trastornos mentales.

3. Materiales y Métodos

Este trabajo de Tesis Doctoral se ha realizado mediante la ejecución de dos estudios complementarios. Cada estudio responde a objetivos e hipótesis específicos. Correspondientemente, cada estudio tiene un diseño y participantes únicos. El primer estudio tiene un enfoque neurofisiológico, el segundo un enfoque psicométrico. Al emplear ambos estudios los métodos de evaluación psicométrica, se facilita la transferencia de los resultados del estudio neurofisiológico a la practica diaria de psiquiatría clínica. El primer estudio aborda los tres primeros objetivos e hipótesis, el segundo estudio da respuesta a los objetivos e hipótesis cuatro a seis.

3.1. Primer Estudio - Neurofisiología

3.1.1. Diseño del Estudio

Se diseñó un estudio neurofisiológico para determinar las características hemodinámicas de las arterias cerebrales medias durante una tarea neuropsicológica empleando ultrasonido transcraneal en pacientes con esquizofrenia y en controles sanos.

3.1.2. Participantes del Estudio

En el estudio participaron un total de 30 controles sanos y 30 pacientes con un diagnóstico de esquizofrenia de acuerdo a los criterios de la 10ª edición de la Clasificación Internacional de Enfermedades CIE-10 (16). Los controles fueron reclutados entre los empleados del Hospital Universitario Psiquiátrico de Zúrich. Los

pacientes con un diagnóstico de esquizofrenia fueron reclutados entre los pacientes que acuden para tratamiento hospitalario o ambulatorio en el Hospital Universitario Psiquiátrico de Zúrich. El estudio fue aprobado por el Comité de Ética del Cantón de Zúrich (BASEC 2019-00814). Todos los pacientes participaron voluntariamente en el estudio, tras firmar el consentimiento informado.

3.1.2.1. Criterios de Inclusión y Exclusión

Para todos los participantes (pacientes con esquizofrenia y controles sanos) se aplicaron los siguientes criterios de inclusión:

- Edad entre 18 y 45 años.
- Diestros por nacimiento.
- Fluidez en alemán escrito y hablado.
- Tener capacidad para dar consentimiento informado.
- Educación básica obligatoria.

Para los pacientes se aplicaron adicionalmente los siguientes criterios de inclusión:

- Diagnóstico de Esquizofrenia, de acuerdo con los criterios diagnósticos de la CIE-10, capitulo F2.
- Duración de la enfermedad mayor a un año.

Para los participantes sanos se aplicaron los siguientes criterios de exclusión:

- Historia previa o actual de un trastorno mental.
- Historia actual de enfermedad somática general.
- Historia actual o previa de enfermedad o condición neurológica.

Para los pacientes se aplicaron los siguientes criterios de exclusión:

- Historia previa o actual de un trastorno orgánico de acuerdo con la CIE-10, capitulo F0.
- Historia previa o actual de un trastorno de dependencia de alcohol u otra substancia (con excepción de tabaco), de acuerdo con la CIE-10, capitulo F1.
- Historia previa o actual de un trastorno afectivo de acuerdo con la CIE-10, capitulo F3.
- Historia previa o actual de un trastorno de ansiedad de acuerdo con la CIE-10, capitulo F4.
- Historia previa o actual de un trastorno de personalidad de acuerdo con la CIE-10, capitulo F6.
- Patología o condición somática general inestable.
- Patología o condición neurológica inestable.

3.1.3. Diagnóstico

El diagnóstico de esquizofrenia se realizó por medio de la exploración clínica y de acuerdo con los criterios diagnósticos estipulados en el capitulo F2 del Código Internacional de Enfermedades. El diagnóstico fue realizado en primera instancia por un médico residente de psiquiatría, y fue confirmado por un médico especialista en psiquiatría en el momento de incluir al paciente en el estudio.

3.1.4. Evaluación

La evaluación comprendió varios ámbitos, incluyendo la evaluación psicométrica, la evaluación cognitiva, la cuantificación de la medicación y la determinación de efectos adversos. La evaluación psicométrica, incluyó la cuantificación de la gravedad del trastorno por medio de las Escalas de Impresión Clínica Global (ICG) (98). La determinación de la carga sintomática de la psicopatología se efectuó por medio de la Escala Breve de Evaluación Psiquiátrica (BPRS) (25). La evaluación cognitiva se realizó por medio del Test del Trazado, parte A y parte B (TMT-A y B) (99). La evaluación de discapacidad y funcionalidad se realizó por medio de la escala "Mini-ICF-APP" (99). Se cuantificó la medicación antipsicótica y se convirtió a equivalentes de Clorpromazina. Los efectos adversos fueron evaluados mediante la Escala de Simpson Angus (SAS) (100) en el caso de los síntomas extrapiramidales y la Escala de Acatisia de Barnes (BARS) (101, 102).

3.1.4.1. Evaluación de Gravedad

La gravedad del trastorno esquizofrénico fue evaluada mediante las Escalas de Impresión Clínica Global (ICG) (98). La ICG es una escala pragmática, de fácil uso e interpretación intuitiva para evaluar la gravedad de un trastorno psiquiátrico. Debido a estas características es una de las escalas que mayor uso tiene en la práctica clínica y de investigación (24, 98, 103-106). La ICG comprende dos sub-escalas: 1. ICG-Gravedad de la Enfermedad (ICG-G), para determinar la gravedad del trastorno psiquiátrico, y 2. ICG-Cambio (ICG-C), para determinar la evolución del cuadro clínico, ya sea una mejoría o un empeoramiento (98).

Tanto la ICG-G como la ICG-C se evalúan utilizando una escala tipo Likert de siete niveles. Para la ICG-G los valores oscilan entre uno “1” es considerado un sujeto sano y siete “7” un sujeto extremadamente enfermo. En la escala ICG-C un valor de uno “1” es considerado una gran mejoría, y un valor de siete “7” un gran empeoramiento, mientras que un valor de cuatro “4” es indicativa de ausencia de cambio. (98). Para la ICG-C el marco de referencia temporal son los siete días previos, mientras que para la ICG-C el marco de referencia temporal es el tiempo transcurrido desde la evaluación previa.

3.1.4.2. Evaluación Psicopatológica

La Escala Breve de Evaluación Psiquiátrica (BPRS) fue inicialmente diseñada para evaluar los síntomas psicopatológicos de los trastornos mentales graves como la esquizofrenia, el trastorno bipolar y la depresión con síntomas psicóticos (25). La BPRS es una de las escalas con mayor difusión para evaluar los síntomas psicopatológicos de la esquizofrenia (26). También se utiliza para evaluar la psicopatología en poblaciones clínicas con otros trastornos mentales graves (31, 33).

La BPRS evalúa la presencia e intensidad de los síntomas psicopatológicos. Consiste en 18 ítems que evalúan 18 síntomas independientes entre sí. Cada síntoma es evaluado mediante una escala de tipo Likert, la cual varía de uno “1” (no presente) a siete “7” (muy grave). Los diferentes síntomas evaluados son: 1. Preocupación somática, 2. Ansiedad psíquica, 3. Aislamiento emocional, 4. Desorganización

conceptual (incoherencia), 5. Autodesprecio y sentimientos de culpa, 6. Tensión, ansiedad somática, 7. Manierismo y posturas extrañas, 8. Grandeza, 9. Humor depresivo, 10. Hostilidad, 11. Suspicacia, 12. Alucinaciones, 13. Enlentecimiento motor, 14. Falta de cooperación, 15. Contenido inusual del pensamiento, 16. Embotamiento, aplanamiento del afecto, 17. Excitación, y 18. Desorientación y confusión.

La BPRS puede ser utilizada a nivel global, de sub-escalas o de ítems aislados. La puntuación total oscila entre 18 y 126 puntos, a mayor puntuación mayor carga sintomática. Para la BPRS se han calculado puntos de corte de acuerdo con la gravedad clínica (27, 35). Valores menores a los 31 puntos corresponden a un nivel de gravedad leve, valores entre 41 y 52 puntos corresponden a un nivel de gravedad marcado, y valores iguales o mayores a los 53 puntos corresponden a un nivel de gravedad extremo (27). La evaluación global puede ser vista como la carga sintomática de un paciente, donde se toma en cuenta no solo la ausencia o presencia de los síntomas, sino también su intensidad. La carga sintomática no es equivalente a la gravedad de un trastorno, puesto que para determinar la gravedad debe ser considerado además el grado de discapacidad y no tan solo la cantidad de síntomas presentes (107, 108).

3.1.4.3. Evaluación Cognitiva

El Test del Trazado (TMT) es parte de la Batería Cognitiva de Consenso Matrics (42). Se trata de un instrumento que evalúa la cognición y la integridad del lóbulo frontal en varios trastornos neuropsiquiátricos, inclusive la esquizofrenia. En contraste con otras pruebas neuropsicológicas, el TMT es de fácil implementación e interpretación,

motivo por el cual es ampliamente utilizado en la práctica clínica y de investigación (109, 110). El TMT es sensible para detectar actividad grafomotora, escaneo visual, atención selectiva, flexibilidad mental y función ejecutiva (109, 110). Los pacientes con esquizofrenia tienen un desempeño bajo en el TMT, con limitaciones en la velocidad de procesamiento y estrategias de procesamiento simultaneo ineficientes (109, 111). Existe evidencia de que, en pacientes con esquizofrenia, los lóbulos frontales en general y el córtex dorsolateral prefrontal en particular juegan un rol importante durante la ejecución del TMT (112, 113).

3.1.4.4. Cuantificación de la Medicación Antipsicótica

La medicación de los pacientes será documentada, incluyendo el nombre comercial, el principio activo y la dosis. Las dosis diarias de los medicamentos serán convertidas a sus dosis estándar diarias acuerdo a las pautas vigentes (114). La dosis diaria de la medicación antipsicótica será convertida a la dosis equivalente de Clorpromazina, (115-117).

3.1.4.5. Evaluación de los efectos adversos de la Medicación

Los efectos secundarios de la medicación serán evaluados con la “Simpson-Angus Scale” (SAS) para medir los efectos extrapiramidales y la “Barnes Acathisia Rating Scale” (BARS) para medir la acatisia.

La “Simpson-Angus Scale” (100) es un instrumento para evaluar síntomas extrapiramidales como consecuencia de un tratamiento antipsicótico. La escala consiste en 10 ítems, que evalúan la presencia de síntomas extrapiramidales y parkinsonianos. Cada ítem es evaluado en una escala de tipo Likert, con 5 niveles de graduación; con un mínimo de cero “0” (ausente ó normal), a un cuatro “4” (extremo). Con los todos los ítems evaluados se obtiene un promedio global. Si el valor de este es menor a 0.3 se considera que no existen síntomas extrapiramidales.

La “Barnes Acathisia Rating Scale” (101, 102) fue desarrollada para determinar la presencia de acatisia, así como para determinar su nivel de gravedad. La Escala consiste en tres subescalas, la dos primera evalúan la percepción subjetiva de la intranquilidad, la segunda la presencia de signos de intranquilidad agitación . Estos son evaluados con una escala tipo Likert de cuatro niveles, en el cual cero “0” denota ausencia y tres “3” la máxima gravedad. Una tercera escala mide la ausencia o presencia global de acatisia, esta escala es evaluada en una escala tipo Likert de seis niveles, donde cero “0” denota la ausencia, uno “1” la presencia cuestionable; los grados dos “2“ a cinco “5” denotan el nivel de gravedad de leve a grave.

3.1.5. Estudio Neurofisiológico - Ultrasonido Transcraneal

Las mediciones de ultrasonido transcraneal se realizaron mediante un ecógrafo Multi-Dop X (DWL Elektronische Systeme GmbH, Sipplingen- Germany). Con transductores duales de dos megahercios (2 MHz) ambas arterias cerebral medias

fueron insonorizadas a una profundidad entre 48 y 55 mm a través de la ventana ecográfica del hueso temporal. Posteriormente los transductores fueron sujetados y fijados por medio de una cinta para evitar artefactos por movimiento. La velocidad media de flujo en las arterias cerebrales media fue gravada continuamente durante todo el experimento, incorporando los datos de cada ciclo cardiaco (86).

3.1.5.1. Paradigma Neuropsicológico - Evaluación Cognitiva

Se requirió a los participantes abstenerse del consume de café y tabaco durante las dos horas previas al experimento neuropsicológico, tiempo necesario para neutralizar los efectos sobre la circulación de ambos (118). Los participantes recibieron información e instrucciones con respecto al experimento neuropsicológico; para evitar efectos de aprendizaje cada paradigma fue presentado una sola vez. El “Trail Making Test” fue presentado en su versión de lápiz y papel. En el “Trail Making Test” Parte A, los participantes tienen que conectar 25 números en orden ascendente (es decir: 1, 2, 3, hasta el 25). En el “Trail Making Test” Parte B, los participantes tienen que conectar números (1 al 13) y letras (de la “A” a la “L”) en orden alternado y ascendente (es decir: 1, A, 2, B, 3, C, hasta 13, L). Los participantes tenían la tarea de resolver ambos “Trail Making Tests” lo mas rápido y exacto posible. La asignación del orden de presentación del Trail Making Test parte A o parte B fue aleatoria.

3.1.5.2. Actividad de Control

En la actividad de control, los participantes obtuvieron una hoja con cuatro círculos, alineados en un cuadrado con una distancia de diez centímetros entre ellos. Los participantes tenían la tarea de conectar aleatoriamente con líneas los círculos a un ritmo de un trazo por segundo para simular el ritmo del "Trail Making Test" Parte A (0.89 +- 0.21 Hz), o a dos trazos por segundo para similar el ritmo del "Trail Making Test" parte B (0.46+-0.15Hz). La actividad de control fue situada de forma aleatoria delante o detrás del correspondiente "Trail Making Test" (97).

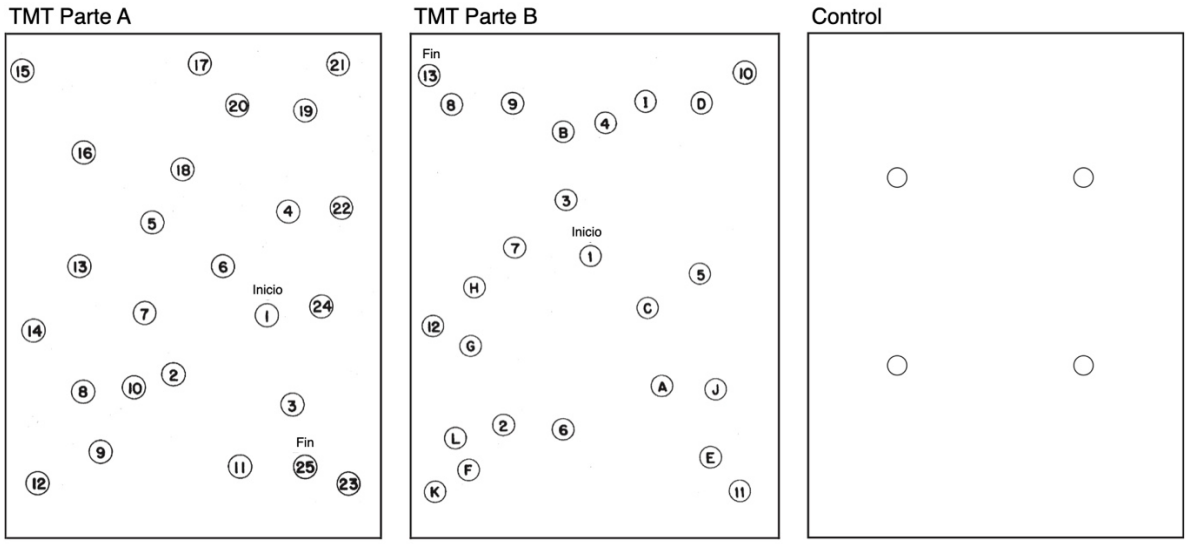

Figura 3: Representación de las pruebas neuropsicológicas y la tarea de control. TMT: Trail Making Test.

3.1.6. Análisis Estadístico

Los participantes del estudio fueron emparejados en los grupos de análisis de acuerdo con la edad y el sexo; con el fin de obtener grupos homogéneos con respecto a estas variables. Los datos obtenidos son presentados en forma de texto, tablas y gráficos empleando estadística descriptiva (mediana, rango, media, desviación estándar,

porcentajes). Posteriormente a la evaluación de los prerrequisitos para cada prueba estadística se analizaron las variables, de acuerdo con si son cualitativas o cuantitativas.

Para el análisis de variables continuas se usó un análisis de varianza (ANOVA), o un análisis de varianza múltiple (MANOVA). Si los prerrequisitos no se cumplían se ejecutó una prueba no- paramétrica como el Kruskal- Wallis Test. La comparación de diferencia en pares se realizó con un Students' t- Test o el Mann- Whitney Test si los prerrequisitos no se cumplieron. La prueba Chi- cuadrado (χ^2) se realizó para comparar diferencias en proporciones. El cálculo del poder de la muestra se realizó post-hoc. La correlación entre variables se calculó con la prueba de correlación de Pearson. El análisis de las variables medidas secuencialmente se realizó empleando los modelos lineales general y modelo aditivo general.

Para analizar la velocidad de flujo, los datos se prepararon de acuerdo con publicaciones anteriores (97). En un primer paso, se transformaron de una frecuencia de 100 Hz a un 1 Hz. En un segundo paso, la medición en las fases de reposo previa y posterior al experimento se normalizaron. Finalmente, los valores obtenidos durante el experimento se transformaron a valores relativos con respecto a las fases de reposo. Para el análisis se emplearon consecutivamente valores relativos.

Para determinar el periodo de análisis se consideró el tiempo que necesiten los participantes para completar cada una de las partes del "Trail Making Test", tomándose como referencia el menor tiempo requerido por un participante. Este

tiempo se aplicó a todos los participantes. Como periodos de reposo se consideraron los 60 segundos previos y posterior a cada ejercicio neuropsicológico.

3.1.6.1. Programas Estadísticos Empleados en el Análisis de los Datos.

Para el análisis de los datos fueron empleados los siguientes programas estadísticos: SPSS versión 22 (IBM Corp.), STATA versión 13.1. (StataCorp) y el programa "R" versión 3.6 y 4.1. En el programa "R" empleamos los siguientes paquetes: "np" (versión 0.60-9), "Likert" (versión 1.3.5), "psych" (versión 1.9.12), y "lavaan" (versión 0.6-5). Para la representación gráfica fueron usados SigmaPlot 11 (Systat Software Inc.) y el programa "R" con el paquete "ggplot" (versión 1.2).

3.1.7. Aspectos Éticos

Los investigadores se comprometieron a respetar todos los aspectos establecidos en la legislación vigente en materia de investigación clínica establecidos en la Declaración de Helsinki, en el Convenio del Consejo de Europa relativo a los derechos humanos y la biomedicina, en la Declaración Universal de la UNESCO sobre los derechos humanos, así como cumplir los requisitos establecidos en la legislación de Suiza y del cantón de Zúrich en el ámbito de la investigación biomédica en humanos, la protección de datos de carácter personal y la protección de pacientes. El protocolo de los estudios clínicos fue aprobado por la comisión cantonal de ética del cantón de Zúrich. Previa a su inclusión en el estudio, se obtuvo el consentimiento informado firmado de todos los participantes.

3.2. Segundo Estudio – Psicometría

3.2.1. Diseño del Estudio

Diseñamos un estudio psicométrico para determinar el desempeño de la escala de funcionalidad- discapacidad “Mini-ICF-APP” en pacientes que requieren hospitalización por un trastorno mental, independientemente de la categoría diagnostica. En una subpopulación balanceada de acuerdo al diagnóstico principal se analizo la relación, por medio del análisis de redes entre la escala psicopatológica “Escala Breve de Evaluación Psiquiátrica, BPRS” y la escala de funcionalidad-discapacidad “Mini-ICF-APP”.

3.2.2. Participantes del Estudio

El Hospital Universitario Psiquiátrico de Zúrich es responsable de cubrir las necesidades de atención en salud mental para la ciudad de Zúrich-Suiza y sus alrededores, abarcando una población de aproximadamente 500.000 habitantes. Los datos clínicos de los pacientes que fueron hospitalizados en el Centro de Psiquiatría Integrativa, del Hospital Universitario Psiquiátrico de Zúrich fueron recolectados como parte de la rutina clínica. Para el estudio y posterior se incluyo a una cohorte de ingresos y egresos hospitalarios en un periodo cinco años consecutivos. En este periodo se contabilizaron un total de 3.295 ingresos. De estos se seleccionaron aleatoriamente 600 pacientes para un subanálisis comparativo.

3.2.2.1. Criterios de Inclusión y Exclusión

Para todos los pacientes se aplicaron los siguientes criterios de inclusión:

- Edad entre 18 y 65 años.
- Diagnóstico de un trastorno mental de acuerdo con los criterios CIE-10.

Para los pacientes se aplicaron los siguientes criterios de exclusión:

- Datos incompletos para las escalas de interés (BPRS y Mini-ICF-APP).

Para los pacientes incluidos en el subanálisis se aplicaron adicionalmente los siguientes criterios de inclusión.

- Primera hospitalización en el periodo de interés.
- Diagnóstico en un trastorno de dependencia de alcohol CIE-10: capitulo F10.
- Diagnóstico en un trastorno del espectro de la esquizofrenia CIE-10: capitulo F20.
- Diagnóstico en un trastorno bipolar CIE-10: capitulo F30 o F31.
- Diagnóstico en un trastorno depresivo CIE-10: capitulo F32 o F33.
- Diagnóstico en un trastorno de ansiedad CIE-10: capitulo F40.
- Diagnóstico en un trastorno de la personalidad del Grupo B CIE-10: Antisocial F60.2; Impulsivo F60.3; Histriónico F60.4 o Narcisista F06.8.
- Selección aleatoria de 100 participantes por grupo diagnóstico.

3.2.3. Diagnóstico

El diagnóstico del trastorno mental que conlleva a la hospitalización, así como el diagnóstico de los trastornos psiquiátricos comórbidos, se realizó por medio de la exploración clínica; de acuerdo con los criterios diagnósticos estipulados en el Código Internacional de Enfermedades. El diagnóstico fue realizado en primera instancia por un médico residente de psiquiatría, y fue confirmado o a su vez corregido por un especialista en psiquiatría.

3.2.4. Evaluación

La evaluación psicométrica comprendió los ámbitos de gravedad, psicopatología y discapacidad y funcionalidad. La cuantificación de la gravedad del trastorno por medio de la “Clinical Global Impression Scales” (CGI) (98). La determinación de la carga sintomática de la psicopatología se efectuó por medio de la “Brief Psychiatic Rating Scale” (BPRS) (25). La evaluación de discapacidad y funcionalidad se realizó por medio de la escala mini-ICF-APP (99).

3.2.4.1. Evaluación de Gravedad

La gravedad del trastorno esquizofrénico fue evaluada mediante la “Clinical Global Impression Scale” (CGI) (98). La CGI es una escala pragmática, de fácil uso e

interpretación intuitiva para evaluar la gravedad de un trastorno psiquiátrico. Debido a estas características es una de las escalas que mayor uso tiene en la práctica clínica y de investigación (24, 98, 103-106). La CGI comprende dos sub-escalas: 1. CGI-Severity of Illness (CGI-S), para determinar la gravedad de un trastorno psiquiátrico, y 2. CGI- Global Improvement (CGI-I), para determinar la evolución del cuadro clínico, ya sea una mejoría o un empeoramiento (98).

Tanto la CGI-S como la CGI-I son evaluadas utilizando una escala de tipo Likert, de siete niveles. Para la CGI-S con un valor de uno “1” es considerado un sujeto sano a siete “7” un sujeto extremadamente enfermo. En la escala CGI-I un valor de uno “1” es considerado una gran mejoría, y un valor de siete “7” un gran deterioro, mientras que un valor de cuatro “4” es indicativa de ausencia de cambio. (98). La CGI-S considera un periodo de siete días previos para su evaluación, mientras que la CGI-I considera el tiempo transcurrido desde una evaluación previa.

3.2.4.2. Evaluación Psicopatológica

La escala psicopatológica “Escala Breve de Evaluación Psiquiátrica, BPRS” (BPRS) fue inicialmente diseñada para evaluar los síntomas psicopatológicos en trastornos mentales graves como la esquizofrenia, el trastorno bipolar y la depresión con síntomas psicóticos (25). La BPRS es una de las escalas con mayor difusión para evaluar los síntomas psicopatológicos de la esquizofrenia (26). También es empleada

para evaluar la psicopatología en poblaciones clínicas, que incluyen otros trastornos mentales graves (31, 33).

La Escala Breve de Evaluación Psiquiátrica, BPRS evalúa la presencia e intensidad de los síntomas psicopatológicos en pacientes. Consiste en 18 ítems, los cuales evalúan 18 síntomas independientes entre sí. Cada síntoma es evaluado mediante una escala de tipo Likert, la cual varía de uno “1” (no presente) a siete “7” (muy grave). Los diferentes síntomas evaluados son: 1. Preocupación somática, 2. Ansiedad psíquica, 3. Aislamiento emocional, 4. Desorganización conceptual (incoherencia), 5. Autodesprecio y sentimientos de culpa, 6. Tensión, ansiedad somática, 7. Manierismo y posturas extrañas, 8. Grandeza, 9. Humor depresivo, 10. Hostilidad, 11. Suspicacia, 12. Alucinaciones, 13. Enlentecimiento motor, 14. Falta de cooperación, 15. Contenido inusual del pensamiento, 16. Embotamiento, aplanamiento del afecto, 17. Excitación, y 18. Desorientación y confusión.

La Escala Breve de Evaluación Psiquiátrica, BPRS puede ser evaluada a nivel global, de sub-escalas o de ítems aislados. La puntuación total de la Escala Breve de Evaluación Psiquiátrica, BPRS oscila entre 18 y 126 puntos, a mayor puntuación mayor carga sintomática. Para la Escala Breve de Evaluación Psiquiátrica, BPRS se han calculado puntos de corte de acuerdo con la gravedad clínica (27, 35). Valores menores a los 31 puntos en la escala BPRS corresponden a un nivel de gravedad leve, valores en la escala BPRS entre 41 y 52 puntos corresponden a un nivel de severidad marcado, y valores en la escala BPRS iguales o mayores a los 53 puntos corresponden a un nivel de severidad extremo (27). La evaluación de la Escala Breve de Evaluación Psiquiátrica, BPRS a nivel global puede ser vista como la carga

sintomática de un paciente, donde se toma en cuenta no solo la ausencia o presencia de los síntomas, sino también su intensidad. La carga sintomática no es equivalente a la gravedad de un trastorno, puesto que para determinar la gravedad debe ser considerado además el grado de discapacidad y no tan solo la cantidad de síntomas presentes (107, 108).

3.2.4.3. Evaluación de Funcionalidad-Discapacidad

La escala Mini-ICF-APP fue diseñada para evaluar la funcionalidad psicosocial de personas con una enfermedad mental con respecto a discapacidad y participación (99, 119). La escala Mini-ICF-APP en su evaluación, considera las circunstancias personales, sociales y laborales de cada paciente; por lo cual la escala muestra un desempeño equiparable a través de las diferentes categorías diagnosticas (99). La escala evalúa trece dominios, los cuales están definidos como ítems individuales. Cada ítem es evaluado en una escala de cinco niveles tipo Likert que va desde cero “0” (ausencia de discapacidad) a cuatro “4” (discapacidad total). Para cada ítem existe un glosario de definiciones (99, 120).

Los dominios de funcionamiento psicosocial- discapacidad evaluados por cada uno de los ítems son los siguientes: 1. Adherencia a reglas y rutinas, 2. Planificación y estructuración de tareas, 3. Flexibilidad, 4. Competencias, eficacia, 5. Resistencia-perseverancia, 6. Asertividad, 7. Contacto con otros, 8. Interacción grupal, 9. Relaciones familiares e íntimas, 10. Actividades de ocio, 11. Cuidado personal, 12.

Movilidad, 13 Competencia para discernir y tomar decisiones. La escala puede ser evaluada a nivel global o individualmente a nivel de cada ítem. La evaluación global comprende un rango de 0 a 52 puntos, con puntos de corte definidos para distintos niveles de gravedad (121, 122).

3.2.5. Análisis Estadístico

Los datos obtenidos son presentados en forma de texto, tablas y gráficos empleando estadística descriptiva (mediana, rango, media, desviación estándar, porcentajes). Posteriormente a la evaluación de los prerrequisitos para cada prueba estadística se analizaron las variables, de acuerdo con si son cualitativas o cuantitativas.

Para el análisis de variables continuas se usó un análisis de varianza (ANOVA), o un análisis de varianza múltiple (MANOVA). Si los prerrequisitos no se cumplían se ejecutó una prueba no- paramétrica como el Kruskal- Wallis Test. La comparación de diferencia en pares se realizó con un Students' t- Test o el Mann- Whitney Test si los prerrequisitos no se cumplieron. La prueba Chi- cuadrado (χ^2) se realizó para comparar diferencias en proporciones. El cálculo del poder de la muestra se realizó post-hoc. La correlación entre variables se calculó con la prueba de correlación de Pearson.

La correlación entre los diferentes ítems de la escala Mini-ICF-APP se realizó por un lado con todo el rango de gradación (es decir de 0 a 4), y, por otro lado, con las variables dicotomizadas de acuerdo con la relevancia clínica; es decir, un valor de 0

a 2 fue considerado “negativo”, mientras que un valor de 3 o 4 fue considerado “positivo” (99, 119). Para el análisis factorial exploratorio se emplearon los ítems dicotomizados para disminuir el rango de multicolinearidad al momento de determinar factores latentes (123).

Para el análisis de componente principales, la dimensión y la estructura factorial se empleó un método de rotación varimax. Un valor Eigenvalue mayor de uno fue el criterio determinante para la extracción factorial. El índice Kaiser-Meier-Olkin (KMO) se empleó para medir si la muestra era adecuada. Para determinar y comparar el ajuste de los diferentes modelos empleamos: los valores Eigenvalues, Chi- cuadrado, el “Comparative Fit Índex (CFI)”, Root Mean Square Residual (RMSR); Root Mean Square Error of Approximation (RMSEA) y el índice de Tucker Lewis (TLI). Los puntos de corte considerados indicativos de un buen ajuste fueron: Eigenvalue mayor 1; a Chi- cuadrado con un valor p menor a 0.05; un CFI con un valor menor o igual a 0.90; un RMSR con un valor menor a 0.08; un RMSEA con un valor menor a 0.08; y un TLI con un valor mayor o igual a 0.95 (124, 125).

Una subpoblación de 600 pacientes fue extraída aleatoriamente con 100 muestras por cada diagnóstico principal (esquizofrenia, trastorno bipolar, ansiedad, depresión, dependencia de alcohol y trastorno de personalidad). La muestra fue balanceada para genero, edad y comorbilidad. Para el análisis de variables continuas se usó un análisis de varianza (ANOVA). La prueba Chi- cuadrado (χ^2) se realizó para comparar diferencias en proporciones. El coeficiente alpha de Cronbach fue empleado para examinar la consistencia interna de las escalas BPRS y Mini-ICF-APP. La simetría y

curtosis de la distribución de ambas escalas fue calculada, el índices de simetría fue empleado para determinar efectos de piso o de techo en el rango de mediciones.

El rango de correlación de Spearman fue calculado con los valores totales de las escalas BPRS y Mini-ICF-APP. Tomando en consideración, las diferencias entre ambas escalas calculamos los valores estandarizadas “z” para cada medición. Con el valor- z se calculo el coeficiente de concordancia correlación entre ambos instrumentos, para determinar su precisión y exactitud (126, 127). Para evaluar el nivel de concertación y solapamiento entre ambas escalas usamos el método de Bland-Altman (128). Para el solapamiento, un diagrama fue creado. La diferencia entre ambas escalas es presentada en la axis-y, mientras que la media en la axis-x, los limites de concertación entre ambas escalas fue calculado adicionalmente (128, 129).

El modelaje de red de las escalas BPRS y Mini-ICF-APP fue calculado empleando el método EBICglasso (Extended Bayesian Information Criterion, Gaussian Least Absolute Shrinkage and Selection Operator), para el grado de reducción empleamos un hiperparámetro (gamma = 0.0) para maximizar la estabilidad y equilibrar la sensibilidad y especificidad de la red (130). Para medir la exactitud de los parámetros de la red, estimamos lo intervalos de confianza de los bordes y el coeficiente de estabilidad empleando un muestreo no paramétrico autodocimante (131). En la representación grafica, los bordes entre nodos representan las correlaciones parciales regularizadas, las cuales estima la relación entre dos variables (ítems) controlando para todo el resto de las variables. Un borde entre dos variables indica una relación de dependencia entre dos variables, la ausencia de un borde indica que

las variables son condicionalmente independientes. Mientras mas Amplio y marcado es el borde, mayor es la asociación entre ambos nodos. Nodos azules indican una relación positiva entre las variables, nodos rojos una relación negativa. Para los nodos (ítems) calculamos los parámetros de centralidad (cercanía, intercesión y fuerza), así como la influencia. Finalmente calculamos los nodos que fungen de puente entre ambas escalas (132).

3.2.5.1. Programas Estadísticos Empleados en el Análisis de los Datos.

Para el análisis de los datos fue empleado el programa “R” (versión 4.0.1), con los siguientes paquetes: “blandir” (versión 0.5.1), “DescTools” (versión 0.99.43), “NetworkTools” (versión 1.3.0), “Bootnet” (versión 1.43) y “qgraph” (versión 1.6.9). Para la representación gráfica fueron usados el programa “R” con los paquetes “ggplot” (versión 3.3.5) y qgraph” (versión 1.6.9).

3.2.6. Aspectos Éticos

Los investigadores se comprometieron a respetar todos los aspectos establecidos en la legislación vigente en materia de investigación clínica establecidos en la Declaración de Helsinki, en el Convenio del Consejo de Europa relativo a los derechos humanos y la biomedicina, en la Declaración Universal de la UNESCO sobre los

derechos humanos, así como cumplir los requisitos establecidos en la legislación de Suiza y del cantón de Zúrich en el ámbito de la investigación biomédica en humanos, la protección de datos de carácter personal y la protección de pacientes. El protocolo de los estudios clínicos fue aprobado por la comisión cantonal de ética del cantón de Zúrich.

4. Resultados - Publicaciones

4.1. Resultados del Estudio 1 (Publicaciones 1 a 3)

Artículo 1: *"Determinants of cerebral hemodynamics during the Trail Making Test in schizophrenia"*

Referencia de la Fuente:
Schuepbach, D., **Egger, S.T.,** Boeker, H., Duschek, S., Vetter, S., Seifritz, E., Herpertz S.C. *„Determinants of cerebral hemodynamics during the Trail Making Test in schizophrenia"* Brain & Cognition. 2016; 109:96-104
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Abstract:
Patients with schizophrenia show deficits in cognitive functioning, and studies on cerebral hemodynamics have revealed aberrant patterns of mean cerebral blood flow velocity (MFV), an equivalent of cerebral blood flow (CBF). Therefore, we carried out a controlled study that assessed MFV in schizophrenia during a well-known neuropsychological task, the Trail Making Test (TMT). We measured MFV in the middle cerebral arteries using functional transcranial Doppler sonography in 15 schizophrenia patients and 15 healthy subjects. In comparison to healthy subjects, patients performed poorer on the TMT-A and the TMT-B, and there was increased cerebral blood flow velocity during the TMT-B. A comparison of subgroups of patients and controls matched in performance on the TMT-B revealed that these patients still showed significantly increased cerebral blood flow velocity. Increased MFV in schizophrenia suggests specific alterations of cerebral hemodynamics during the Trail Making Test, Part B, which are not detect- able during visuomotor activity, and which are independent of performance. These findings emphasize the pathophysiological importance of cognitive functioning in schizophrenia, but cast doubts whether performance in this particular test plays a relevant role for CBF abnormalities in schizophrenia.

Factor de Impacto: 2.43 (2016)

Determinants of cerebral hemodynamics during the Trail Making Test in schizophrenia

that the DLPFC is critical for proper performance of the TMT-B (Stuss et al., 2001). The TMT has two parts: a series of numbers (TMT-A) or a series of alternating numbers and letters (TMT-B) have to be connected in ascending order (Tombaugh, 2004). The TMT-A assesses graphomotor speed, visual scanning and selective attention, while the TMT-B provides information on mental flexibility and executive functioning. Patients with schizophrenia show decreased performance on the TMT-B as compared to healthy subjects (Heinrichs & Zakzanis, 1998).

Previous findings in healthy subjects emphasize that the TMT is suitable for assessing hemodynamic changes in the middle cerebral arteries (MCA; Boban, Crnac, Junakovic, & Malojcic, 2014; Misteli et al., 2011); in particular, the TMT-B has been reported to show a favorable activation potential for MCA (Boban et al., 2014). A recent near infrared spectroscopy study (NIRS) showed reduced prefrontal activation during the TMT in schizophrenia (Fujiki et al., 2013). The investigation of cerebral hemodynamics during the TMT is interesting for several reasons: The Trail Making Test is widely used in clinical practice (Tombaugh, 2004) or for research purposes in patients with schizophrenia. It has been predominantly applied as a correlate of executive functioning (TMT-B); there are no studies that pinpoint cerebral hemodynamics during the TMT in schizophrenia. Moreover, to the best of our knowledge, no study has investigated cerebral blood flow velocity or related measures during normal or decreased performance of the TMT in schizophrenia. A positron emission tomography study investigating resting cerebral blood flow and the Trail Making Test in schizophrenia reported hypometabolism in the frontal lobes and hypermetabolism in temporoparietal-limbic regions as a neurobiological basis of TMT-B performance impairment in this disorder (Horacek et al., 2006). There is evidence that frontal and subcortical regions including white matter tracts are involved in the pathophysiology of schizophrenia (Pérez-Iglesias, Tordesillas-Gutiérrez, McGuire, Barker, & Roiz-Santiañez, 2010).

Functional transcranial Doppler sonography (fTCD) is a non-invasive method to assess hemodynamic characteristics of the cerebral arteries (Duschek & Schandry, 2003; Stroobant & Vingerhoets, 2000) which provides continuous measurements of mean cerebral blood flow velocity. This technique has a high temporal resolution, but it acquires no direct anatomical image. Functional transcranial Doppler sonography of basal cerebral arteries has been applied in psychophysiological research (Duschek & Schandry, 2003; Stroobant & Vingerhoets, 2000), including attention, planning and abstraction tasks (Duschek, Schuepbach, & Schandry, 2008; Frauenfelder, Schuepbach, Baumgartner, & Hell, 2004; Schuepbach et al., 2002). The middle cerebral arteries (MCA) are of special interest when examining the Trail Making Test because the arterial territory of the MCA includes the lateral part of the cerebral hemispheres (Tatu, Moulin, Bogousslavsky, & Duvernoy, 1998) - in other words the DLPFC, and also, but not exclusively, portions of subcortical structures like the striatum or the thalamus. There is solid evidence that executive functions such as the TMT-B activate neuronal circuitries that comprise the DLPFC, the temporal cortex, the basal ganglia and the thalamus (Stuss, 2011). Studies using fTCD in schizophrenia during cognitive effort are sparse (Feldmann et al., 2006; Schuepbach, Goenner, et al., 2002; Schuepbach, Weber, et al., 2007). However, this technique is less costly and lower demanding and burdening for patients as compared to functional magnetic resonance imaging (fMRI), as it is stable with respect to movement artifacts and does not need to immobilize patients (Knecht et al., 1998; Lohmann, Ringelstein, & Knecht, 2006). Furthermore, there is an excellent temporal resolution, that is acquisition of data at a pace of 1/100 s, and MFV changes are detected within 1 s or less (Schuepbach, Boeker, Duschek, & Hell, 2007).

We addressed the following issues in this report: First, we examined cerebral blood flow velocity during the TMT-A and TMT-B in patients with schizophrenia, and implemented visuomotor control tasks to accommodate for cerebral hemodynamic changes during motor and visual activities of the TMT. Based on the available literature (Fujiki et al., 2013), we hypothesized decreased cerebral hemodynamics in schizophrenia during the TMT. Second, in analogy to a study by Henseler, Falkai, and Gruber (2009), we expected that cerebral blood flow velocity would be reduced in patients irrespective of the performance level. Third, we sought to confirm available evidence that neuropsychological performance in schizophrenia does not yield the typical associations as found in healthy subjects (Ojeda et al., 2010), such as age dependence. Fourth, as we found no published studies of MFV or related measures in patients with schizophrenia showing extrapyramidal symptoms, and as akathisia is very frequent in this disorder (Kane et al., 2009), we examined the impact of extrapyramidal symptoms (EPS) and akathisia on MFV during the Trail Making Test.

2. Methods

2.1. Subjects

Fifteen patients with chronic schizophrenia and 15 age-matched healthy subjects participated in this study. Patients fulfilled the WHO-ICD-10 criteria for Schizophrenia (F20) (WHO, 1992). The following exclusion criteria applied to the patients: (1) affective or organic brain disorders, (2) substance abuse for the last 3 months prior to the examination or a lifetime diagnosis of substance dependence, including a positive urine test for psychotropic substances, (3) mental retardation, and (4) migraine and other headaches. Within 24 h of the fTCD measurements, psychopathology was assessed using the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962) and the Clinical Global Impression Scale (CGI; Bech & Ahlfors, 1993). Secondary effects of antipsychotics on the extrapyramidal system were examined with the Simpson-Angus Scale (EPS, total score; Simpson & Angus, 1970) and the Barnes Akathisia Scale (BAS, global score; Barnes, 1989). Healthy subjects had no known general, neurological or psychiatric condition. All patients with schizophrenia took antipsychotic medication: Four individuals additionally took an antidepressant and/or a mood stabilizer. Details can be found in Table 1 and the Supplementum. Healthy subjects did not take any regular medication. All participants were right-handed (Salmaso & Longoni, 1985). Participants did not consume caffeine or nicotine for at least 2 h before the test. Prior to study inclusion, a total of four subjects were excluded, for the following reasons: no temporal bone window (1), signal instability (2), ventricular extrasystolia (1). The study was approved by the local ethics committee and all participants provided written informed consent.

2.2. Equipment

Doppler measurements were performed with a Multi-Dop X instrument (DWL Elektronische Systeme GmbH, Sipplingen-Germany). Two dual 2 MHz transducers were attached and fixed with a headband. Both MCA were insonated at depths of 48–55 mm through the temporal bone window. A monitor with a standard screen saver program (Starfield, Microsoft Corp., USA) (Schuepbach, Merlo, et al., 2002) was positioned at a distance of one meter to the subject. The examiner observed the performance of the experimental subject at all times during the testing. Speaking, whistling, singing to oneself, chewing or any motor activity other than instructed was not permitted (Schuepbach, Goenner, et al., 2002). However, the 2 MHz transducers were fixed with a headband, so motions of the head did not alter the position of the transducers. This view is supported by published evidence that

Table 1
Sociodemographic and clinical characteristics of the study sample.

	Patients (n = 15)	Healthy subjects (n = 15)	t/χ^2
(a) Sociodemographic variables			
Age	33.20 ± 6.02	33.87 ± 7.68	0.27
Gender (male/female)	10/4	10/5	0.69
Education (yrs)	12.77 ± 2.18	19.17 ± 4.17	5.27***
Parental education (yrs)	13.75 ± 3.05	15.47 ± 3.83	1.33
(b) Clinical variables			
Duration of illness (years)	10.43 ± 5.95	n.a.	n.a.
Number of hospitalizations	4.5 ± 3.7	n.a.	n.a.
In- and outpatients	10/5	n.a.	n.a.
BPRS	36.53 ± 8.07	n.a.	n.a.
BAS	0.73 ± 0.88		
EPS	0.36 ± 0.50		
CGI	4.33 ± 1.16	n.a.	n.a.
Chlorpromazine equivalent dosage (mg/day)	481.71 ± 272.99	n.a.	
(c) Cognitive performance			
TMT-A (sec.)	44.93 ± 21.80	31.00 ± 7.43	2.34*
TMT-B (sec.)	93.20 ± 28.69	66.20 ± 18.19	3.05**

Values are mean ± standard deviation (except ratios).
Abbreviations: BAS – Barnes Akathisia Scale; BPRS – Brief Psychiatric Rating Scale; CGI – Clinical Global Impression Scale; EPS – Simpson-Angus Scale; n.a. – not applicable; sec. – seconds; *t* – *t*-value of independent sample *t*-test with diagnostic grouping as between subject factor; TMT-A and TMT-B – Trail Making Test, Part A and Part B; $\chi 2$ – chi square; yrs – years.
* p = 0.031.
** p = 0.005.
*** p < 0.001.

functional transcranial Doppler is virtually robust to movement artifacts (Knecht et al., 1998; Lohmann et al., 2006). All subjects included in this study had a temporal bone window that allowed bilateral localization of the MCA.

2.3. Stimulus

Participants underwent a standardized briefing. They were instructed about the nature of the paradigm and conducted a practice session. To minimize habituation, both TMTs were applied only *once*. The order of presentation was random and carefully balanced between diagnostic groups.

We administered the TMT as a paper and pencil test. In the TMT-A, subjects had to connect 25 numbers in ascending order (1, 2, 3,...,25). In the TMT-B, numbers (1–13) and letters (A–L) had to be connected alternately in ascending order (1,A,2,B,3, C,...,13,L) (Bowie & Harvey, 2006; Tombaugh, 2004). Subjects had to solve the TMT as quickly and accurately as possible.

In a control task (CT), participants had to connect circles, placed in a 10 by 10 cm square pattern, in a random way. One line had to be drawn at a frequency of 1.0 or 0.5 Hz (paced acoustic signal), in order to reproduce the frequency during the TMT-A (0.89 ± 0.21 Hz) and the TMT-B (0.46 ± 0.15 Hz), respectively. The CT was intended to simulate visuomotor scanning during the TMT, and was placed randomly either before or after each TMT (Supplementum). There was a break of 60 s between the TMT and CT, during which subjects watched the screen saver (Schuepbach, Hell, & Baumgartner, 2005). The examiner silently indicated the start of the task by a hand signal.

2.4. Data collection

2.4.1. Performance

We used completion time as performance measure. For performance accuracy, we obtained error rates as follows: zero errors, one or more errors. Since subjects made no errors during the TMT-A, we restricted analysis of performance accuracy to the TMT-B.

2.4.2. Cerebral hemodynamics

We continuously recorded MFV data during time intervals of interest, integrating MFV data over each cardiac cycle. These data were time-locked to the start and end of each time interval of interest (TMT-A, TMT-B, control A/B, rest) (Misteli et al., 2011). For details of a typical test sequence, see the Supplementum. Offline analysis of MFV comprised the following steps described in a previous study (Misteli et al., 2011): (a) offline export of the digitized MFV (sampling frequency 100 Hz) data to a spreadsheet program (MS-Excel, Microsoft Corp., USA); (b) integration of MFV from 100 Hz sampling to 1 Hz; (c) normalization of digitized data with reference to pre- and post-task rest phases (60 s intervals of rest with 30 s between the first and last 15 s); and (d) relative MFV (relative to the resting state) values were averaged for time intervals of interest and converted to percentage values. Handling of artifacts: Similarly to Duschek et al. (2008), we screened periods of interest for MFV values outside the 60–150% range of the mean MFV recording of a subject. However, due to careful screening of instable signals prior to study inclusion (see Section 2.1), no period of interest had to be discarded.

All MFV values in this paper are *relative* MFV, i.e. the change in cerebral blood flow velocity as compared to the resting phase. Since the fastest performance for the TMT-A and TMT-B was 14 and 28 s, respectively, only these periods were considered for statistical analyses.

2.4.3. Laterality

We calculated the laterality (LA) for both TMTs and control tasks; and the laterality index (LI) on a second wise basis, as described previously (Misteli et al., 2011; Njemanze, 2005):

$$LI' = [(\text{Right MFV} - \text{Left MFV})/(\text{Right MFV} + \text{Left MFV})] \times 100$$

2.5. Statistical analyses

We present data as mean ± standard deviation. The Kolmogorov-Smirnov test was used to test for normal distribution. For categorical data (gender, performance accuracy), the Chi-square test was applied. Independent samples *t*-tests were used to compare age, education and performance between groups.

Group-wise correlation analyses were carried out for the following possible associations, using Pearson's product moment correlation coefficient: (a) Sociodemographic/clinical variables and task performance, (b) performance between TMT-A and TMT-B, (c) medication dosage and performance, and (d) performance and averaged MFV. If data were not normally distributed, we carried out nonparametric correlation analyses with using Spearman's Rho. To avoid inflation of Type II errors, we applied a Bonferroni correction for multiple comparisons, and set the alpha level at a value of 0.017 for these analyses.

Separate repeated-measures multivariate analyses of variance (MANOVAs) were calculated with condition (task vs. control), hemisphere (left vs. right) and time as within-subject factors, diagnostic grouping as between-subject factor, and MFV and LI as dependent variables, respectively. Significant effects were examined by univariate analyses of variance (ANOVA) where appropriate.

As patients with schizophrenia showed a significantly decreased performance, and as we found significantly increased MFV during the TMT-B, we sought to create two diagnostic groups with very similar performance during this task, in analogy to Henseler et al. (2009). Therefore, we divided the TMT-B performance group wise into percentiles. Then, for healthy subjects, we

discarded the best performers who were beyond the 25th percentile, and for patients, we excluded those with a performance above the 90th percentile. The resized groups consisted of 12 healthy subjects and 8 patients and showed an almost identical performance. We carried out statistical analyses as with the entire sample. Details on performance are provided separately in the Supplementum. Furthermore, we carried out multiple correlation analyses using Pearsońs product moment correlation coefficient to examine the association between performance and average MFV. In order to avoid inflation of Type II errors, we set alpha at a level of 0.005.

For data analysis, akathisia was dichotomized into either no or mild forms (subsuming questionable or mild akathisia), and correspondingly also for EPS ratings. The link between those patients with and without akathisia or EPS on overall cerebral hemodynamics during visuomotor activity was assessed using separate repeated measures MANOVA with MFV as the dependent measure, control tasks (control A vs. control B), hemisphere and time as within subject factor, and dichotomized BAS or EPS scores as between subject factor. For statistical analyses, the alpha level was set at 0.05 unless otherwise indicated.

We used SPSS version 22 (IBM Corp.) for statistical analyses, STATA version 13.1. (StataCorp) for Fisher's r to z transformations, and SigmaPlot 11 (Systat Software Inc.) for graphs.

3. Results

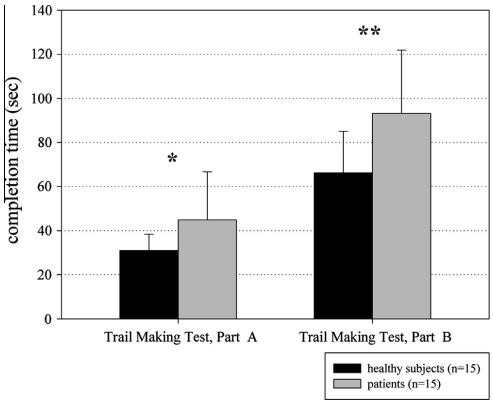
Demographic and clinical characteristics are presented in Table 1. There were no significant differences between groups in terms of age or gender distribution ($p > 0.6$). Healthy subjects had a significantly longer duration of education, although parental education did not significantly differ between diagnostic groups ($p = 0.2$). Akathisia was questionable (nonspecific inner tension and fidgety movements, $n = 3$) or mild (awareness of restlessness in the legs and so forth, $n = 4$) in seven patients, and extrapyramidal symptoms were mostly minimal or mild, and pronounced in one patient. According to the values of psychopathology and illness severity, patients with schizophrenia were chronically ill, with a current moderate severity of illness (Leucht et al., 2006).

3.1. Performance

In comparison to healthy subjects, patients needed significantly more time to complete both TMTs ($F(1,28) = 11.07$, $p = 0.002$, partial $\eta^2 = 0.28$), Fig. 1. Association between the TMT-A and TMT-B: In healthy subjects, increased performance during the TMT-A was, by trend, associated with increased performance during the TMT-B ($r = 0.56$, $p = 0.032$); there was no significant correlation in the patient group ($r = 0.32$, $p = 0.2$). Seven patients and 5 healthy subjects, respectively, made errors during the TMT-B, and this difference was not significant ($\chi^2(1) = 0.56$, $p = 0.3$). In other words: Patients were slower, but there was no significant difference in accuracy between diagnostic groups.

3.1.1. Performance and sociodemographic/clinical variables

For patients, there was no significant correlation between age and performance (TMT-A: $r = 0.14$, $p = 0.63$, TMT-B: $r = 0.08$, $p = 0.78$). However, younger healthy subjects were highly significantly faster than older ones for the TMT-A ($r = 0.82$, $p < 0.001$) (Fig. 2), and by trend also for the TMT-B ($r = 0.48$, $p = 0.07$). Fisher's r to z transformation for the TMT-A and age yielded a z-difference of 0.68 between diagnostic groups. Assuming a power of 0.7 and an alpha of 0.05, we obtained a total sample size of 30, with each group comprising 15 subjects, and thus conclude that there was



sufficient power of the study sample. There were no other significant associations in healthy subjects ($p > 0.3$).

In patients with schizophrenia, the following positive correlations emerged: More severe psychopathology as assessed by the BPRS as well as an increased CGI score were significantly associated with decreased performance during the TMT-B ($r = 0.61$, $p = 0.015$; Spearman's Rho = 0.70, $p = 0.004$, respectively).

Medication and performance: Chlorpromazine equivalents were not significantly associated with performance (TMT-A: $r = 0.40$, $p = 0.1$, TMT-B: $r = -0.27$, $p = 0.3$).

3.2. Mean cerebral blood flow velocity (MFV)

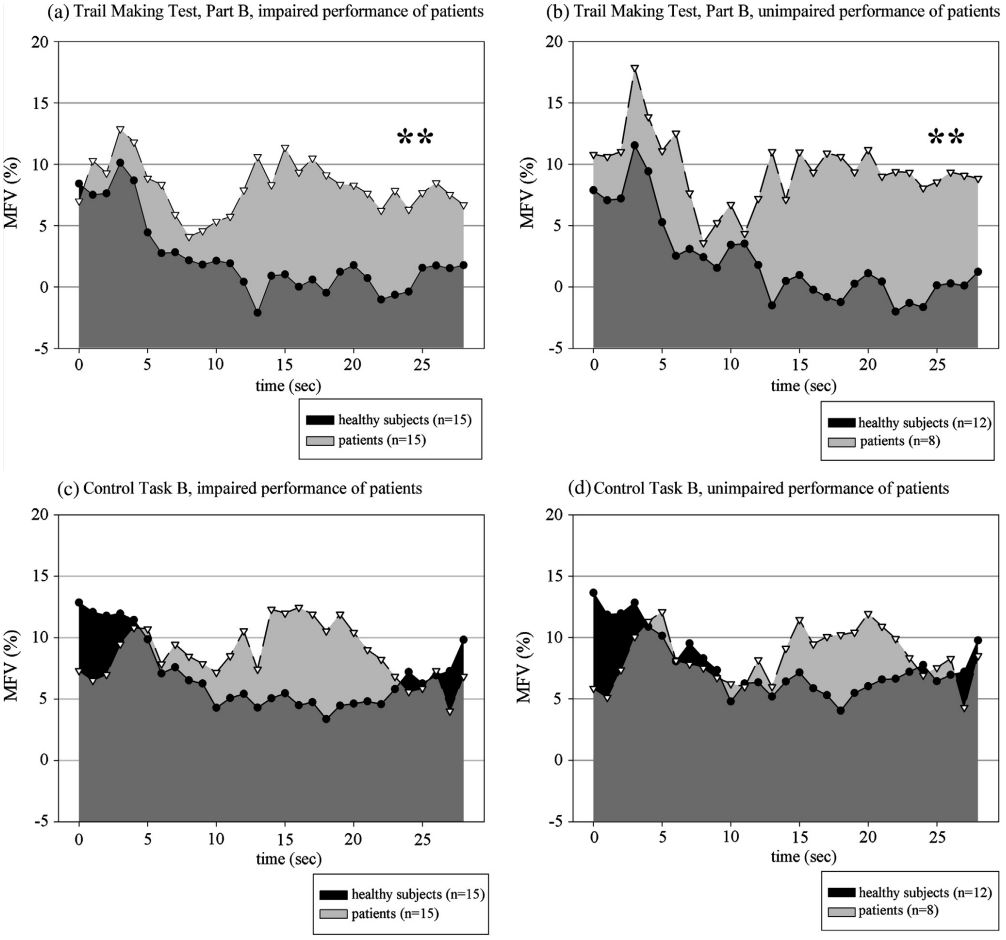
There were no significant differences in MFV standard deviations between diagnostic groups ($p > 0.05$, Supplementum). MFV during the TMT-A and TMT-B: Within the first 3 s, patients showed a strong increase, which was somewhat more pronounced than in healthy subjects, followed by a steady state. Details are presented in Fig. 3.

3.2.1. TMT-A/control task

In both conditions, patients showed an MFV increase as compared to healthy subjects ($F(1,28) = 4.42$, $p = 0.045$, partial $\eta^2 = 0.14$). However, there was no significant group by condition effect ($p = 0.6$). No significant group differences emerged during the initial phase (0–5 s) of the TMT-A.

3.2.2. TMT-B/control task

Multivariate analyses yielded a significant group by condition interaction (Wilk's Lambda = 0.82, $F(1,28) = 6.21$, $p = 0.019$, partial $\eta^2 = 0.18$), and there was a significant MFV increase for patients as compared to healthy subjects for both conditions ($F(1,28) = 5.48$,



rformance (b and d) are presented. ** $p < 0.01$. Abbreviation: MFV, mean cerebral blood flow velocity.

$p = 0.027$, partial $\eta^2 = 0.16$). There were no further significant effects ($p > 0.1$).

(a) *Univariate analyses within groups:* No significant MFV differences between the TMT-B and control B were found in patients ($F(1) = 0.27$, $p = 0.61$, partial $\eta^2 = 0.02$). However, in healthy subjects, there was a highly significant MFV increase during control B as compared to the TMT-B ($F(1) = 19.52$, $p < 0.001$, partial $\eta^2 = 0.58$). In other words, we observed increased MFV for control B in healthy subjects, but not in patients with schizophrenia.
(b) *Univariate analyses between groups:* Compared to healthy subjects, patients showed significantly increased MFV during TMT-B ($F(1,28) = 9.40$, $p = 0.005$, partial $\eta^2 = 0.25$), while no such increase was found during the control task ($F(1,28) = 1.12$, $p = 0.3$, partial $\eta^2 = 0.04$), Fig. 3a and c. Analysis of initial and later phases of the TMT-B yielded non-significant MFV differences initially (0–5 s after the start), followed by significantly increased MFV during the later phase in schizophrenia (data not shown). There were no significant effects of hemisphere ($p > 0.1$).

3.2.3. Unimpaired performance in schizophrenia and MFV

There was no significant difference in performance during the TMT-B in the resized diagnostic groups ($t(18) = 0.05$, $p = 1.0$) (Supplementum), the same applied for the TMT-A ($t(18) = 0.44$, $p = 0.6$). For the TMT-B, multivariate analyses, analogously to Section 3.2.2, showed a highly significant group by condition interaction (Wilk's Lambda = 0.53, $F(1,18) = 16.03$, $p < 0.001$, partial $\eta^2 = 0.47$), and a significant MFV increase for patients as compared to healthy subjects ($F(1,18) = 4.74$, $p = 0.043$, partial $\eta^2 = 0.21$). The results of the univariate analyses corresponded to those of the complete groups:

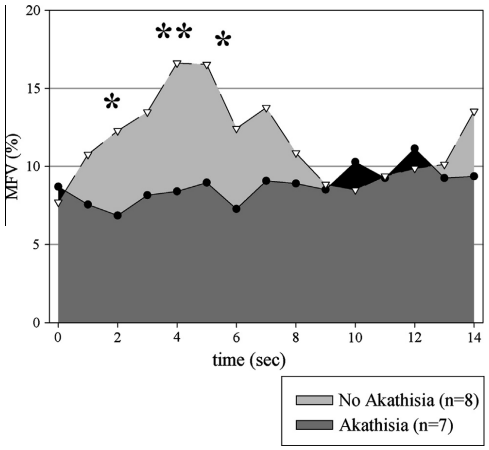
(a) *Univariate analyses within groups:* In patients, there were no significant MFV differences between the TMT-B and control B ($F(1) = 0.60$, $p = 0.5$, partial $\eta^2 = 0.08$); in healthy subjects, there was a highly significant MFV increase during control B as compared to the TMT-B ($F(1) = 29.08$, $p < 0.001$, partial $\eta^2 = 0.73$).
(b) *Univariate analyses between groups:* Patients as compared to healthy subjects showed significantly increased MFV during the TMT-B ($F(1,18) = 11.21$, $p = 0.004$, partial $\eta^2 = 0.38$), while no such increase was found during the control task ($F(1,18) = 0.14$, $p = 0.7$, partial $\eta^2 = 0.01$). The MFV time courses are presented in Fig. 3b and d.

In other words: In schizophrenia, unimpaired performance during the Trail Making Test, Part B, was not associated with normalized CBF. This is in agreement with correlation analyses, in which we found no significant associations between performance and average MFV during this test (left MCA: $r = -0.21$, $p = 0.5$, right MCA: $r = -0.33$, $p = 0.3$).

In both groups, task performance during both Trail Making Tests was not significantly associated with MFV ($p > 0.1$). Moreover, there were no significant effects of hemisphere in above analyses ($p > 0.1$).

3.2.4. Akathisia and MFV

Subjects with mild akathisia showed significantly decreased MFV during control tasks compared to those without akathisia ($F(1,13) = 6.23$, $p = 0.027$, partial $\eta^2 = 0.32$) (Fig. 4). Antipsychotic dosage was not a significant covariate ($F(1,12) = 0.40$, $p = 0.5$, partial $\eta^2 = 0.03$). There were no further significant results, especially EPS was not a significant between-subject factor ($F(1,13) = 0.42$, $p = 0.5$, partial-$\eta^2 = 0.03$).



0.05, ** $p = 0.005$. Abbreviation: MFV, mean cerebral blood flow velocity.

3.3. Lateralization

There were no significant lateralization differences between diagnostic groups ($p > 0.2$) during the TMT-A and TMT-B. This is in line with results of MFV analyses, in which we found no significant effect of hemisphere (see Sections 3.2.2 and 3.2.3).

4. Discussion

Using a controlled study design, we demonstrated that patients with schizophrenia specifically increased cerebral blood flow velocity during the Trail Making Test, Part B. Notably, performance as in healthy subjects did not normalize CBF. Patients with mild akathisia showed decreased CBF during visuomotor activity. Finally, there was no significant association between age and task performance in patients with schizophrenia, in contrast to findings in healthy subjects.

Neuronal activity and cerebral blood flow are tightly coupled (Iadecola, 2004; Wolf, 2015), and the hemodynamic changes in the MCA are therefore a result of the activation of cortical areas. A previous neuroimaging study found distinct activation patterns for successfully solving the TMT-A and TMT-B (Zakzanis, Mraz, & Graham, 2005), such as dorsolateral and medial frontal brain areas. Some of these changes appear to be attributable to visual and motor activity necessary for solving the task (Allen, Owens, Fong, & Richards, 2011; Zakzanis et al., 2005). In our study, these confounders were separately determined by a visuomotor control task - hence, implicitly, also the impact of arterial blood pressure (ABP), heart rate (HR) and PCO2.

4.1. Cerebral hemodynamics during the Trail Making Test, Part B

In schizophrenia, the hemodynamic pattern during the TMT-B differed significantly from healthy subjects. Both groups showed an initial and bilateral increase in MFV. While healthy subjects returned to lower levels, patients showed a second peak and remained on a significantly increased MFV level. Thus, the early cerebral hemodynamic response was nearly identical for both groups. This may be a temporally limited result of initial brain

activation in response to a cognitive stimulus. Similar findings have been previously reported in other tasks (Boban et al., 2014; Duschek et al., 2008; Schuepbach, Boeker, et al., 2007). A further explanation might be that systemic hemodynamics contributes to the initial CBF raise (Duschek, Heiss, Schmidt, Werner, & Schuepbach, 2010), and that this factor is not significantly different between diagnostic groups.

The findings of increased cerebral blood flow velocity in schizophrenia during the TMT-B is in contrast to our expectation of a decreased signal and also in contrast to results from a recently published study using NIRS, in which patients showed decreased prefrontal cortical activation (Fujiki et al., 2013). In line with our study, patients performed worse than healthy subjects. There might be several explanations for the discrepant findings: First, fTCD and NIRS do not measure the same hemodynamic correlate, cerebral blood flow velocity vs. oxygenated/deoxygenated hemoglobin, respectively. It is suggested that cerebral blood flow velocity corresponds to deoxygenated hemoglobin (Kubo et al., 2008). Second, the regions of interest are different: functional transcranial Doppler, as applied in our study, acquires the signal from the middle cerebral artery which itself supplies the lateral part of the cerebral hemispheres (Tatu et al., 1998), also including subcortical structures like the thalamus. On the other hand, NIRS allows regions of interest to be localized more precisely, with the limitation that predominantly cortical areas can be accessed (Fujiki et al., 2013). There is evidence that executive functions such as the Trail Making Test, Part B have several neuroanatomical and neurofunctional networks that, in a simplistic manner, comprise frontal cortical, basal ganglia and thalamic structures (Stuss, 2011); hence not only cortical structures. Third, the performance measure in the study by Fujiki et al. (2013) was not completion time, making a direct comparison of performance measures difficult. Fourth, the Trail Making Test in our study was not repeated in order to avoid training effects. There is evidence that repetition of cognitive tasks alters performance and brain activity (Kelly, Hester, Foxe, Shpaner, & Garavan, 2006).

On the other hand, there is evidence from a functional magnetic resonance imaging study (fMRI) that patients with schizophrenia fail to deactivate brain regions during a word generation task. The authors (John et al., 2011) observed excessive activations of the bilateral caudate nuclei and rostral prefrontal cortices, inferior frontal gyrus, insula, cingulate gyrus and claustrum. Furthermore, Horacek et al. (2006) reported, among others, hypermetabolism in temporoparietal-limbic regions as neurobiological basis of TMT performance in schizophrenia, although this study was restricted to resting CBF.

Hence, we suggest that in schizophrenia, the significant increase in bilateral cerebral blood flow velocity during the TMT-B found in this study either (a) represents an impaired neurovascular response while solving a cognitive task, or (b) is a correlate of failed deactivation of regions within the arterial territory of the MCA. We have previously reported that CBF modulation is blunted in schizophrenia patients (Schuepbach, Weber, et al., 2007).

4.2. Unimpaired performance in schizophrenia and cerebral hemodynamics

An interesting finding of this study is the increased CBF during the Trail Making Test, Part B, which persists despite virtually normal performance of patients with schizophrenia. In a functional imaging study in schizophrenia using a working memory paradigm (Henseler et al., 2009), performance difference was not a significant cofounder of the abnormal fMRI signal in schizophrenia; furthermore, performance matching in that study (Henseler et al., 2009) did not result in alterations of signal differences between schizophrenia patients and healthy subjects. A similar approach was chosen by Pedersen et al. (2012) using the Wisconsin Card Sorting Test, a well-known paradigm of executive functioning. They suggested that patients with schizophrenia show increased brain activity as compared to healthy subjects in order to catch up with normal performance (Pedersen et al., 2012). As pathological performance during the TMT-B was not associated with cerebral blood flow velocity, we suggest that other factors are responsible for the pathological neurovascular response – for example, factors that are inherent to the severity of the disorder such as dysfunctional neuronal integrity, or to secondary effects of medication.

4.3. Cerebral hemodynamics and akathisia

We found decreased CBF during visuomotor activity in patients with mild akathisia, especially at the beginning. Akathisia is one form of extrapyramidal symptoms (EPS) that can arise due to anti-dopaminergic action of antipsychotic medication. One decisive area for this manifestation is the striatum – a structure that is densely populated by dopamine D2 receptors (Agid et al., 2007). In clinical terms, akathisia is a movement disorder with restlessness, and comprises subjective and/or objective symptoms. Akathisia is frequent, with up to 70% of patients who receive antipsychotics suffering from the disorder (Kane et al., 2009). In other words: Akathisia is clinically relevant, and it is sometimes a very disabling and distressing condition. Rather surprisingly, despite its clinical importance, we were unable to find studies investigating CBF or related measures in patients suffering from akathisia. Moreover, no study has investigated the impact of akathisia on systemic hemodynamics in schizophrenia. Hence, it is hard to tell whether CBF during visuomotor activity is substantially cofounded by parameters of systemic hemodynamics in patients with and without akathisia. Interestingly, akathisia was not a significant grouping factor of cerebral blood flow velocity during performance of the TMT-A and TMT-B. This could mean that cerebral hemodynamics while solving a cognitive task is not gravely affected by the presence of mild akathisia. Our observation that performance measures were practically the same between these patient groups (data not shown) is in line with such a notion. However, there is evidence that akathisia can deteriorate cognition (Fervaha et al., 2015; Kim & Byun, 2007). The present data are preliminary in nature, in terms of data analysis and number of subjects. Moreover, akathisia was only mild. It appears quite reasonable to assume that more severe akathisia alters cognition and probably cerebral hemodynamics. Further research is urgently warranted to assess the effects of akathisia on CBF during cognitive effort. Intriguingly, the EPS score of the Simpson-Angus scale (Simpson & Angus, 1970) was not a significant factor of CBF. One possible explanation might be that the distribution and extent of these symptoms were skewed and the sample size simply too small to yield a significant role. A further hypothesis might be that acute EPS and akathisia do not share exactly the same pathophysiological correlate. However, we were unable to find studies on pathophysiological differences between akathisia and EPS. A recent review stated that the pathophysiology of akathisia is unknown (Lohr, Eidt, Alfaraj, & Soliman, 2015). In sum, we propose that decreased CBF in schizophrenia patients with akathisia is a correlate of a more compromised neural system – and potentially a source of decreased performance in this disorder (Pedersen et al., 2012).

4.4. Cerebral hemodynamics during visuomotor scanning

During the TMT-A, both groups showed a similar hemodynamic pattern. There was an initial increase in MFV and a return to lower levels after a few seconds, with patients stabilizing at a slightly

increased level than at resting state. Another Doppler study of the Trail Making Test revealed an initial increase in MFV in healthy subjects (Boban et al., 2014). Increased metabolism has been replicated with functional near-infrared spectroscopy (NIRS) in young and elderly healthy subjects (Muller et al., 2014).

4.5. Performance

In healthy controls, we found a strong correlation between age and declining performance; this was more pronounced for the TMT-A than the TMT-B. In schizophrenia patients, performance was not linked to age. This finding is in line with reports of stable cognitive impairments throughout the course of schizophrenia (O'Carroll, 2000). However, when looking at evidence of cognitive decline in old age in this disorder, it should be kept in mind that the highest age of patients in this study was 43 years (Harvey, Reichenberg, & Bowie, 2006). In accordance with the lack of correlation in performance between the TMT-A and TMT-B in schizophrenia, we suggest that cognitive performance does not reflect the same underlying mechanism as in healthy subjects (Ojeda et al., 2010).

Higher BPRS and CGI scores were associated with decreased performance during the Trail Making Test, Part B, a rather intuitive result that fits well with the available literature (Altamura et al., 2015).

4.6. Limitations

Some limitations of our study are inherent to the Doppler method. The presented MFV values were relative and not absolute values. We did not acquire a direct anatomical image, in contrast to fMRI. However, we have previously shown that, in a very diverse way, fTCD detects significant brain behavior relationships during executive functioning (Schuepbach, Boeker, et al., 2007; Schuepbach, Huizinga, et al., 2009; Schuepbach, Skotchko, et al., 2012). Antipsychotic medication could also influence CBF, a rather complex effect, which is dependent on schizophrenia itself, antipsychotic dose, duration of treatment and other factors (Goozee, Handley, Kempton, & Dazzan, 2014). Although gender is a fundamental confounder of brain physiology (Misteli et al., 2011; Schuepbach et al., 2012), it was not possible to conduct a gender analysis due to the small number of female participants. Clearly, future studies should include a larger number of patients.

Heart rate and arterial blood pressure modulate MFV during cognitive and motor activity (Duschek et al., 2010; Panerai, Eyre, & Potter, 2012). In this study, we implemented a control task intended to tap into a very similar motor and visual activity as elicited during the TMT. From the study of Duschek et al. (2010), we can infer that ABP and HR each contribute about 20% to MFV during a cued reaction time paradigm. In our investigation, MFV in patients did not significantly differ between the TMT-B and the control task. The literature suggests that the ABP fraction exerts a potentially discrepant input on MFV during cognitive activity as compared to simple motor action (Panerai et al., 2012). Hence, ABP appears to be one relevant contribution to increased MFV during cognition as compared to motor activity. Our study yielded significantly increased MFV during the control condition as compared to the TMT-B in healthy subjects, which is accordance with findings from results of a previous publication (Misteli et al., 2011). It remains to be clarified whether a more complex control condition such as in our study provokes an increased ABP fraction on the MFV signal in comparison to the cognitive challenge. Random movements potentially activate the central executive (Annoni & Pegna, 1997). We agree with Panerai et al. (2012) that MFV during cognitive activity should not be used as a sole correlate for mental activity, but instead should be controlled for ABP or corresponding motor and visual activity as carried out in this study. Nonetheless, potentially altering factors such as anxiety symptoms or hypo-/hyperventilation (Giardino, Friedman, & Dager, 2007) could not be observed in any participant. In our study design, we included a control task to compensate for any subtle or undistinguished confounding factors (Feldmann et al., 2006; Misteli et al., 2011).

4.7. Conclusions

Patients with schizophrenia showed a poorer performance while solving the Trail Making Test, Part B and an aberrant cerebral hemodynamic pattern with increased CBF compared to healthy subjects. When performance matching was carried out, cerebral hemodynamics in schizophrenia did not return to normal levels. Mild akathisia was a significant modulator of cerebral hemodynamics during visuomotor activity, leading to decreased CBF in schizophrenia. These results support the notion that schizophrenia has a profound effect on cerebral hemodynamics, especially during the Trail Making Test, Part B, and that performance does not play a significant role. Akathisia alters cerebral hemodynamics during visuomotor activity, and this study raises questions about the influence of akathisia on cerebral blood flow, and whether or not akathisia and other forms of EPS have a distinct pathogenesis. The paucity of available studies using CBF or related measures in schizophrenia and akathisia is striking. These unprecedented results support the notion that fTCD is a unique technique to assess cognitive functioning in diverse populations, because the measurements comprise not only cortical but also subcortical structures. It is especially well suited for individuals who cannot be completely immobilized during measurements.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bandc.2016.09.002.

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Artículo 2: *"Psychopathological Symptom Load and Distinguishable Cerebral Blood Flow Velocity Patterns in Patients with Schizophrenia and Healthy Controls: a functional Transcranial Doppler (fTCD) study"*

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Abstract:

Introduction: Schizophrenia is a severe psychiatric disorder, with executive dysfunction and impaired processing speed playing a pivotal role in the course of the disease. In patients with schizophrenia, neurocognitive deficits appear to be related to alterations in cerebral hemodynamics. It is not fully understood if psychopathological symptom load (i.e. presence and severity of symptoms) is also related to alterations in cerebral hemodynamics. We aim to study the relationship between psychopathological symptom load and cerebral hemodynamics in the Middle Cerebral Artery (MCA) during a cognitive task in patients with schizophrenia and healthy controls.

Methodology: Cerebral hemodynamics in the MCA were examined in 30 patients with schizophrenia and 15 healthy controls using functional Transcranial Doppler (fTCD) during the Trail Making Test (TMT). Psychopathological symptoms were measured using the Escala Breve de Evaluación Psiquiátrica, BPRS (BPRS). Patients were dichotomized according to BPRS scores: mild-moderate (BPRS <41, n=15) or marked-severe (BPRS≧41, n=15). Mean blood flow velocity (MFV) in the MCA and processing speed of the TMT were analyzed. Cerebral hemodynamics were analyzed using the general additional model (GAM) with a covariate analysis of variance (ANCOVA) for group comparisons. Results: Patients and healthy controls were comparable regarding demographics. Patients had a slower processing speed for the TMT-A (patients-severe: 52s, patients-moderate: 40s, healthy-controls: 32s, $p=0.019$) and TMT-B (patients-severe: 111s, patients-moderate: 76s, healthy-controls: 66s, $p<0.001$)). Patients demonstrated differing hemodynamic profiles in both TMTs: TMT- A ($F(6, 1792) = 17$, $p<0.000$); TMT-B ($F(6, 2692) = 61.93$, $p<0.000$), with a delay in increase in MFV and a failure to return to baseline values.

Conclusions: Patients with schizophrenia demonstrated slower speeds of processing during both the TMT-A and TMT-B. The speed of processing deteriorated with increasing psychopathological symptom load, additionally a distinct cerebral hemodynamic pattern in the MCA was observed. Our results further support the view that severity of schizophrenia, particularly psychopathological symptom load, influences performance in neurocognitive tasks and is related to distinct patterns of brain hemodynamics.

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ents-moderate: 76s, healthy-controls: 66s, $p < 0.001$)]. Patients demonstrated differing hemodynamic profiles in both TMTs: TMT- A [$F_{(6, 1,792)} = 17$, $p < 0.000$); TMT-B [$F_{(6, 2,692)} = 61.93$, $p < 0.000$], with a delay in increase in MFV and a failure to return to baseline values.

Conclusions: Patients with schizophrenia demonstrated slower speeds of processing during both the TMT-A and TMT-B. The speed of processing deteriorated with increasing psychopathological symptom load, additionally a distinct cerebral hemodynamic pattern in the MCA was observed. Our results further support the view that severity of schizophrenia, particularly psychopathological symptom load, influences performance in neurocognitive tasks and is related to distinct patterns of brain hemodynamics.

Keywords: transcranial doppler, schizophrenia, symptomalogy, trail making test, cognition, hemodynamics

INTRODUCTION

Schizophrenia is a severe psychiatric disorder which is characterized by hallucinations, delusions and blunted affect (1). Although not part of the diagnostic criteria, cognitive impairment is also a common feature of schizophrenia, often occurring before the onset of the first psychotic episode and continuing throughout the course of the disease (2, 3), with cognitive impairment and executive functions playing a pivotal role for outcome and prognosis, as well as being major determinants of quality of life and well-being (4, 5).

Cognitive impairment and executive function are measured by numerous neuropsychological assessment tools, including the Trail Making Test (TMT)-A and TMT-B. In contrast to other neuropsychological instruments, the TMTs are easy to use; their interpretation is straightforward. Consequently, they are widely used in both research and clinical practice (6, 7). The TMTs are considered to be sensitive to cognitive dysfunction and frontal lobe integrity, assessing graphomotor activity, visual scanning, selective attention, mental flexibility and executive functioning (6, 7). Patients with schizophrenia show impaired performance in the TMT, with deficits in processing speed and inefficient simultaneous processing strategies (6, 8). There is evidence that in patients with schizophrenia, the frontal lobes, particularly the dorsolateral prefrontal cortex (DLPFC), play a pivotal role in executing the TMTs (9, 10).

Cognitive performance is partly determined by the brain's ability to increase blood supply to the areas activated during a cognitive task. Due to the skull's anatomic conditions, the increase in diameter of the cerebral arteries is limited; an increase in cerebral blood supply is achieved by increasing blood flow velocity in the cerebral arteries. Therefore, we consider Mean Flow Velocity (MFV) a valid indicator for brain activity (11, 12). Transcranial Doppler (TCD) is a versatile, non-invasive method for assessing the cerebral arteries' functioning and hemodynamic characteristics (11, 13). TCD provides a continuous measurement of blood flow velocity with high temporal resolution. However, TCD has low anatomical resolution and is not able to deliver a direct brain image. Despite this limitation, TCD has been used to study physiological and hemodynamic conditions in several neurological diseases and psychiatric disorders (11, 13, 14). The neurocognitive impairment in schizophrenia appears to be related to alterations in blood flow in several brain areas, including the DLPFC (15–18).

The middle cerebral arteries (MCA) irrigate the brain's lateral hemispheres, including the DLPFC, subcortical structures, basal ganglia and the striatum (19). A number of these structures, principally the DLPFC, striatum and thalamus, are activated during the TMT (17), making fTCD a suitable method for the physiological and hemodynamic assessment of brain activity in these areas during a neurocognitive task (20). Previous studies using functional TCD (fTCD) in patients with schizophrenia and healthy controls showed clear differences in the MCA hemodynamic pattern during the TMT (14); to what extent there are also hemodynamic differences between those affected with schizophrenia, in relation to the number and severity of symptoms (i.e., symptom load) is thus far unexplored.

Our study aims to determine the relationship between psychopathological symptom load (in healthy controls and patients with schizophrenia) and cerebral hemodynamics in the MCA during a neurocognitive task. New results may contribute to increased use of fTCD as an assessment tool in neuropsychiatric disorders, particularly schizophrenia. We examined cerebral blood flow velocity during the TMT in patients with schizophrenia and healthy controls, using a visuomotor control task to compensate for hemodynamic changes resulting solely from the motor and visual activities during the TMT.

MATERIALS AND METHODS

Subjects

Thirty patients fulfilling the WHO-ICD 10 (21) criteria for schizophrenia participated in this study; they were age and sex-matched with 15 healthy controls. The healthy controls had no medical, neurological or psychiatric condition at the time of examination; they were recruited for a previous study conducted by our research group, using the same examination protocol and equipment (14). All participants were right-handed. All patients with schizophrenia were taking antipsychotic medication. The following exclusion criteria applied to patients: 1. affective disorder (according to ICD-10: F3); 2. organic brain disorder (according to ICD-10: F0); 3. active substance abuse disorder (according to ICD-10: F1) in the 3 months before inclusion; 4. unstable neurological; or 5. medical condition. Basic demographic characteristics of the participants were collected. Besides the participants' education, we included the mean education of their parents to disentangle poor educational performance attributable to early onset of the disorder or familial accumulation. The competent ethics committee approved the study, all participants provided written informed consent.

Clinical Assessment and Psychometric Measurements

Within 24 h of the fTCD measurement, psychopathological symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS) (22), overall clinical severity of symptoms was assessed using the Clinical Global Impression Scale (CGI) (23). For this study, the daily antipsychotic dose was converted to chlorpromazine equivalents according to current guidelines (24, 25). Effects of antipsychotics on the extrapyramidal system were examined using the Simpson- Angus Scale (SAS) (26) and the Barnes Akathisia Scale (BAS) (27, 28).

The BPRS is one of the most frequently used scales to measure psychopathology in patients with schizophrenia, systematically assessing the presence and severity of symptoms. It consists of 18 single items assessing different symptoms. Each item is evaluated according to a seven-item Likert scale, ranging from "1" (not present) to "7" (extremely severe). Thus, the sum score ranges from 18 to 126. We used the BPRS sum score as a measure of the psychopathological symptom load. Participants were classified according to BPRS sum scores, as "non-affected" or healthy controls; those with a diagnosis of schizophrenia and a BPRS score below 41 points were classified as "mild-moderate," those with a BPRS score of 41 points or more were classified as "marked- severe"(29).

Equipment and Cerebral Blood Flow Measurements

Doppler measurements were performed using a Multi-Dop X instrument (DWL Elektronische Systeme GmbH, Sipplingen-Germany). Two dual 2 MHz transducers were attached and fixed with a headband. Both MCAs were insonated at depths of 48–55 mm through the temporal bone window. The 2 MHz transducers were fixed with a headband, so motion artifacts of the head did not alter the position of the transducers. This approach is supported by published evidence demonstrating that functional transcranial Doppler is fairly robust to movement artifacts (30). As indicated by measurement artifact data, we screened for MFV values outside the 60–150% range of the mean MFV recording of a subject before, after and during the cognitive task.

Cerebral Hemodynamics and Cognitive Task

Subjects were asked to abstain from caffeine and nicotine consumption 2 h prior to the examination (31). MFV data were continuously recorded during the psychological paradigm, integrating MFV data for each cardiac cycle. Participants underwent a standardized briefing. They were instructed about the nature of the study and the psychological paradigm. To reduce learning effects, the cognitive task was presented only once. We administered the TMTs as a paper and pencil test. In the TMT-A, subjects had to connect 25 numbers in ascending order (i.e., 1, 2, 3,..., 25). In the TMT-B, participants had to connect numbers (1–13) and letters (A–L) alternately in ascending order (i.e., 1, A, 2, B, 3, C,..., 13, L). Subjects had to solve the TMTs as quickly and accurately as possible. In the control task participants were asked to randomly connect circles placed in a 10 by 10 cm square. Lines had to be drawn at a pace of 1.0 or 0.5 Hz to simulate the pace of the TMT-A (0.89+−0.21 Hz) and the TMT-B (0.46+−0.15Hz). The control task simulates visuomotor scanning during the TMTs. The control task was placed randomly before or after each TMT, with a break of 60 s between each task.

Statistical Analysis

Data are presented in tables using simple descriptive statistics (mean, standard deviation, percentages). For the analysis of group differences, specific statistical tests were performed. Continuous data were analyzed using a univariate analysis of variance (ANOVA), with a secondary *t*-test to evaluate model differences. The chi-square test was applied to categorical data. A *post hoc* power analysis was conducted, using the effect sizes for differences in completion time between the TMT-A and TMT-B.

For the purposes of analysis, the MFV consisted of the following elements, following procedures used in a previous study (20): (a). integration of MFV from 100 Hz sampling to 1 Hz; (b). normalization of digitized data with reference to pre-and post-task rest phases (60s intervals of rest with 30s between the first and last 15s); and (c) relative MFV (relative to resting state) values, averaged and converted to percentage values. All MFV values in this paper are relative MFV, i.e., cerebral blood flow velocity change compared with resting phase values. For analysis of the TMT-A and B, the time to be analyzed was dictated by the time required by the fastest participant to complete the task.

The general additional model (GAM); was used for graphical representation, as well as to statistically evaluate the change in mean flow velocity over time (in seconds), controlled for side and sex. The advantage of non-parametric tests, such as the general additional model, lies in their greater flexibility regarding assumptions about data (32–34). The GAM allows for regression and weight analysis at both fixed and random variable level (or for discrete and continuous variables) (33). Using a non-parametric test allows for a realistic visual comparison of flow velocity, facilitating the inference of its clinical relevance (35, 36). Accordingly, a better representation of dynamic and inter-dependent results such as blood flow is provided. However, the mathematical and statistical analysis and consequently, comparison of the GAMs outcomes is more complex (34, 37). Therefore, a covariate analysis of variance (ANCOVA) was used to evaluate differences in the GAM of blood flow velocity obtained for each group and side. Thus, allowing us to determine whether a statistical difference between the hemodynamic curves was demonstrated., A pairwise-comparison was conducted to determine the time frames in which the curves differed from one another.

RESULTS

Demographics and Clinical Characteristics

Patients and control subjects were comparable regarding age, sex and years of parent's education. Years of own education for those with schizophrenia was significantly shorter than healthy controls, with no difference between severity groups. Patients with a marked-severe psychopathological symptom

load obtained significantly higher CGI-S scores than those with moderate symptomatology [3.60 ± 1.06 vs. 5.20 ± 0.68, $F_{(1, 28)} = 24.44$, $p < 0.001$]. The duration of illness and hospitalization rates did not differ significantly between patient groups. Each participant with a diagnosis of schizophrenia had an antipsychotic prescribed, some two. Most antipsychotics prescribed were second-generation antipsychotics. There were no significant differences regarding the antipsychotics prescribed (data not shown) and dose (as chlorpromazine equivalents). Furthermore, the rate of extrapyramidal motor symptoms and akathisia was also similar (see **Table 1**). The *post hoc* power analysis reached a power of 1-ß of 0.99.

TMT Performance

In comparison to healthy controls, patients with schizophrenia required significantly more time to complete both TMTs. Furthermore, more severely ill patients took significantly longer to complete the test than those classified as mild-moderately ill; TMT-A [patients-severe: 52.3 ± 30.8; patients-moderate: 40.2 ± 12.7; healthy-controls: 31.0 ± 7.4, $F_{(2, 42)} = 4.38$, $p = 0.019$] and TMT-B [patients-severe: 66.2 ± 18.9; patients-moderate: 75.5 ± 22.9; healthy-controls: 111.1 ± 20.9, $F_{(2, 42)} = 19.08$, $p < 0.001$]. Since the fastest performance on the TMT-A was 20s, and for the TMT-B 30s, these are the time periods considered for statistical analysis. There was no statistically significant difference between groups regarding the rate of errors on the TMTs (see **Table 1**).

Mean Cerebral Blood Flow Velocity During the TMT-A

For healthy-controls, there was a significant change in MFV over time [$F(s)_{(3.991, 4.912)} = 15.43$, $p < 0.001$], with a hemispheric difference in MFV [$F_{(1, 266)} = 10.55$, $p = 001$]; in the *post hoc* pairwise analysis we identified that the hemispheric (right > left) difference was only significant for the first 10 s of the measurement period. For those mildly-moderately affected, there was also a change of MFV over time [$F(s)_{(7.403, 8.356)} = 6.707$, $p < 0.001$], we did not find a hemispheric difference in the MFV [$F_{(1, 266)} = 0.979$, $p = 0.323$]; with the *post hoc* pairwise analysis also demonstrating no hemispheric differences at any time point. Finally, in those with higher psychopathological symptom load, we found a change in MFV over time [$F(s)_{(8.087, 8.767)} = 9.746$, $P < 0.001$], with a hemispheric difference (left > right) in the MFV [$F_{(1, 266)} = 7.71$, $p < 0.001$]; the *post hoc* pairwise comparison indicating that this difference was only significant during the middle phase of the measurement (s 9 to 14). There is a statistically significant difference between the curves of the three groups under comparison [$F_{(6, 1,792)} = 17$, $p < 0.000$].

Group differences and hemispheric differences in MFV during the TMT-A are graphically represented (**Figure 1**). The mean flow velocity in both middle cerebral arteries shows a similar pattern for all three groups during the TMT-A; in the first 5–10 s, there is an increase in blood flow followed by a steady decrease. Healthy controls reached the peak of blood flow 2 s faster than those with schizophrenia. Furthermore, those with marked-severe psychopathological symptom load show a delayed and higher increase and a slighter decrease in the blood blow velocity in the left MCA.

Mean Cerebral Blood Flow Velocity During the TMT-B

Healthy controls demonstrate a change of MFV over time [$F(s)_{(4.890, 5.952)} = 23.04$, $p < 0.001$], without a hemispheric difference in MFV [$F_{(1, 406)} = 0.693$, $p = 0.405$] during the TMT-B. Those mild-moderately affected also showed a change in MFV over time [$F(s)_{(8.106, 8.779)} = 18.62$, $p < 0.001$], without a hemispheric difference in MFV [$F_{(1, 406)} = 1.117$, $p = 0.291$], the *post hoc* pairwise comparison, however, demonstrated a difference for the first eight s of the measurement period. Those more severely affected also demonstrated a change in MFV over time [$F(s)_{(5.750, 6.882)} = 3.888$, $p < 0.001$], and a hemispheric difference in MFV [$F_{(1, 406)} = 28.42$, $p < 0.001$]; with the pairwise *post hoc* comparison revealing a significant difference for the first 5 s and in the middle phase of the measurement period (s 18 to 21). There is a statistically significant difference between the curves of the three comparison groups [$F_{(6, 2,692)} = 61.93$, $p < 0.000$).

Group differences and hemispheric differences in MFV during the TMT-B are graphically represented (**Figure 2**). Healthy controls reach a peak in blood flow after 5 s, with a continuous decrease. Those with mild-moderate psychopathological symptom load also reach the first peak after 7 s, followed by a slight decrease and a second lower peak. Finally, those with more severe schizophrenia show a discrepancy between both MCAs. Both MCAs form two peaks, the first just a few seconds after beginning the task, the second after 20 s. The right MCA shows a lower increased MFV, demonstrating a lower initial peak than the left MCA 20 s after beginning the task.

DISCUSSION

Using an age and gender-balanced sample population, including patients with schizophrenia and healthy controls, we examined the mean blood flow velocity during the TMT-A and TMT-B in the middle cerebral artery using functional transcranial doppler. In our study, participants with a higher psychopathological symptom load (represented by higher BPRS scores) demonstrated slower processing speed (with similar accuracy) during the TMT-A and TMT-B, compared with participants with fewer symptoms and healthy controls. The hemodynamic pattern also demonstrated a clearly distinguishable profile between patients with schizophrenia and healthy controls. The differences were more marked in those with higher symptom severity and when the complexity of the cognitive task increased (i.e., TMT-B over TMT-A). In summary, our results demonstrate a relationship between psychopathological symptom load, cognitive demand, decreased processing speed and distinct hemodynamic patterns in the MCA during the TMT-A and TMT-B.

Healthy controls in our study demonstrate in both the TMT-A and TMT-B, an initial increase in cerebral blood flow, which returns smoothly to baseline values, thus reproducing previous

TABLE 1 | Demographic and clinical characteristics of the sample.

	Non- affected *N* = 15	Mild-moderate *N* = 15	Marked-severe *N* = 15		
Demographic Variables				Statistics	*p*
Age (in years)	33.87 (7.68)	34.05 (7.73)	32.40 (5.38)	$F_{(2, 42)} = 0.222$	0.80
Sex (male/female)	10/5	10/5	12/3	$X^2_{(2, 45)} = 0.865$	0.65
Education (in years)	19.17 (4.17)[a]	13.07 (2.60)[a]	13.10 (2.48)[a]	$F_{(2, 42)} = 18.313$	<0.001
Parents' Education (in years)	15.47 (3.83)	14.70 (3.00)	13.97 (3.03)	$F_{(2, 42)} = 0.769$	0.47
Clinical variables					
BPRS	–	30.27 (4.91)[b]	43.73 (3.67)[b]	$F_{(1, 28)} = 72.421$	<0.001
CGI-S	–	3.60 (1.06)[b]	5.20 (0.68)[b]	$F_{(1, 28)} = 24.436$	<0.001
Chlorpromazine equivalent dosage (mg/d)		531.67 (165.69)	543.33 (176.14)	$F_{(1, 28)} = 0.035$	0.85
EPS	–	3.47 (2.10)	4.93(7.91)	$F_{(1, 28)} = 0.481$	0.49
BAS	–	0.53 (0.74)	1.07 (0.96)	$F_{(1, 28)} = 2.89$	0.10
Duration of illness (in years)	–	8.67 (6.91)	12.20 (4.04)	$F_{(1, 28)} = 2.922$	0.09
Number of hospitalizations	–	3.47 (2.03)	5.13 (4.70)	$F_{(1, 28)} = 1.587$	0.22
Cognitive performance					
TMT-A (duration in seconds)	31.00 (7.43)[c]	40.20 (12.66)[c]	52.27 (30.84)[c]	$F_{(2, 42)} = 4.388$	0.019
TMT-B (duration in seconds)	66.20 (18.89)[c]	75.53 (22.98)[c]	111.13 (20.99)[c]	$F_{(2, 42)} = 19.085$	<0.001

Pairwise comparison: [a]non-affected > mild-moderate and marked-severe; [b]marked-severe > mild-moderate: [c]marked-severe < mild-moderate < non-affected.

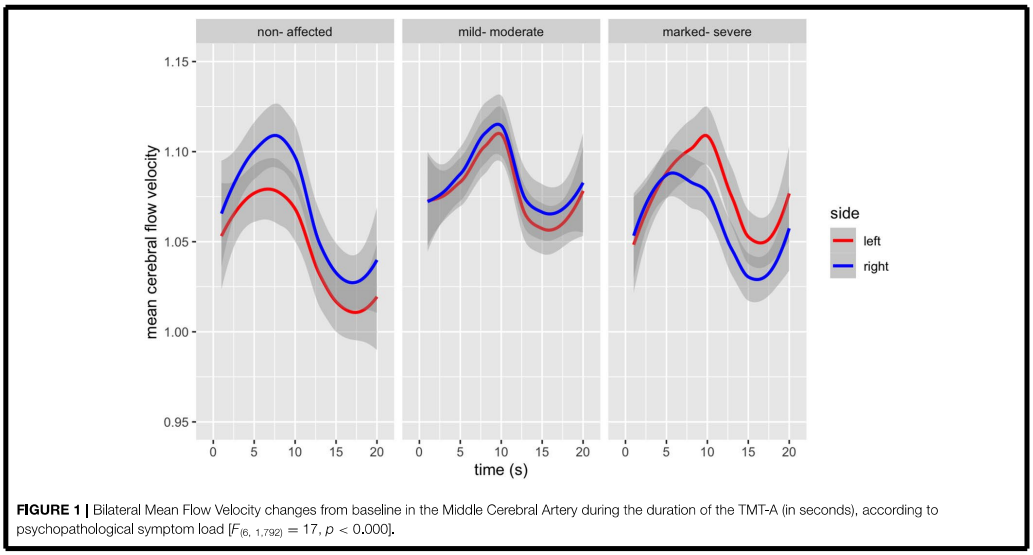

FIGURE 1 | Bilateral Mean Flow Velocity changes from baseline in the Middle Cerebral Artery during the duration of the TMT-A (in seconds), according to psychopathological symptom load [$F_{(6, 1,792)} = 17$, $p < 0.000$].

findings in healthy subjects (38). Patients with schizophrenia fail to reproduce this pattern. Firstly, the increase in MFV is delayed; secondly, the MFV fails to return to baseline values. The differences in the hemodynamic pattern for patients with schizophrenia are accentuated, as psychopathological symptom load and cognitive demand increases (i.e., TMT-B over TMT-A). Processing speed may mediate the demonstrated differences in hemodynamic pattern according to symptom severity and cognitive demand for the TMT-A and TMT-B. This lends further support to the notion that neuronal activity and cerebral blood flow are closely coupled; with MFV resulting from the activation of (or correspondingly the failure to deactivate) cortical areas in the MCA's irrigation territory (9, 12, 19, 39, 40). Patients with schizophrenia demonstrate increased brain activity (as indicated by a higher MFV) for lower performance (i.e., slower processing speed) compared to healthy controls (16).

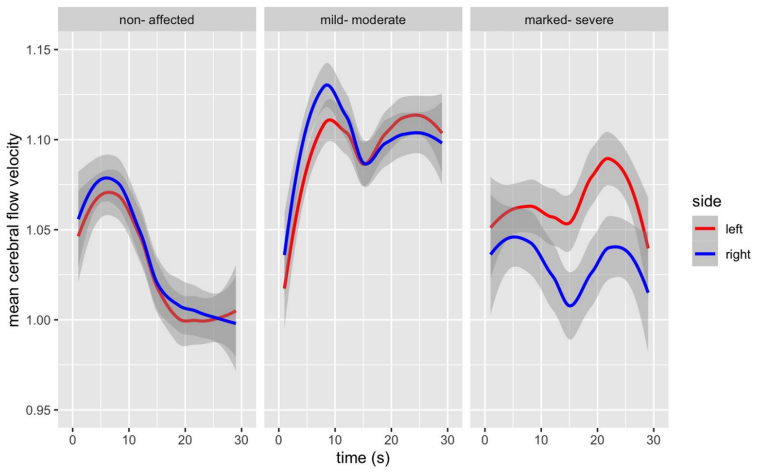

FIGURE 2 | Bilateral Mean Flow Velocity changes from baseline in the Middle Cerebral Artery during the duration of the TMT-B (in seconds), according to psychopathological symptom load [$F_{(6,\ 2,692)} = 61.93$, $p < 0.000$].

Neuroimaging studies demonstrate different brain activation patterns for the TMT-A and TMT-B. In the case of the TMT-A, areas involved in graphomotor speed, visual scanning, and selective attention are activated, whereas for the TMT-B, activated areas relate to mental flexibility and executive functioning (8). Previous findings also report a positive correlation between the TMT-B and hemodynamic activity in the MCA; this may be due to activation of the DLPFC, temporal cortex, basal ganglia and the thalamus during the TMT-B (17, 18). Several of these neuroanatomical areas are also involved in psychopathology and the neurocognitive anomalies related to schizophrenia (14, 41). Studies (including ours) using fTCD demonstrate a correlation between performance and hemodynamic patterns (14–16). This lends support to the view that factors inherent to schizophrenia as well as to other conditions characterized by executive dysfunction, such as dysfunctional neuronal integrity, accelerated white matter aging, hypoperfusion and increased vascular resistance (42–45) may play a role. Since our sample was matched for age and gender, we cannot make any inferences regarding the effects of aging on our results. In the absence of a direct anatomical image, taking into account that the irrigation territory of the MCA is extensive, our findings in this respect are not conclusive.

Our study has some other limitations which must be taken into account in order to better understand and interpret our findings. The lack of further neurocognitive assessments limits our results to the cognitive abilities measured by the TMTs. Taking into account that patients and healthy controls showed similar error rates (i.e., both were accurate), the main difference between the subsamples is processing speed. Medication, particularly antipsychotics, can impair cognitive performance, whether directly or through side effects (46–50), Furthermore, they can also influence hemodynamics (47). In our design, we did not directly control for this potentially confounding factor. Nonetheless, we did not find a difference regarding the dose and side effects of antipsychotics among patients with schizophrenia. Those with a higher psychopathological symptom load had a longer course of the disease with higher rates of hospitalization, which may be related to more severely impaired cognitive performance (51, 52). The influence of systemic circulation on cerebral blood flow, especially heart rate and arterial blood pressure, is controlled for using a random motor activity (53, 54). The control task aims to compensate for subtle alterations in circulation and other confounding factors through relative values compared to resting phase values before and after the paradigm (53). Furthermore, all participants were medically and neurologically stable, with no circulatory anomalies at the time of the study. Other potential confounders, such as anxiety, hypo- or hyperventilation (55), were not observed during the measurement procedure.

In summary, patients with schizophrenia performed less satisfactorily on both TMTs. Performance deteriorated with increasing symptom load, parallel with a distinct cerebral blood flow pattern in the MCA. Our results further support the view that schizophrenia, particularly symptom load and thus severity, influences performance in neurocognitive tasks, whilst being related to distinct brain hemodynamic patterns. Furthermore, these results support the use of fTCD as a brain imaging

technique capable of studying brain hemodynamics during neurocognitive tasks.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Kantonale Ethikkommission of Zurich. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SE and DS conceived the presented idea, carried out the experiment, and analyzed the results and prepared the manuscript. JB and ES aided in interpreting the results and supervised the manuscript. KR and SV contributed to the interpretation of the results. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Artículo 3: *"Functional Transcranial Doppler: selection of methods for statistical analysis and representation of changes in flow velocity"*

Referencia de la Fuente:

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doi:10.1002/hsr2.400

Abstract:

Introduction: Transcranial Doppler (TCD) is method used to study cerebral hemodynamics. The analysis majority of TCD studies are conducted at group level, pooling change in flow velocity over several subjects. Analysis of variance are the most frequently applied statistical methods However, due to the dynamic nature of flow velocity, non- parametric tests, may allow for a better representation of results.

Methods: During a visuo-motor task, the mean flow velocity (MFV) in the middle cerebral artery (MCA) in healthy-subjects was measured using TCD. All MFV values were converted to relative values, i.e. compared with resting values. The results obtained were analyzed using the general linear model (GLM) and the general additional models (GAM). Both methods of analysis were compared against with each other.

Results: The sample comprised 30 healthy participants, aged 33.87±7.48 years; 33% females. The MFV for the first 20 seconds was 1.06±0.07 in the right-MCA and 1.08±0.07 in the left-MCA. Both MCAs showed a steady increase in MFV, returning to resting state. GL- and GA-Models showed a statistically significant change in MFC (GLM: $F(2, 3598) = 16.76$, $p<0.001$; GAM: $F(2, 3598) = 21.63$, $p<0.001$); as well as differences in hemispheric side and gender. Comparing the models using a Chi-square test for goodness of fit yields a significant difference $X2 (9.9556) = 0.6836$, $p= <0.000$. With a superiority of the models using GAM. Discussion GLM and GAM of the MFV yielded similar results; the model using the GAM resulted in a better measurement of fit. The GAM's advantage becomes clearer when the mean flow velocity curves are visualised; yielding a more realistic approach to brain hemodynamics, thus allowing for an improvement in interpretation of the mathematical and statistical results.

Conclusion: Our results demonstrate the utility of the GAM for the analysis of hemodynamic measurements.

Factor de Impacto: 1.56 (2020)

RESEARCH ARTICLE

Functional transcranial Doppler: Selection of methods for statistical analysis and representation of changes in flow velocity

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Abstract

Introduction: Transcranial Doppler (TCD) is a method used to study cerebral hemodynamics. In the majority of TCD studies, regression analysis and analysis of variance are the most frequently applied statistical methods. However, due to the dynamic and interdependent nature of flow velocity, nonparametric tests may allow for better statistical analysis and representation of results.

Method: The sample comprised 30 healthy participants, aged 33.87 ± 7.48 years; with 33% (n = 10) females. During a visuo-motor task, the mean flow velocity (MFV) in the middle cerebral artery (MCA) was measured using TCD. The MFV was converted to values relative to the resting state. The results obtained were analyzed using the general linear model (GLM) and the general additional model (GAM). The fit indices of both analysis methods were compared with each other.

Results: Both MCAs showed a steady increase in MFV during the visuo-motor task, smoothly returning to resting state values. During the first 20 seconds of the visuo-motor task, the MFV increased by a factor of 1.06 ± 0.07 in the right-MCA and by a factor of 1.08 ± 0.07 in the left-MCA. GLM and GAM showed a statistically significant change in MFV (GLM:$F(2, 3598) = 16.76$, $P < .001$; GAM:$F(2, 3598) = 21.63$, $P < .001$); together with effects of hemispheric side and gender (GLM:$F(4, 3596) = 7.83$, $P < .005$; GAM:$F(4, 3596) = 2.13$, $P = .001$). Comparing the models using the χ^2 test for goodness of fit yields a significant difference χ^2 $(9.9556) = 0.6836$, $P < .001$.

Conclusions: Both the GLM and GAM yielded valid statistical models of MFV in the MCA in healthy subjects. However, the model using the GAM resulted in improved fit indices. The GAM's advantage becomes even clearer when the MFV curves are visualized; yielding a more realistic approach to brain hemodynamics, thus allowing for an improvement in the interpretation of the mathematical and statistical results. Our results demonstrate the utility of the GAM for the analysis and representation of hemodynamic parameters.

Stefan Vetter and Daniel Schuepbach these authors have contributed equally to this work.

/10.1002/hsr2.400

KEYWORDS
functional Transcranial Doppler (fTCD), general additional model (GAM), general linear model (GLM), healthy participants, hemodynamics, statistical analysis

1 | INTRODUCTION

Transcranial Doppler (TCD) is a non-invasive imaging method, with high temporal resolution. It is robust, less expensive, and easier to use than other neuroimaging techniques used to assess cerebral blood flow.[1,2] One drawback of TCD, however, is the lack of a direct neuroanatomical image.[1,2] Over the past few decades, TCD has been used to study cerebral hemodynamics in the main cerebral arteries[1,3] in a wide range of neurological and psychiatric conditions, thereby increasing our knowledge of the pathophysiological anomalies of such disorders.[1,4-7] Furthermore, it is also used to refine diagnostic and prognostic approaches in conditions such as stroke, vascular cognitive impairment, and vascular depression.[8-10]

The general linear model (GLM) can accommodate both quantitative and categorical variables in a mathematical model. The label "linear modelling" has traditionally been used to refer to regression analysis; however, technically ANOVAs are particular instances of the GLM.[11] The suitability of the GLM for many different types of study design accounts for its widespread use in a wide range of research areas, including psychology, medicine, and biology. The majority of studies of hemodynamics employing TCD use the GLM (as either regression modeling or analysis of variance) for statistical analysis; analysis is generally conducted at group level, pooling change in flow velocity over several subjects.[1,2,4,5] Due to the dynamic nature of flow velocity and its dependence on previously achieved velocity, the graphic representation of a linear model may be counter-intuitive. Nonparametric tests, including time-series analysis and the general additional model (GAM), allow for a better representation of dynamic and interdependent results; however, their mathematical and statistical analysis is more complex than for the GLM and therefore comparison is more demanding.[11,12]

The aim of this study is to improve the statistical analysis and representation of the hemodynamic parameters obtained using functional TCD. During a visuo-motor control task, the mean flow velocity (MFV) in the middle cerebral artery (MCA) in healthy subjects was measured using TCD. The results obtained were analyzed using the general linear regression and the general additional models. The results of both methods of analysis were compared with each other in terms of model fit and interpretability. Analyzing dynamic and interdependent variables such as flow velocity, we expect nonparametric statistical analysis such as the GAM to outperform parametric methods such as the GLM regarding statistical modeling and interpretability of the data.

2 | METHODS

2.1 | Sample population

Thirty healthy right-handed subjects with no medical, neurological, or psychiatric condition at the time of examination participated in this study. The participants had a mean age of 33.87 ± 7.48; 33% (n = 10) females. All participants were native German speakers, with a mean education of 19.17 ± 4.06 years and average intelligence of IQ 127.60 ± 8.13 as measured using the multiple-choice vocabulary intelligence test [German: Mehrfachwahl-Wortschatz-Intelligenztest: MWT-A].[13,14] The ethics committee of the Canton of Zurich-Switzerland approved the study (BASEC: 2019-00814), and all participants provided written informed consent.

2.2 | Equipment and cerebral flow measurements

Doppler measurements were performed using a Multi-Dop X instrument (DWL Elektronische Systeme GmbH, Sipplingen—Germany). Two dual 2 MHz transducers were used to insonate both MCAs at depths of 48-55 mm through the temporal bone window.[15] The transducers were fixed with a headband, so motions of the head did not alter the position of the transducers. As indicated by measurement artifact data, we screened for MFV values outside the 60% to 150% range of the mean MFV recording of a subject. This approach is supported by published evidence, demonstrating that functional TCD is robust to position and movement artifacts.[16,17]

2.3 | Visuo-motor task and cerebral hemodynamics

Caffeine and nicotine can influence brain hemodynamics; therefore, subjects were asked to abstain from the consumption of both 2 hours prior to examination.[18] Vital parameters, including respiratory frequency, heart rate, and blood pressure, were measured before placing and after removal of the transducers. All participants had normal vital parameters; no signs of anxiety or distress were observed.[19,20] MFV data were recorded continuously before, during, and after the visuo-motor task, integrating MFV data for each cardiac cycle. In a paper-pencil visuo-motor task, participants were asked to randomly connect circles (placed in a 10 by 10 cm square) with lines. Lines had to be drawn at a pace of 1.0 Hz. This task simulates the visual scanning and hand movements, which usually occur during a neuropsychological paper-pencil test, thus controlling for neurocognitive effort.[21-25]

2.4 | Statistical analysis

For the purposes of analysis, the MFV was converted to values relative to steady state, following procedures used in previous

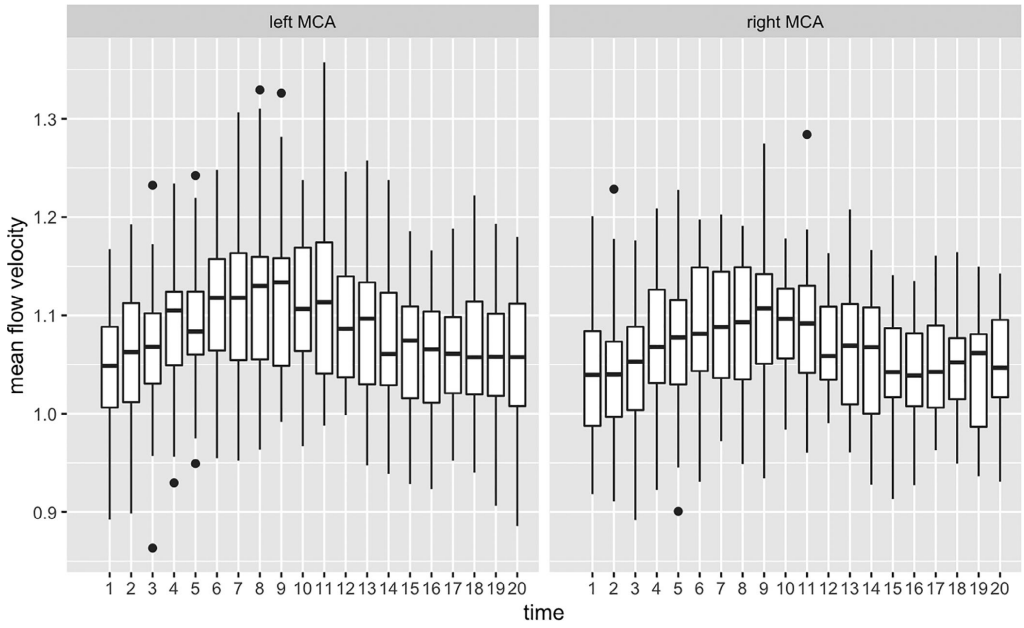


FIGURE 1 Distribution of measured mean flow velocity (MCA, middle cerebral artery)

studies[23,24,26]: (a) integration of MFV from 100 Hz sampling to 1 Hz; (b) normalization of digitized data with reference to pre-and post-task rest phases (60 seconds intervals of rest with 30 seconds between the first and last 15 seconds); and (c) relative MFV values (relative to the resting state) were averaged and converted to percentage values. All MFV values in this article are relative MFV, that is, the change in cerebral blood flow velocity compared with resting phase values.[16,24] The visuo-motor task comprised a time frame of at least 20 (range 20 to 22) seconds for all participants; thus, the first 20 seconds will be considered for analysis.

Data are presented in tables, using simple descriptive statistics (mean, SD, percentages). The data were fitted in a general linear model (GLM) and a general addition model (GAM), to model the change in MFV during the visuo-motor task (ie, time). The fit indices (Akaike information criterion—AIC; generalized cross-validation—GCV; and R^2) of the models were extracted for comparison, and an ANOVA was performed to assess the statistical differences between models. Finally, both models were presented visually.

3 | RESULTS

3.1 | Hemodynamics

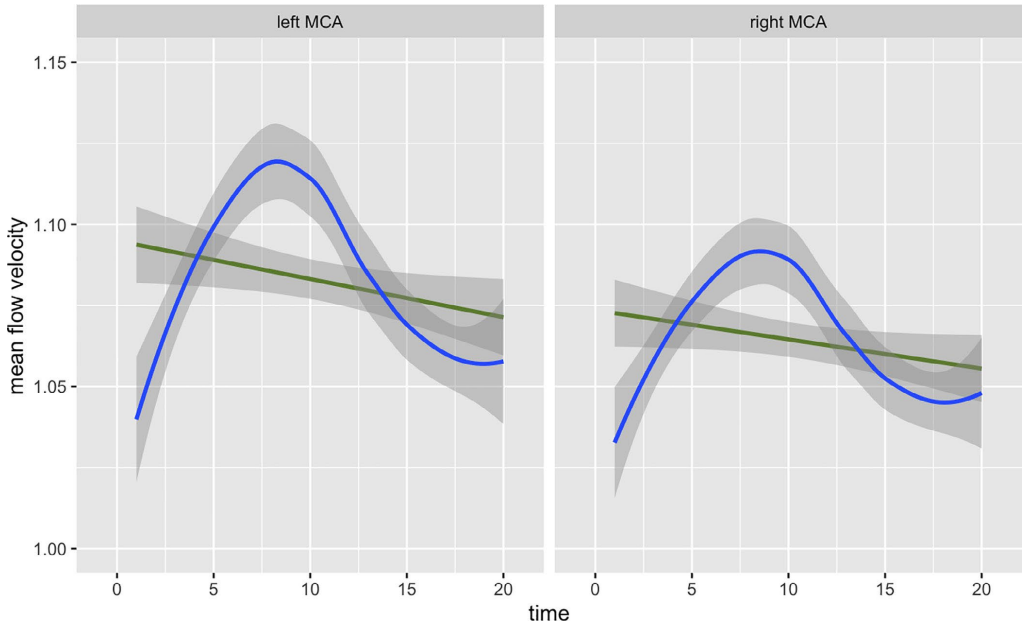
The MFV for the first 20 seconds increased by a factor of 1.07 ± 0.07 in relation to the resting state; the MFV in the right MCA increased by a factor of 1.06 ± 0.07; and the MFV in the left MCA increased by a factor of 1.08 ± 0.07. The distribution of the MFV raw values for each time unit (second) is represented in Figure 1. For both MCAs, there is a steady increase in flow velocity lasting approximately 8 seconds, returning to the resting state after approximately 15 seconds. The increase in flow velocity is slightly higher for the left MCA (see Figures 1 and 2).

3.2 | General linear model (GLM)

We calculated the GLM change for the MFV during the course of the measurement period (F (2, 3598) = 16.76, P < .001). We found a significant hemispheric difference (F (3, 3597) = 4.534, P = .033), together with differences attributable to hemispheric side and gender (F (4, 3596) = 7.828, P = .005). The fit indices across the models remained stable. For further details, see Table 2.

3.3 | General additional model (GAM)

We calculated the GAM change for the MFV during the course of the measurement period (F (2, 3598) = 21.63, P < .001). A hemispheric side difference was also demonstrated (F (3, 3598) = 4.687, P =.03), together with differences attributable to hemispheric side and gender (F (4, 3596) = 2.129, P = .001). The fit indices, particularly R^2, were



062 $F(4, 3596) = 2.129$ =.001

improved when additional variables were added to the model. For further details, see Table 1.

3.4 | Model comparison

Comparing the models using a chi-square test for goodness of fit yields a significant difference (χ^2 (9.9556) = 0.6836, $P < .001$). For further details, see Table 1.

4 | DISCUSSION

In a sample of healthy participants, we measured the MFV in the MCA during a visuo-motor task without cognitive effort, using TCD. The resulting hemodynamic curve demonstrated a steady increase in MFV, smoothly returning to resting state values. The obtained pattern resembles previous findings in healthy probands,[21,27-29] as well as those with a psychiatric or neurologic condition.[26,30,31] The resulting hemodynamic curve probably results from the activation of brain areas responsible for visuo-motor activity.[32,33] The left MCA showed a slightly greater increase in MFV; this finding is most likely attributable to the fact that our study sample was exclusively right-handed.[33,34]

Through the assessment of MFV, during a visuo-motor task in healthy probands, we avoid the effects of cognitive effort and pathophysiological anomalies of any given disorder.[22,27,31,35,36] This removes the requirement for clinical interpretation of our hemodynamic findings,[5,18,37,38] allowing the focus to remain on the statistical analysis and visual representation of MFV.

The change in MFV in the MCA during a visuo-motor task was analyzed using both the GLM and the GAM. Both approaches were

valid for analysis and yielded similar results. However, the model using the GAM resulted in better measurement of fit indices, with this difference between indices reaching statistical significance. This is particularly the case when gender is included as a variable in the statistical model, resulting in improved fit indices and allowing further differentiation of the hemodynamic curves between groups. Age is also a known factor influencing brain hemodynamics.[39] However, an interim analysis demonstrated no significant differences for the age groups represented in our sample, which we consider to be a reflection of the somewhat homogeneous age range of our sample.[40] The GAM's advantage becomes even clearer when the MFV curves are visualized, yielding a more realistic appreciation of brain hemodynamics. The curve obtained using the GAM demonstrates a remarkable similarity to the distribution of the raw MFV values. The modeling procedure, statistical analysis, and interpretation of hemodynamic parameters are a complex task.[11] The use of mathematical and statistical modeling identifies statistical differences between hemodynamic patterns; however, it is the visual inspection of such patterns, which facilitates the inference of clinical relevance..[2,7,11,18]

The advantage of nonparametric, in comparison with parametric or linear models, lies in their greater flexibility regarding assumptions about data, minimizing the impact of measurement outliers,[11,41,42] while remaining sensitive to small changes, which might occur in only a fraction of the observation period or in a limited time frame.[43,44] This certainly applies to brain blood flow velocity, where changes occur gradually over time. This results in minimal differences between near measurement neighbors (ie, in short time slots) but increasing differences with more distant (ie, in larger time slots) measurement points.[12,43,44]

Our study has some limitations, which must be taken into account when interpreting our results. We conducted our analysis exclusively with MFV measured using TCD in the MCA during a visuo-motor task.[3] While the MCA is undoubtedly the most important cerebral artery from a neuroanatomical perspective, the remaining cerebral arteries and the basilar artery also have waste irrigation territories, with their own clinical implications/relevance.[15,33,45,46] Although MFV is the most commonly analyzed TCD index, there are others that are considered important.[15] TCD parameters such as peak systolic velocity, end-diastolic velocity, pulsatility index, and resistivity index all provide insight into brain hemodynamics from a different physiological perspective.[47] Taking into account the underlying data structures of these indices, together with the robustness of nonparametric analysis, our opinion is that the use of the GAM would also lead to better statistical modeling and visualization for these indices.

Nonparametric tests, such as the general additional model, have several advantages over parametric tests. They have greater flexibility regarding assumptions about data.[11,41,42] Furthermore, they offer a better representation of dynamic and interdependent results, such as blood flow.[41] Using the GAM we were able to present a realistic visualization of cerebral flow velocity, thus facilitating the understanding of its clinical implications.[43,44] However, the mathematical and statistical analysis and, consequently, comparison of the GAMs outcomes is more demanding than for parametric methods. In our view, combining these with parametric tests may help to overcome these difficulties.[11,12,26] Our results demonstrate the additional utility of performing nonparametric tests for the analysis of dynamic and interdependent measurements (such as cerebral flow velocity), thus allowing for an improvement in visualization and interpretation of the mathematical and statistical results, leading to a more intuitive understanding of complex physiological processes.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

TRANSPARENCY STATEMENT

The manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted.

AUTHORS' CONTRIBUTIONS

Conceptualization: Stephan T. Egger, Stefan Vetter, Daniel Schuepbach
Formal Analysis: Stephan T. Egger, Daniel Schuepbach
Investigation: Stephan T. Egger, Daniel Schuepbach
Methodology: Stephan T. Egger, Stefan Vetter, Daniel Schuepbach
Project Administration: Erich Seifritz, Stefan Vetter, Daniel Schuepbach
Resources: Erich Seifritz, Stefan Vetter, Daniel Schuepbach
Supervision: Julio Bobes, Erich Seifritz
Writing—Original Draft Preparation: Stephan Egger
Writing—Reviewing and Editing: all authors

These authors have contributed equally to this work: Stefan Vetter, Daniel Schuepbach.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

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4.2. Resultados del Estudio 2 (Publicaciones 4 a 5)

Artículo 4: *"Exploring the factor structure of the mini-ICF-APP, according to the main diagnosis"*

Referencia de la Fuente:

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Abstract:

Introduction: Psychosocial functioning is a key factor determining prognosis, severity, impairment and quality of life in people who have a mental disorder. The mini-ICF-APP was developed to provide a standardised classification of functioning and disability. However, despite its gaining popularity little is known about its structure and performance. This paper examines the structure of the mini-ICF-APP using factor analysis techniques.

Materials and methods: In a clinical sample of 3178 patients, with psychiatric diagnoses from several ICD-10 categories, we analysed internal consistency, item inter-correlations and the factorial structure of the data, with reference to ICD-10 diagnostic categories; Neurocognitive Disorders; Alcohol Use Disorders; Substance Use Disorders; Schizophrenia and Psychotic Disorders; Bipolar Disorder; Major Depressive Disorder; Anxiety Disorders; Personality Disorders; and Neurodevelopmental Disorders.

Results: We found good internal consistency and item inter-correlations (Cronbach alpha = 0.92) for the mini-ICF-APP. We were able to identify pivotal domains (flexibility, assertiveness and intimate relationships), which demonstrate sub-threshold influences on other domains. The factor analysis yielded a one-factor model as ideal for the whole sample and for all diagnostic categories. For some diagnostic categories the data suggested a two or three-factor model, however, with poorer fit indices.

Conclusions: The factor structure of the mini-ICF-APP appears to modify according to the main diagnosis. However, a one-factor model demonstrates better fit regardless of diagnostic category. Consequently, we consider the mini-ICF-APP to be a trans-diagnostic measurement instrument for the assessment and grading of psychosocial functioning. The use of the mini-ICF-APP sum score seems to best reflect the degree of impairment in an individual, even taking into account that affected domains may lead to sub-threshold effects on other domains.

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ORIGINAL ARTICLE

Exploring the factor structure of the mini-ICF-APP in an inpatient clinical sample, according to the psychiatric diagnosis

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KEYWORDS
Mini-ICF-APP;
Psychosocial functioning;
Mental health;
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Factor analysis;
Factor structure

Abstract
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Results: We found good internal consistency and item inter-correlations (Cronbach alpha = 0.92) for the mini-ICF-APP. We were able to identify pivotal domains (flexibility, assertiveness and intimate relationships), which demonstrate sub-threshold influences on other domains. The factor analysis yielded a one-factor model as ideal for the whole sample and for all diagnostic categories. For some diagnostic categories the data suggested a two or three-factor model, however, with poorer fit indices.

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PALABRAS CLAVE
Mini-ICF-APP;
Funcionamiento psicosocial;
Salud mental;
Trastorno psiquiátrico;
Análisis factorial;
Estructura factorial

Exploración de la estructura factorial de la escala Mini-ICF-APP en una muestra clínica de pacientes hospitalizados con arreglo al diagnóstico psiquiátrico

Resumen
Introducción: El funcionamiento psicosocial es un factor clave que determina el pronóstico, la gravedad, el deterioro y la calidad de vida de las personas con trastornos mentales. La escala Mini-ICF-APP fue desarrollada para aportar una clasificación estandarizada del funcionamiento e incapacidad. Sin embargo, a pesar de su creciente popularidad, se conoce poco su estructura y desempeño. Este documento examina la estructura de Mini-ICF-APP, utilizando técnicas de análisis factoriales.
Materiales y métodos: En una muestra clínica de 3.178 pacientes, con diagnósticos psiquiátricos de diversas categorías ICD-10, analizamos la consistencia interna, inter-correlaciones de ítems y estructura factorial de los datos, con referencia a las categorías diagnósticas ICD-10, trastornos neurocognitivos, trastornos de abuso de alcohol, trastornos de consumo de substancias, esquizofrenia y trastornos psicóticos, trastorno bipolar, trastorno depresivo mayor, trastorno depresivo, trastornos de ansiedad, trastornos de personalidad y trastornos neuroevolutivos.
Resultados: Encontramos buena consistencia interna e inter-correlaciones de ítems (alfa de Cronbach = 0,92) para Mini-ICF-APP. Pudimos identificar dominios fundamentales (flexibilidad, asertividad y relaciones íntimas), que demostraron influencias subumbrales en otros dominios. El análisis factorial produjo un modelo unifactorial ideal para la muestra total y para todas las categorías diagnósticas. Para algunas de estas, los datos sugirieron un modelo de dos o tres factores, aunque, sin embargo, con peores índices de ajuste.
Conclusiones: La estructura factorial de la escala Mini-ICF-APP parece modificarse con arreglo a los principales diagnósticos. Sin embargo, un modelo unifactorial demuestra un mejor ajuste, independientemente de la categoría diagnóstica. Por tanto, consideramos que la escala Mini-ICF-APP es un instrumento de medida trans-diagnóstico para la evaluación y clasificación del funcionamiento psicosocial. El uso de la puntuación de sumas de la escala Mini-ICF-APP refleja mejor el grado de deterioro en un individuo, aun teniendo en cuenta que los dominios afectados podrían llevar a efectos subumbrales en otros dominios.

Introduction

Psychiatric disorders are accompanied by limitations in psychosocial functioning and adjustment. Psychosocial functioning is a more important determinant for prognosis, severity, impairment and quality of life for those suffering from mental disorders than psychiatric diagnosis itself.[1,2] Currently, psychiatric diagnoses rely principally on symptoms experienced and observed behaviour.[3–5] Despite the importance of psychosocial functioning, the correlation between diagnosis, symptom load and psychosocial impairment is weak.[6,7] This has led to an ongoing discussion about the reliability and validity of psychiatric diagnosis in general and scales measuring symptomatology in particular.[5,8] In order to close this gap, the WHO (World Health Organization) designed and developed the ICF (International Classification of Functioning), recognising psychosocial functioning as a key element for health and well-being.[8,9]

The ICF focusses on the resources and potential of humans beings to engage in activities and participate in life, regardless of mental (or physical) condition.[9] Despite its importance, the ICF is not frequently used in day to day clinical practice; due mainly to the duration and complexity of the assessment.[5,6] Several instruments have been developed in order to bridge this gap[10]; including the mini-ICF-APP.[11,12] It is a 13-item scale, developed for the assessment of psychosocial functioning in people with mental health problems, regardless of diagnosis.[12] It describes

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and classifies disorders of activity and capacity, which may lead to restrictions in social participation.[12] Since its development publications, including the first publication, on the mini-ICF-APP have demonstrated it possesses good psychometric properties together with reliability and validity across the spectrum of psychiatric diagnoses.[13–17]

Since its development the mini-ICF-APP has been regularly implemented by health care providers, insurance companies and pension funds to assess disability and work impairment.[18,19] It is one of the routine instruments used to determine access to services and financial support (e.g. disability pension).[18,20] Evaluation with the mini-ICF-APP should reflect the ability of an individual to function in their own personal and social context.[12,21] The mini-ICF-APP can be interpreted at both item or sum score levels; with illness severity associated with more significant limitations in activity and capacity.[17] The use of the mini-ICF-APP sum-score should however be treated with caution since it cannot be considered a global incapacity index. Patients with limitations in pivotal dimensions may experience impairment due to the impact of these on other domains.[10,12]

For a psychometric instrument to establish itself in clinical practice, and in particular as part of routine clinical assessment, its performance and interpretation must be known in advance. This can only be achieved through scientific scrutiny.[10,18] Although the mini-ICF-APP shows good reliability and validity, several of its psychometric properties have not been thoroughly investigated.[10] The mini-ICF-APP sum score is frequently reported as an outcome, and does seem to relate to severity (i.e. incapacity), independent of psychiatric diagnosis.[17,21] Therefore, we are interested in identifying whether individual items of the mini-ICF-APP show different performance patterns according to diagnosis, using an exploratory factor analysis, in order to describe its factorial structure according to the main ICD-10 diagnostic categories.[3]

Materials and methods

Measures

Clinical Global Impression Scales (CGI)

Severity was rated using the Clinical Global Impression Scales.[22] The CGI scale is a pragmatic, self-explanatory, assessment tool for psychiatric disorders. Due to its straightforward implementation and comprehensibility it is widely used in clinical practice and research .[22–27] The CGI consists of three subscales: 1. Severity of Illness (CGI-S), 2. Global Improvement (CGI-I), and 3. Efficacy Index (CGI-E).[22] Both CGI-S and CGI-I are rated on a seven-point Likert scale; the CGI-S from ''1'' (healthy subject) to ''7'' (extremely ill subject); the CGI-I from ''1'' (significant improvement) to ''7'' (most severe deterioration), whereby a score of ''4'' indicates no change.[22] The CGI-S and CGI-E take into account the past week, whilst the CGI-I rating relates to the time elapsed since the first/previous CGI-S assessment.

Mini-ICF-APP

The mini-ICF-APP consists of thirteen items, each one evaluating ONE capacity or domain of functioning: (1) adherence to regulations and routines; (2) planning and structuring of tasks; (3) flexibility; (4) competency/efficacy; (5) endurance; (6) assertiveness; (7) contact with others; (8) group integration; (9) family and intimate relationships; (10) leisure activities; (11) self-care; (12) mobility; and (13) competence to judge and decide.

The evaluation of each item must take into account the patient's personal and social context.[12] Comprehensible anchor-point definitions are provided for every item,[10,12] which are rated on a five-point Likert-scale from 0 (no disability) to 4 (total disability). Items rated with either three or four are considered to merit/require clinical intervention.[4,12] Correspondingly, we consider items rated three or more as clinically relevant (positive). The sum score of the mini-ICF-APP ranges from 0 to 52 points; with cut-off values defining severity: mild from 3 to 7 points; moderate from 8 to 15 points; marked from16 to 24 points; severe 25 to 37; and extremely severe 38 or more points.[17,21]

Sample and procedure

The Centre for Integrative Psychiatry is part of the Psychiatric University Hospital of Zurich. It offers an integrative psychiatric and psychotherapeutic treatment programme for adult patients (aged 18–65 years) with a psychiatric disorder. As part of the routine clinical care and quality assessment patient and health-related data is collected; including the assessment of psychosocial functioning using the mini-ICF-APP. We analysed the mini-ICF-APP data from a five-year cohort of consecutive patients hospitalised for treatment ($n = 3295$). Around four per cent (3.55%, $n = 117$) of the sample were excluded due to two or more missing items from the mini-ICF-APP. Patients excluded due to missing data did not differ from those with a complete data set regarding sex, age, education, civil status and main diagnosis. The final sample used for subsequent analyses comprised 3178 patients. The competent ethics committee approved the use of the data for further analysis and publication [KEK-ZH BASEC-Nr.: 2017-01766]. This data set was also used in a previous publication, although with a different aim and statistical analysis.[12]

Raters and training

Raters were either psychiatrists, psychiatry residents or clinical psychologists. All raters received regular training in the use of the measurement instruments. The study instruments assess the seven days prior to admission. Ratings were conducted within the first 72 h of hospitalisation. Ratings were based on information obtained from clinical interview and direct behavioural observations; together with information provided by nursing staff, social workers and others involved in the treatment process.

Diagnosis and diagnostic groups

Diagnoses were made by a psychiatry resident according to ICD-10 criteria[3] and were confirmed or corrected by a senior psychiatrist. According to ICD-10 diagnostic categories we defined nine diagnostic groups[21]: NCD: Neurocognitive Disorders (ICD-10: F0); AUD: Alcohol Use Disorders (ICD-10:

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F10: SUD: Substance Use Disorders (ICD 10: F11-19); SPD: Schizophrenia and Psychotic Disorders (ICD-10: F2); BPD: Bipolar Disorder (ICD-10: F30-31); MDD: Major Depressive Disorder (ICD 10: F32-33); AXD: Anxiety Disorders (ICD-10: F4-F5); PD: Personality Disorders (ICD-10: F6); and NDD: Neurodevelopmental Disorders (ICD-10: F7-F9).

Statistical analysis

The analysis included only participants with a complete data set at admission (one missing item on the mini-ICF-APP was acceptable). Simple descriptive statistics were used to represent the demographic and clinical characteristics of the sample; an analysis of variance (ANOVA) was performed to analyse differences between diagnostic groups. We used multivariate regression to determine the correlation between demographic (i.e. gender, age, civil status, education) and clinical variables with main diagnosis, mini-ICF-APP sum score and CGI-S. The internal consistency of the mini-ICF-APP was assessed using Cronbach's alpha.

For item correlation we used the complete spectrum of severity for every item, as well as dichotomous variables. Therefore, each response item was transformed into a dichotomous variable according to clinical relevance; items rated three or four were considered positive, with values ranging from zero to two as negative.[11,12] For the exploratory factor analysis (EFA), we chose to use only the dichotomous rating of the items in order to reduce multicollinearity and determine possible latent factors.[28] The Principal Component Analysis (with a Varimax rotation method) determined the number of factors to be extracted, as well as determining dimensionality and factor structure.

An eigenvalue greater than one is a prerequisite for factor extraction. The Kaiser–Meier–Olkin (KMO) index was used to measure sampling adequacy. For the assessment and comparability of the fit of the possible models we used: Eigenvalues; Chi-Square, the Comparative Fit Index (CFI); the Root Mean Square Residual (RMSR); Root Mean Square Error of Approximation (RMSEA) and the Tucker Lewis Index (TLI). Cut-off values considered indicative for a good fit were: an Eigenvalue > 1; a Chi-square p value >0.05; a CFI value $\leq$0.90; a RMSR value <0.08; a RMSEA <0.08; and a TLI $\geq$ 0.95.[29,30]

All statistical analyses were conducted using the statistical software ''R'' (v3.6.1), for multivariate regression analysis we used the package ''np'' (v0.60-9); for analysis of the Likert scales we used the package ''Likert'' (v1.3.5), and for psychometric tests including the exploratory factor analysis we used the packages ''psych'' (v1.9.12) and ''lavaan'' (v0.6-5).

Results

The sample included for analysis was aged between 16 and 77 years (43.50 $\pm$ 11.88) years; with 66.36% males. The majority of the sample was single, had completed an apprenticeship or college/university education. Patient admission was mostly voluntary (94.93%), with a mean length of stay of 41.49 $\pm$ 44.73 days; with a right skewed distribution. The CGI-S value for severity was 5.27 $\pm$ 0.91. The total sum score of the mini-ICF-APP was 18.53 $\pm$ 10.34, with a mean sum of positive items of 2.30 $\pm$ 3.08 with a right skewed distribution.

Gender distribution reached statistical significance for patients with AUD; this may be an artefact of the large sub-sample size. The shift in gender distribution for PD is also noteworthy although not clinically significant. Patients with SPD were more likely to have only completed primary school education (showed a higher proportion of primary education), reaching marginal significance. There were no further clinically significant differences between the diagnostic groups. For further details, see Table 1.

A general linear model found no statistically significant correlation between the mini-ICF-APP scores (sum score or total items with clinically relevant scores) and the main diagnosis, after correction for demographic parameters (age, gender, civil status, education). The correlation between the mini-ICF-APP sum score and the CGI-S score was statistically significant, for the whole sample and all diagnostic groups.

Item performance, internal consistency, and Intercorrelation

The distribution of severity for each mini-ICF-APP item is shown in Fig. 1. The internal consistency for the mini-ICF-APP ratings for the whole spectrum of severity yields a Cronbach's alpha value of 0.93. The dichotomous mini-ICF-APP scale yields a Cronbach's alpha value of 0.87. Cronbach alpha values > 0.80 indicate good levels of internal consistency; however, values > 0.90 might indicate multicollinearity.[31] The higher Cronbach alpha value yield for items covering the whole spectrum of severity (i.e. from none to severe) suggested multicollinearity, which was confirmed when analysing the correlation between single items.[31]

The inter-correlation of the mini-ICF-APP items is shown in Table 2. In the upper half, the inter-correlation for the whole spectrum of severity (from none to severe); in the lower for clinically relevant items (i.e. items with a rating of three or four). We considered correlation indices > 0.50 as relevant.[32] The inter-correlation of items was higher when using the whole spectrum of severity, as foreseen in the mini-ICF-APP manual.[12]

Exploratory factor analysis

The KMO calculated was 0.92, supporting the adequacy of sampling for factor analysis. We calculated possible EFA models for the total sample and all diagnostic categories, based on the eigenvalues presented. In our opinion only eigenvalues greater than one are indicative of the presence of a meaningful model. For the total sample and for most diagnostic groups, a one or two-factor structure seems to be the preferred model. However, MDD, AXD and PD had values suggesting a three- or even four-factor model. Table 3 summarises the eigenvalues obtained together with fit indices for all possible models. Due to the large sample size Chi-square was positive for all models,[28,33] therefore we consider this non-informative.

We calculated the factor loadings for both one- and two-factor models, for the total sample and for each diagnostic

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Table 1 Demographic and clinical characteristics of the study sample.

	Total $n=3178$	NCD $n=46$	AUD $n=1734$	SUD $n=141$	SPD $n=478$	BPD $n=80$	MDD $n=272$	AXD $n=112$	PD $n=286$	NDD $n=29$	*p*-Value
Age in years (mean, SD)	43.50 (11.88)	43.56 (10.21)	45.00 (11.65)	42.50 (10.83)	41.23 (12.71)	43.84 (12.30)	43.43 (11.25)	40.75 (10.90)	39.74 (11.68)	43.28 (13.38)	n.s.
Gender											
Male *n*, (%)	2109 (66.36)	33 (71.74)	1289 (74.34)	80 (56.74)	290 (60.67)	44 (55.00)	147 (54.04)	68 (60.71)	135 (47.20)	23 (79.31)	*AUD
Female *n*, (%)	1069 (33.64)	13 (28.26)	445 (25.66)	61 (43.26)	188 (39.33)	36 (45.00)	125 (45.96)	44 (39.29)	151 (52.80)	6 (20.69)	n.s.
Civil Status n, (%)											
Single	1746 (54.94)	27 (58.70)	819 (47.23)	75 (53.19)	373 (78.03)	34 (42.50)	126 (46.32)	58 (51.790	211 (73.78)	23 (79.31)	n.s.
Married	536 (16.87)	8 17.39	331 (19.09)	26 (18.44)	34 (7.11)	14 (17.50)	76 (27.94)	18 (16.070	26 (9.09)	3 (10.34)	n.s
Separated	132 (4.15)	0 (0)	86 (4.96)	3 (2.13)	9 (1.88)	6 (7.50)	12 (4.41)	7 (6.25)	8 (2.80)	1 (3.45)	n.s
Divorced	702 (22.08)	11 (23.91)	457 (26.36)	35 (24.82)	58 (12.13)	25 (31.25)	51 (18.75)	26 (23.21)	38 (13.29)	1(3.45)	
Widowed	57 (1.80)	0 (0)	3 (0.17)	2 (1.42)	4 (0.84)	1 (1.25)	7 (2.57)	3 (2.68)	1 (0.35)	1 (3.45)	n.s
Unknown	5 (0.16)	0 (0)	3 (0.17	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.70)	0 (0)	n.s
Education n, (%)											
Primary school	591 (18.60)	15 (32.61)	190 (10.96)	19 (13.48)	159 (33.26)	21 (26.25)	68 (25.00)	32 (28.57)	82 (28.67)	5 (17.24)	*SPD
Secondary school	103 (3.24)	0 (0)	55 (3.17)	2 (1.42)	25 (5.23)	7 (8.75)	6 (2.21)	0 (0)	7 (2.45)	19 (65.52)	n.s.
Apprenticeship	1766 (55.57)	25 (54.35)	1091 (62.92)	87 (61.70)	168 (35.15)	29 (36.25)	132 (48.53)	61 (54.46)	154 (53.85)	1 (3.45)	n.s.
College/university	388 (12.21)	1 (2.17)	261 (15.05)	18 (12.77)	39 (8.16)	16 (20.00)	28 (10.29)	8 (7.14)	17 (5.94)	0 (0)	n.s.
None/unknown	328 (10.32)	4 (8.70)	135 (7.79)	5 (3.55)	87 (18.20)	5 (6.25)	38 (13.97)	11 (9.82)	26 (9.09)	4 (13.79)	n.s.
Length of stay (mean, SD)	41.49 (44.73)	37.61 (32.91)	34.21 (33.24)	37.88 (29.41)	50.22 (44.95)	57.44 (52.04)	53.29 (58.08)	58.85 (47.09)	50.44 (76.03)	47.00 (42.90)	n.s.
Severity CGI (mean, SD)	5.27 (0.91)	5.41 (1.02)	5.17 (0.90)	5.18 (1.06)	5.61 (0.89)	5.46 (0.84)	5.34 (0.85)	5.25 (0.92)	5.22 (0.87)	5.21 (0.78)	n.s.
mini-ICF-APP (mean, SD)											
Sum score	18.53 (10.34)	20.57 (11.30)	16.91 (10.34)	20.13 (11.28)	22.01 (10.61)	20.91 (10.20)	19.88 (9.20)	19.94 (9.09)	18.80 (8.79)	19.83 (9.08)	n.s
Positive items	2.30 (3.08)	3.13 (3.80)	1.84 (2.77)	2.56 (3.44)	3.53 (3.69)	2.83 (3.54)	2.60 (3.00)	2.72 (2.92)	2.20 (2.63)	2.69 (3.30)	n.s

Significance levels: n.s.: non-significant; *: $p<0.5$; **: $p<0.01$; ***: $p<0.001$.

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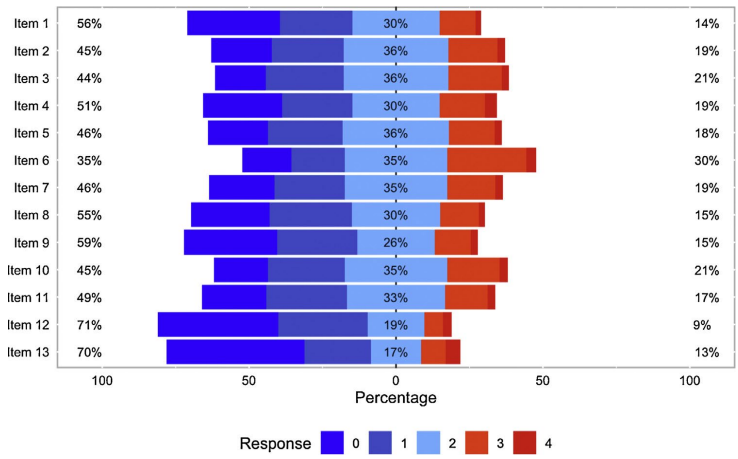

Figure 1 Response to each Item (Item 1: adherence; Item 2: planning; Item 3: flexibility; Item 4: competency; Item 5: endurance; Item 6: assertiveness; Item 7: contact; Item 8: group; Item 9: relations; Item 10: leisure; Item 11: self-care; Item 12: mobility; and Item 13: judgement) for the whole spectrum of severity (Likert type scale: 0 = none; 1, minimal; 2 = mild; 3 = moderate and 4 = severe).

Table 2 Inter-correlation between Items. In the lower half the dichotomous ratings are presented. In the upper half the ratings using the whole spectrum of severity are presented (inter-correlations > 0.50 are bold).

	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13
Item 1: adherence	1	**0.64**	**0.55**	**0.52**	0.49	0.49	0.36	0.49	0.53	0.40	0.43	0.47	0.39
Item 2: planning	0.44	1	**0.67**	**0.65**	**0.60**	**0.60**	0.49	0.53	0.57	0.44	**0.59**	0.46	0.38
Item 3: flexibility	0.42	**0.55**	1	**0.61**	**0.60**	**0.57**	**0.53**	**0.56**	**0.58**	0.49	**0.56**	0.42	0.37
Item 4: competency	0.37	**0.50**	0.48	1	**0.60**	**0.54**	0.49	**0.53**	**0.56**	0.44	**0.58**	0.45	0.43
Item 5: endurance	0.38	0.46	0.48	0.48	1	**0.56**	**0.58**	**0.52**	**0.56**	0.48	**0.52**	0.38	0.38
Item 6: assertiveness	0.34	0.47	0.47	0.41	0.44	1	**0.55**	0.44	0.44	0.41	0.48	0.33	0.27
Item 7: contact	0.20	0.35	0.40	0.33	0.44	0.38	1	**0.52**	**0.50**	0.44	0.49	0.29	0.30
Item 8: group	0.29	0.36	0.41	0.32	0.36	0.28	0.35	1	**0.77**	**0.55**	**0.58**	0.46	0.42
Item 9: relations	0.34	0.40	0.44	0.38	0.39	0.31	0.36	**0.57**	1	**0.54**	**0.59**	**0.50**	0.49
Item 10: leisure	0.28	0.31	0.37	0.31	0.33	0.29	0.28	0.36	0.34	1	0.47	0.34	0.29
Item 11: self-care	0.28	0.43	0.42	0.40	0.35	0.31	0.30	0.36	0.37	0.29	1	0.48	0.46
Item 12: mobility	0.29	0.22	0.22	0.23	0.23	0.17	0.16	0.27	0.30	0.20	0.23	1	**0.60**
Item 13: judgement	0.25	0.22	0.23	0.26	0.24	0.16	0.19	0.25	0.35	0.17	0.27	0.43	1

category. Loadings > 0.70 were considered relevant.[17] The results are presented in Table 4. Overall, we found a robust loading for each item in the one-factor model; the distributions of items on the different factors in the two-factor model were not consistent across diagnostic groups as previously outlined (data not shown).

Discussion

The findings of our exploratory factor analysis of the mini-ICF-APP in a clinical population support the validity of the mini-ICF-APP for the assessment and categorisation of patients with a psychiatric disorder according to their level of functional impairment. Our results do not support the search for sub-factors relating to the functionality of patients with a given diagnosis. Furthermore, our results support the use of the scale as a whole for this purpose; confirming the usefulness of the sum-score for evaluation purposes.

The results we obtained are comparable to results from previous studies, yielding similar sum-scores for the mini-ICF-APP and similar severity gradings according to the CGI-S; moreover, values for internal consistency are identical.[13–16,34] In contrast to previous publications examining the mini-ICF-APP, we were able to study a large clinical population. Furthermore, we included psychiatric disorders underrepresented in previous publications; including alcohol and substance use disorders; personality disorders and neurocognitive/neurodevelopmental disorders.[17] This allows for a broader interpretation of the results obtained.

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Table 3 Cronbach's Alpha. Eigenvalues and fit indices for the different factor models, according to diagnostic group.

		1 Factor Model					2 Factor Model				
	Alpha	EV	CFI	RMSR	RMSEA	TLI	EV	CFI	RMSR	RMSEA	TLI
Total	0.93	5.222	0.882	0.053	0.080	0.859	1.246	0.903	0.048	0.079	0.881
NCD	0.90	6.130	0.881	0.053	0.087	0.858	1.434	0.881	0.051	0.087	0.860
AUD	0.87	5.073	0.881	0.053	0.088	0.857	1.284	0.881	0.053	0.087	0.855
SUD	0.89	5.920	0.881	0.054	0.087	0.857	1.282	0.925	0.045	0.069	0.909
SPD	0.90	5.792	0.872	0.055	0.087	0.847	1.177	0.922	0.045	0.071	0.905
BPD	0.91	6.335	0.882	0.053	0.086	0.859	1.348	0.885	0.052	0.086	0.859
MDD	0.84	4.475	0.884	0.053	0.087	0.861	1.317	0.896	0.053	0.084	0.870
AXD	0.82	4.287	0.884	0.053	0.086	0.861	1.481	0.908	0.052	0.076	0.887
PD	0.82	4.214	0.882	0.054	0.088	0.859	1.240	0.888	0.053	0.086	0.859
NDD	0.89	5.939	0.881	0.054	0.087	0.857	1.420	0.897	0.051	0.084	0.874
		3 Factor Model					4 Factor Model				
	Alpha	EV	CFI	RMSR	RMSEA	TLI	EV	CFI	RMSR	RMSEA	TLI
Total	0.93	0.907	-	-	-	-	0.702	-	-	-	-
NCD	0.90	1.131	0.885	0.052	0.086	0.860	0.830	-	-	-	-
AUD	0.87	0.881	-	-	-	-	0.769	-	-	-	-
SUD	0.89	0.924	-	-	-	-	0.845	-	-	-	-
SPD	0.90	0.865	-	-	-	-	0.770	-	-	-	-
BPD	0.91	1.017	0.896	0.050	0.082	0.873	0.843	-	-	-	-
MDD	0.84	1.202	0.948	0.036	0.061	0.933	0.926	-	-	-	-
AXD	0.82	1.171	0.924	0.049	0.076	0.899	1.104	0.924	0.046	0.071	0.904
PD	0.82	1.140	0.849	0.036	0.083	0.936	0.904	-	-	-	-
NDD	0.89	1.206	0.847	0.051	0.081	0.870	0.995	-	-	-	-

EV: Eigenvalue; CFI: Comparative Fit Index; RMSR: Root Mean Square Residual; RMSEA: Root Mean Square Error of Approximation; TLI: Tucker Lewis Index.

In our exploratory factor analysis, the one-factor model showed the best-fit indices for all diagnostic groups as a whole as well as for each diagnostic group considered individually.[28,32,33] For several diagnostic groups, a two- or three-factor model was suggested by the data; however, their fit indices were not consistently superior to the one-factor model,[28,33] whilst having generally lower item-loadings for each possible factor (Table 4). Taking into account the parsimony criterion, we consider the one-factor model preferable.[29,30]

Previous analyses of the factor structure of the mini-ICF-APP report two- and a three-factor solutions.[16,34] Neither the factor structures nor the item distribution were replicated in our analysis. This may result from differences in sample size and diagnoses compared to previous studies.[16,28,34] We see this corroborated in our analysis, as different factor structures and item loadings were generated for different diagnostic categories.

The analysis of the loadings and inter-correlation of the different items of the mini-ICF-APP, showed that certain items hold a pivotal position. The rating of ''flexibility'' (Item 3), ''assertiveness'' (Item 6) and ''intimate relationships'' (Item 9) yield a high correlation with the remaining items (particularly when the whole spectrum of severity is considered). Furthermore, these items hold high loading values across diagnostic categories. We consider this finding unsurprising since these elements are important for coping with challenges in life and adapting to circumstances as well as overcoming adversity.[35,36]

Although our sample size was large, some diagnostic categories (NCD, BPD, AXD and NDD) were underrepresented (<130, ratio 1:10) which is suboptimal for factor analysis.[32] Therefore, the analysis conducted for these diagnostic categories should be interpreted with caution, the data is however included for the sake of completeness. Furthermore, several diagnostic categories used (i.e. NCD, PD and NDD) include an extremely heterogeneous group of diagnoses. This may explain the lack of difference in age for those with a neurocognitive disorder (NCD), since the group includes not only patients with a form of Dementia (ICD-10: F00 to F03) but also with other organic brain disorders (e.g. Delirium-ICD-10: F05).

Our analysis has confirmed the development and design of the mini-ICF-APP,[11,12] as an instrument for measuring psychosocial functioning in patients suffering from a psychological disorder. Furthermore, although patterns of functioning, (i.e. impairment) vary across the different psychiatric diagnoses, some pivotal domains remain constant. In accordance with our results, we consider the mini-ICF-APP to be a universally applicable tool for the assessment and grading of psychosocial functioning.

When interpreting our results, it must be taken into account that the study data was collected from patients requiring hospitalisation for treatment; a higher symptom load is likely which may influence certain domains of psychosocial functioning, particularly at the time of admission.[37–40] The distinct influence of symptoms on psychosocial functioning could be accountable for the latent

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Table 4 Factor loading for every possible factor model according to diagnostic category (values >0.70 are bold); with the exception of the one factor model, the superscript denotes the factor each item is loading to.

	1 Factor Model												
Item	1	2	3	4	5	6	7	8	9	10	11	12	13
Total	.55	.68	**.71**	.65	.66	.58	.55	.62	.66	.50	.59	.43	.42
NCD	.43	**.71**	.68	.66	**.71**	.65	**.79**	.64	**.84**	.42	.61	**.70**	.57
AUD	.58	.68	**.70**	.64	.65	.53	.53	.61	.65	.48	.57	.47	.44
SUD	.53	**.70**	**.70**	.65	.69	.45	**.70**	**.72**	**.71**	.50	.76	.59	.55
SPD	.62	**.70**	**.72**	.66	**.72**	.66	.58	.68	**.70**	.60	.61	.47	.45
BPD	.53	.68	**.80**	**.71**	**.72**	.67	.62	.58	**.78**	.47	**.73**	**.72**	.60
MDD	.46	**.71**	.67	.62	.66	.60	.48	.49	.52	.49	.51	.31	.39
AXD	.44	.67	.68	.62	.46	**.75**	.30	.57	.61	.38	.53	.20	.35
PD	.38	.60	**.74**	.58	.50	.59	.50	.54.	.62	.48	.55	.24	.20
NDD	**.72**	**.73**	**.78**	**.77**	.57	.49	.62	.64	**.85**	.21	.69	.57	.47
	2 Factor Model												
Item	1	2	3	4	5	6	7	8	9	10	11	12	13
Total	$.48^{1}$	$.67^{1}$	$\mathbf{.71}^{1}$	$.62^{1}$	$.64^{1}$	$.63^{1}$	$.52^{1}$	$.46^{1}$	$.51^{2}$	$.45^{1}$	$.50^{1}$	$.63^{2}$	$.63^{2}$
NCD	$.65^{2}$	$.58^{1}$	$.58^{1}$	$.55^{1}$	$\mathbf{.91}^{1}$	$.69^{1}$	$\mathbf{.80}^{1}$	$.54^{1}$	$.63^{2}$	$.61^{2}$	$.49^{1}$	$.62^{2}$	$.48^{2}$
AUD	$.48^{1}$	$.65^{1}$	$.68^{1}$	$.63^{1}$	$.64^{1}$	$.58^{1}$	$.52^{1}$	$.46^{1}$	$.51^{2}$	$.45^{1}$	$.52^{1}$	$.68^{2}$	$.68^{2}$
SUD	$.53^{1}$	$.58^{1}$	$\mathbf{.73}^{1}$	$.61^{1}$	$\mathbf{.73}^{1}$	$.49^{1}$	$.56^{1}$	$.59^{2}$	$.60^{2}$	$.39^{2}$	$.60^{1}$	$\mathbf{.74}^{2}$	$\mathbf{.72}^{2}$
SPD	$.53^{1}$	$\mathbf{.73}^{1}$	$.67^{1}$	$.60^{1}$	$.66^{1}$	$.69^{1}$	$.49^{1}$	$.63^{2}$	$.68^{2}$	$.45^{2}$	$.47^{2}$	$.53^{2}$	$.55^{2}$
BPD	$.54^{2}$	$.50^{1}$	$\mathbf{.75}^{1}$	$.64^{2}$	$.66^{1}$	$.57^{1}$	$\mathbf{.83}^{1}$	$.52^{1}$	$\mathbf{.73}^{1}$	$.40^{1}$	$.53^{1}$	$\mathbf{.83}^{2}$	$\mathbf{.77}^{2}$
MDD	$.50^{1}$	$.67^{1}$	$.62^{1}$	$.56^{1}$	$.62^{1}$	$.68^{1}$	$.36^{2}$	$.67^{2}$	$.68^{2}$	$.47^{2}$	$.46^{2}$	$.27^{1}$	$.30^{1}$
AXD	$.47^{1}$	$.77^{1}$	$.59^{1}$	$.53^{1}$	$.35^{2}$	$\mathbf{.74}^{1}$	$.53^{2}$	$\mathbf{.74}^{2}$	$\mathbf{.75}^{2}$	$.31^{2}$	$.51^{1}$	$.27^{1}$	$.26^{2}$
PD	$.38^{1}$	$.61^{1}$	$\mathbf{.74}^{1}$	$.58^{1}$	$.50^{1}$	$.59^{1}$	$.50^{1}$	$.60^{2}$	$.62^{1}$	$.47^{1}$	$.54^{1}$	$.24^{1}$	.20
NDD	$\mathbf{.74}^{1}$	$\mathbf{.80}^{1}$	$.63^{1}$	$\mathbf{.73}^{2}$	$.44^{1}$	$.64^{1}$	$.54^{1}$	$.62^{2}$	$.64^{2}$	$.15^{1}$	$.63^{1}$	$\mathbf{.79}^{2}$	$.58^{2}$
	3 Factor Model												
Item	1	2	3	4	5	6	7	8	9	10	11	12	13
Total	-	-	-	-	-	-	-	-	-	-	-	-	-
NCD	$\mathbf{.83}^{3}$	$.58^{1}$	$.59^{1}$	$.56^{1}$	$\mathbf{.80}^{1}$	$\mathbf{.77}^{1}$	$\mathbf{.78}^{1}$	$.48^{1}$	$.55^{1}$	$.55^{3}$	$.66^{2}$	$.62^{2}$	$\mathbf{.74}^{2}$
AUD	-	-	-	-	-	-	-	-	-	-	-	-	-
SUD	-	-	-	-	-	-	-	-	-	-	-	-	-
SPD	-	-	-	-	-	-	-	-	-	-	-	-	-
BPD	$.55^{2}$	$.57^{1}$	$.66^{1}$	$.61^{2}$	$.64^{1}$	$.61^{1}$	$\mathbf{.77}^{1}$	$\mathbf{.82}^{3}$	$.63^{3}$	$.31^{3}$	$.45^{2}$	$\mathbf{.80}^{2}$	$\mathbf{.75}^{2}$
MDD	$.44^{1}$	$.65^{1}$	$.66^{1}$	$.52^{1}$	$.62^{1}$	$.67^{1}$	$.37^{2}$	$.68^{2}$	$.65^{2}$	$.47^{2}$	$.45^{2}$	$.62^{3}$	$.54^{3}$
AXD	$.42^{1}$	$.59^{1}$	$.69^{1}$	$.46^{1}$	$.53^{1}$	$.66^{1}$	$.51^{2}$	$\mathbf{.73}^{2}$	$\mathbf{.71}^{2}$	.34	$.68^{3}$	$.32^{3}$	$.24^{3}$
PD	$.45^{1}$	$.68^{1}$	$.63^{1}$	$.59^{1}$	$.44^{1}$	$.54^{1}$	$.37^{2}$	$.92^{2}$	$.50^{2}$	$.35^{2}$	$.39^{2}$	$.48^{3}$	$.39^{3}$
NDD	$\mathbf{.77}^{1}$	$\mathbf{.73}^{1}$	$.54^{3}$	$\mathbf{.79}^{2}$	$.62^{3}$	$.57^{1}$	$\mathbf{.81}^{3}$	$.58^{2}$	$.62^{2}$	$.23^{1}$	$.53^{1}$	$\mathbf{.73}^{2}$	$.53^{2}$
	4 Factor Model												
Item	1	2	3	4	5	6	7	8	9	10	11	12	13
Total	-	-	-	-	-	-	-	-	-	-	-	-	-
NCD	-	-	-	-	-	-	-	-	-	-	-	-	-
AUD	-	-	-	-	-	-	-	-	-	-	-	-	-
SUD	-	-	-	-	-	-	-	-	-	-	-	-	-
SPD	-	-	-	-	-	-	-	-	-	-	-	-	-
BPD	-	-	-	-	-	-	-	-	-	-	-	-	-
MDD	-	-	-	-	-	-	-	-	-	-	-	-	-
AXD	$.49^{1}$	$.63^{1}$	$.69^{1}$	$.47^{1}$	$.45^{1}$	$\mathbf{.70}^{1}$	$.68^{4}$	$.47^{4}$	$\mathbf{.83}^{3}$	$.27^{2}$	**.89**	$.27^{2}$	$.43^{3}$
PD	-	-	-	-	-	-	-	-	-	-	-	-	-
NDD	-	-	-	-	-	-	-	-	-	-	-	-	-

factor structure found for the different diagnostic groups. We consider the use of the sum-score an easy and intuitively understood method; taking into account that symptoms as well as psychosocial functioning domains seem to have a sub-threshold impact on others;[17] consequently, increasing the total degree of impairment. In conclusion, we would encourage the use of the mini-ICF-APP to determine levels of psychosocial impairment in people suffering from a mental

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disorder in order to shape therapy accordingly, with a view to reestablishing the ability to cope with life and overcome adversity.[41]

Conclusions

The mini-ICF-APP is an assessment and rating tool to assess psychosocial functioning, in people with a mental disorder regardless of psychiatric diagnosis. We identified a one-factor model, including all items, as the one with the best-fit values, irrespective of diagnostic category. Accordingly, we consider the mini-ICF-APP as a trans-diagnostic measurement instrument for the evaluation of all aspects of psychosocial functioning. The use of the mini-ICF-APP sum score seems to reflect the degree of impairment suffered by an individual, even taking into account that pivotal domains may lead to sub-threshold effects on others.

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Artículo 5: *"Utility and Validity of the Brief Psichiatric Rating Scale, BPRS (BPRS) as a Transdiagnostic Scale: Teaching an old Dog new Tricks"*

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Schmid. H.M., Hofmann, A.B., Bobes, J., Seifritz, E., Vetter, S., **Egger, S.T.**, "*Utility and Validity of the Escala Breve de Evaluación Psiquiátrica, BPRS (BPRS) as a Transdiagnostic Scale: Teaching an old Dog new Tricks"* Assessment [in revision]

Abstract:

Psychiatric diagnoses show a high rate of comorbidity and diagnostic instability, especially in severely ill and chronic patients. The Escala Breve de Evaluación Psiquiátrica, BPRS (BPRS) was originally conceived to access psychopathology in several psychiatric disorders, making it a candidate for a transdiagnostic instrument. We analyzed the utility and validity of the BPRS in a balanced, diagnostic heterogeneous sample of 600 psychiatric patients. As a comparator, we chose the mini-ICF-APP, a scale used to measure functioning and impairment across the diagnostic spectrum. Both scales had good internal consistency. The BPRS and the mini-ICF-APP showed a moderate correlation, with good levels of agreement. We were able to identify general symptoms present across the diagnostic spectrum, influencing severity and a cluster of symptoms specific for each diagnosis. Our results show the utility and validity of the BPRS as a transdiagnostic assessment tool.

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Utility and Validity of the Brief Psychiatric Rating Scale (BPRS) as a Transdiagnostic Scale: Teaching an old Dog new Tricks

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Utility and Validity of the Brief Psychiatric Rating Scale (BPRS) as a Transdiagnostic Scale: Teaching an old Dog new Tricks

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Abstract:

Psychiatric diagnoses show a high rate of comorbidity and diagnostic instability, especially in severely ill and chronic patients. The Brief Psychiatric Rating Scale (BPRS) was originally conceived to access psychopathology in several psychiatric disorders, making it a candidate for a transdiagnostic instrument. We analyzed the utility and validity of the BPRS in a balanced, diagnostic heterogeneous sample of 600 psychiatric patients. As a comparator, we chose the mini-ICF-APP, a scale used to measure functioning and impairment across the diagnostic spectrum. Both scales had good internal consistency. The BPRS and the mini-ICF-APP showed a moderate correlation, with good levels of agreement. We were able to identify general symptoms present across the diagnostic spectrum, influencing severity and a cluster of symptoms specific for each diagnosis. Our results show the utility and validity of the BPRS as a transdiagnostic assessment tool.

Keywords:

Psychopathology, Psychosocial Functioning, Transdiagnostic, Psychometrics, Network Analysis, HiTOP

Introduction/Background

Due to the lack of reliable and readily available biological markers, the development and research of psychiatric treatment and, consequently, their outcomes are conducted mainly by assessing symptoms through psychometric measurement instruments (Moller, 2009; Salvi et al., 2005). Although a consistently increasing number of diagnosis-specific psychometric instruments have been developed over the past decades, including those designed to assess subsyndromal and symptom domains, instruments dimensionally measuring psychopathology across the diagnostic spectrum are still rare (Stanton et al., 2020). Furthermore, a discrepancy between the markedness of psychopathology and functional impairment has constantly been identified (Kapur et al., 1981; Michel et al., 2018; Reed et al., 2009).

The Brief Psychiatric Rating Scale (BPRS) was developed as a measurement instrument to assess the change (i.e., improvement or deterioration) in psychopathology in a wide variety of severe psychiatric disorders, namely depression with psychotic symptoms, bipolar affective disorder, and schizophrenia (Overall & Gorham, 1962; Shafer, 2005). In addition, a combination of BPRS items was used to infer recovery in patients with schizophrenia (Andreasen et al., 2005). Due to its psychometric properties, the BPRS also features the potential to accurately assess symptomatology in non-psychotic disorders and is also used to determine the severity of symptoms in studies without a specific diagnose (Heekeren et al., 2020; Kalisova et al., 2014; Kisely & Campbell, 2015).

Regarding the taxonomy of psychiatric disorders, recent approaches tend to leave the traditional order defined in widely used classifications like DSM-5 or ICD-10 (Kotov et al., 2017), since, due to several limitations, many courses of disorder cannot be described satisfactorily, specifically in those suffering from a high degree of psychiatric comorbidity or high levels of general psychopathology, and in case the main diagnosis may shift over time (Caspi & Moffitt, 2018; Plana-Ripoll et al., 2019). For instance, the frequent occurrence of comorbidity causes more difficult clinical decision-making and complicates research on these disorders, also, arbitrary boundaries exist in order to fit dimensional symptoms into categorical variables. As a result, a fundamentally different approach to classify psychiatric disorders, the Hierarchical Taxonomy of Psychiatric Disorders (HiTOP) was developed. It identifies six core dimensional spectra, although with varying degrees of validity (Kotov et al., 2017; Kotov et al., 2021).

While there is research on the psychometric properties of the BPRS in thought disorders, such as schizophrenia, schizoaffective, or bipolar disorder, there is a lack of studies systematically analyzing the performance of the BPRS in other diagnostic groups (Shafer, 2005). Therefore, we designed a study

to determine the utility and validity of the BPRS as a measurement instrument capable of assessing the dimensional aspects of psychopathology in a heterogeneous diagnostic group of patients. Furthermore, we aim to evaluate symptoms present across the diagnostic dimensional spectrum related to functional impairment and severity.

Methods

Study design and population

The Department of Psychiatry, Psychotherapy and Psychosomatics, as part of the Psychiatric University Hospital of Zurich, is responsible for the treatment of adult patients (ages 18 to 65) in the city of Zurich, Switzerland, and its surroundings, with a catchment area of approximately 500.000 inhabitants. In its different treatment centers, it globally accounts for approximately 4000 hospitalizations per year. A series of psychometric measures to assess disease severity and psychosocial functioning is performed for each patient upon admission and discharge to evaluate treatment quality and outcomes. Between January 1st, 2018 and December 31st, 2020, we systematically collected the admission BPRS and mini-ICF-APP in patients hospitalized for treatment. We report how we determined our sample size, all data exclusions, all manipulations, and all measures in the study. The Ethics Committee of the Canton of Zurich authorized the use of the anonymized data for research and publication purposes (BASEC: 2018-01906).

Clinical Assessment and Diagnosis

Clinical ratings were carried out by attending psychiatrists, psychiatry residents, or clinical psychologists. In addition, relevant information was derived from clinical interviews and observation and information provided by nursing staff, social workers, and significant others. Psychiatric diagnoses were made by the clinician responsible for the treatment according to the ICD-10 (WHO, 1992) criteria. A senior psychiatrist thereafter confirmed these diagnoses. We subsequently assigned all diagnoses to the core dimensions of psychiatric disorders (i.e., internalizing, externalizing, and thought disorder) (Kotov et al., 2017; Kotov et al., 2021). The following ICD-10 diagnostic categories included: Internalizing Disorders, comprising of Anxiety (F4) and Major Depressive Disorder (F32 and F33); Externalizing Disorders, including Alcohol Use Disorder (F10) and Cluster B Personality Disorders (Antisocial F60.2; Impulsive F60.3; Histrionic F60.4 and Narcissistic F06.8); and finally, Thought Disorders, including Mania and Bipolar Disorder (F30 and F31) as well as Schizophrenia Spectrum Disorder (F2). All remaining diagnostic categories were excluded.

Clinical Rating Scales

The Brief Psychiatric Rating Scale (BPRS) was developed to measure changes in a comprehensive set of psychopathologic symptoms present in major psychiatric diagnoses (Overall & Gorham, 1962). It consists of 18 single items assessing the following symptoms: 1. somatic concern, 2. anxiety, 3. emotional withdrawal, 4. conceptual disorganization, 5. feelings of guilt, 6. tension, 7. mannerisms and

posturing, 8. grandiosity, 9. depressive mood, 10. hostility, 11. suspiciousness, 12. hallucinatory behavior, 13. motor retardation, 14. uncooperativeness, 15. unusual thought content, 16. blunted affect, 17. excitement, and 18. disorientation. Each item is evaluated according to a seven-item Likert scale, ranging from "1" (not present) to "7" (extremely severe). Thus, the summary score ranges between 18 to 126, with a higher score indicating more severe symptomatology (Overall & Gorham, 1962).

The mini-ICF-APP was developed as a short observer-rated scale to assess the level of functioning (Linden & Baron, 2005; Linden et al., 2009). It consists of thirteen domains: 1. adherence to regulations and routines, 2. planning and structuring of tasks, 3. flexibility, 4. competency/efficacy, 5. endurance, 6. assertiveness, 7. contact with others, 8. group integration, 9. family and intimate relationships, 10. leisure activities, 11. self-care, 12. mobility and 13. competence to judge and decide. Each item is rated on a five-point Likert scale from "0" (no disability) to "4" (total disability). The manual provides definitions for each item. Capabilities have to be assessed in reference to a specific context (e.g., workplace, work in general, household). Added up, the scale ranges from 0 to 52 points, while higher scores indicating a reduced overall functionality (Linden et al., 2009).

The Clinical Global Impression Scale is a brief, easy-to-use, pragmatic tool to assess the severity of a psychiatric disorder (CGI-S) (Guy, 1976). It uses a seven-point Likert scale response format ranging from 1 representing the "healthy subject" to 7 the "extremely ill subject".

Statistical Analysis

Patients were classified according to their main treatment diagnosis as defined above, patients not filling in one of these categories were discarded. We calculated the sample size to detect low effect sizes between six groups, with alpha of 0.05 and beta of 0.95. The calculated sample size was 563 participants. To have a balanced sample, we randomly selected 100 patients within each main diagnosis (matched for comorbid substance use disorder and comorbid personality disorder). The sample's demographic and clinical characteristics are represented using descriptive statistics (percentage, mean, SD). Differences in proportions between groups were calculated using the Chi-square (χ^2) test. Differences in means were calculated using analysis of variance (ANOVA).

Internal consistency of the BPRS and mini-ICF-APP was examined using the Cronbach's alpha coefficient. Skewness and kurtosis of both scales were determined. Skewness is used to determine ceiling or floor effects. The BPRS sum score was correlated to the mini-ICF-APP sum score using

Spearman's Rank Correlation. Considering the differences in the rating of the scales, we calculated the z-scores for both scales. The Concordance Correlation Coefficient was calculated using the z-scores to examine the level of accuracy and precision between two measures (King & Chinchilli, 2001; Lin, 1989). To evaluate the agreement between the two scales, we used the Bland-Altman Plot (Bland & Altman, 1986). The difference between both scales was plotted on the y-axis, while the mean was plotted on the x-axis. The confidence interval and the limits of agreement for both scales were calculated (Bland & Altman, 1986; Carkeet, 2015).

The network model of the scales (BPRS and mini ICF-APP) was calculated using an "Extended Bayesian Information Criterion" (EBIC) and the "Least Absolute Shrinkage and Selection operator" (LASSO) regularization method, implemented within a single Gaussian random fields network. For the degree of shrinking, we used a low hyperparameter (gamma = 0.0) to maximize the stability of the network and balance sensitivity and specificity (Epskamp et al., 2018). To test the accuracy and stability of the network parameters, we estimated confidence intervals on the edge-weights and the correlation stability coefficient using non-parametric bootstrapping (Epskamp & Fried, 2018). Within the graphical representation, edges are the lines between the nodes representing regularized partial correlations, which help estimate the relationship between two variables while controlling for all other variables. An edge indicated a dependent relationship between variables; the absence indicates that they are conditionally independent. Blue edges are used to represent positive associations, while red edges represent negative associations. The wider and more saturated an edge is represented, the stronger the association. We calculated centrality indices (closeness, betweenness and strength) and expected influence of each item within the respective symptom (BPRS) and functional (mini-ICF-APP) network. We also calculated a bridge expected influence strength metric to quantify the influence of symptoms (BPRS) and functional domains (mini-ICF-APP) (Jones et al., 2021).

Analysis was performed using R Statistical Software (version 4.0.1). The packages "DescTools" (version 0.99.43) and "blandr" (version 0.5.1) were used for the calculation of the Concordance Correlation Coefficient The Bland Altman Plot as well as the Limits of. Network Analyses were created using the packages "NetworkTools" (version 1.3.0), "Bootnet" (version 1.43), and "qgraph" (version 1.6.9).

Results

In the observation period we collected health related data of 1438 psychiatric patients; 1173 of them with a diagnosis of interest for the analysis. The smallest group was bipolar disorder with 158 patients, and the largest alcohol use disorders with 279 patients. A total sample of 600 psychiatric inpatients, equally distributed among six diagnostic categories (alcohol use disorder, major depressive disorder, anxiety disorders, bipolar disorder, schizophrenia, and personality disorders) was analyzed. The mean age was 41.5 (SD = 12.8; median 40, range 18-65) years. Women accounted for 45.5% (n = 273) of the sample. The demographic characteristics of the sample are summarized in Table 1. Except for those with the diagnosis of a personality disorder, patients had similar age and gender distribution. However, patients with a personality disorder were significantly younger, with a higher proportion of female patients ($\chi^2(5, 600) = 28.21$, $p<.001$).

The mean BPRS sum score was 45.4 (SD = 14.4), the mean mini-ICF-APP sum score was 19.93 (SD = 8.21), and the mean CGI-S score was 5.55 (SD = 0.84), reflecting a clinically "markedly ill" to "severely ill" patients. The BPRS and mini-ICF-APP sum scores progressively increased from patients diagnosed with alcohol use disorder, personality disorder, anxiety disorders, major depressive disorder, bipolar disorder, to schizophrenia. The CGI-S score and severity categorization ("markedly ill") were similar among all diagnostic groups. The internal consistency ranged from good to excellent with the BPRS having a Cronbach's alpha of .87, whilst the mini-ICF-APP had a Cronbach's alpha of .92. The Pearson correlation coefficient for the BPRS and mini-ICF-APP scales was .53 (95% CI: .46 to .58, $t = 15.08$, $df = 598$, $p<.001$). The Concordance Correlation Coefficient was .52 (95%CI: .46 to .58). The Bland Altman Plot shows a good overlap between both scales, with just 2.5% (n = 15) outliers, a Lower Limit of Agreement of -1.91 (95% CI -2.04 to -1.77), and an Upper Limit of Agreement of 1.91 (95% CI: 1.77 to 2.04). For further details, see Table 2 and Figure 1.

The calculated networks were highly stable. The BPRS and mini-ICF-APP networks had a correlation stability coefficient of .75, while the joint network featured a correlation stability of .67. All of them indicate a robust network (Epskamp et al., 2018; Epskamp & Fried, 2018). Thus, they allow to adequately determine and interpret the centrality, clustering, and influence of the single symptoms and functional domains for both scales and the bridges between symptoms (BPRS) and functional domains (mini-ICF-APP).

Regarding the BPRS symptoms, the highest centrality values were "unusual thought", "blunted affect", and "suspiciousness", in descending order. The symptoms with the strongest influence were "unusual

thought", "uncooperativeness", and "suspiciousness" (see Figure 2A). We detected three clusters of symptoms corresponding to the externalizing, internalizing, and thought disturbance domains. The externalizing cluster included items evaluating tension, mannerisms and posturing, hostility, uncooperativeness, and excitement. The internalizing cluster had two cores, the first including anxiety and guilt, the second encompassing emotional withdrawal, depressive mood, motor retardation and blunted affect. The thought disturbance cluster included conceptual disorganization, suspiciousness, hallucinations, and unusual thought content, with disorientation orbiting this cluster. Somatic concern fluctuated between the externalizing and internalizing clusters, while grandiosity fluctuated between the externalizing and thought content clusters (see Figure 2A).

Focusing on the mini-ICF-APP network, the functional domains with the highest centrality were "relationships", "assertiveness", and "competency", in descending order. The functional domains with the highest influence were "group interactions", "relationships", and "competency" (for further details, see Figures 2B). The symptoms (BPRS) and the functionality domains (mini-ICF-APP) showed a close interplay. The highest bridge influence could be measured for "uncooperativeness", "hostility", and "conceptual disorganization" on the BPRS side, and "adherence", "relationships", and "competence to judge" on the mini-ICF-APP side (See Figure 2B). Within the mini-ICF-APP network, we could identify four clusters. The first addresses interpersonal relations, contact with others, group integration, relationships, and leisure activities. The second cluster involves daily activities, consisting of self-care, mobility, and competence to judge and decide. The third cluster entails working capabilities, planning, and structuring of tasks, flexibility, competency/efficacy, and endurance; with a central cluster involving adherence to routines and assertiveness (See Figure 2B).

Functional domains showed a greater bridge strength. Adherence to routines was the most influential node, followed by competency/efficacy, self-care, and competence to judge and decide. Nodes on the symptom network with the most bridge strength were: somatic concern, conceptual disorganization, tension, mannerism, and uncooperativeness. The bridge formed between "adherence to routines" and "uncooperativeness" has a central position in the joint network of symptoms and functional domains (See Figure 3).

Discussion

The main finding of our study is the utility and validity of the BPRS as a transdiagnostic measurement tool, capable of reliably capturing both general and disorder-specific psychopathological symptoms in a wide range of diagnostic categories. Our results also corroborate the utility and feasibility of the mini-ICF-APP as a transdiagnostic measurement instrument. The results from the network analysis strengthen the notion that there is a close interplay between symptoms and functionality domains, with special focus on some pivotal elements on both sides. Therefore, these findings corroborate the notion that a certain psychopathological threshold has to be achieved before symptoms lead to functional impairment and trigger help-seeking behavior (Michel et al., 2018). Thus, we were able to partially disentangle the overall manifestation of psychopathological symptoms from the severity of functional impairment of a psychiatric disorder.

The BPRS and mini-ICF-APP showed significant internal consistency, indicative of their applicability across the diagnostic spectrum. The correlation coefficients between both scales were moderate and lower than in previous reports (Balestrieri et al., 2013). This might be due to the different distribution of both scales. As BPRS featured a right skewness, due to the less distinctive psychopathological symptoms of those with an externalizing disorder. Nonetheless, no participant achieved the lowest possible score on the scale, therefore, a real floor effect can be ruled out for our sample (Koedel & Betts, 2010; McHorney & Tarlov, 1995). The differences between BPRS and mini-ICF-APP results, support previous findings that show that symptom severity is not unconditionally sufficient to explain functional impairment (Garcia-Velazquez et al., 2017) and, that several specific psychiatric disorders might manifest less marked symptoms but a similar burden of disease (Egger et al., 2019; Linden & Baron, 2005). Despite the moderate correlation indices, the BPRS and mini-ICF-APP show a great degree of overlap and agreeableness, indicating that both scales could accurately assess the severity of a psychiatric disorder, although from a different perspective (Gerke, 2020; Haghayegh et al., 2020), and thus complement each other.

The BPRS was capable of capturing the dimensional nature of psychopathology from several diagnoses and simultaneously delimiting the characterizing symptoms and clusters for every single diagnosis (Shafer, 2005). Further determining BPRS as a suitable dimensional and transdiagnostic measurement instrument depicting psychopathology (Stanton et al., 2020). The degree of centrality of certain symptoms and functional domains involving thought and judgement capabilities, assertiveness and self-efficacy, the ability to relate to others, as well as the aptitude to adhere to routines, conventions, and rules, denotes their pivotal role in the network. Furthermore, they are the domains where a psychiatric disorder becomes self-evident, namely in taking care and sustaining of oneself, fulfilling obligations,

and maintaining relationships (Galderisi et al., 2018; Galderisi et al., 2020; Izquierdo et al., 2021; Jimeno et al., 2020). The markedness of these symptoms seems to determine the severity and maintenance of a mental disorder (Borsboom & Cramer, 2013; Zimmerman et al., 2018), where distinct psychiatric disorders can lead (at least temporarily) to similar degrees of functional impairment (Garcia-Velazquez et al., 2017). By including several distinctive diagnostic groups, our results show general psychopathology factors are present along different diagnostic categories (Aristodemou & Fried, 2020; Caspi et al., 2014; Smith et al., 2020). This reinforces the notion that psychiatric disorders affect thought and language (Kircher et al., 2018; Vogeley, 2018), and therefore, requires a primary approach for diagnosis as well as for treatment through speech and communication.

The BPRS is thus able to reflect general psychopathology, as well as diagnostic specific symptoms. The clusters of symptoms we found on the BPRS scale overlap with the previously reported factorial structure of the BPRS for several disorders and conditions (Shafer, 2005). The symptoms and functional domains we found to be central within the network structure are among the first targets of any psychiatric or psychotherapeutic intervention: namely the building of a common language and understanding as well as the establishment of confidence in relationships and a trustworthy therapeutic alliance (Jimeno et al., 2020; Lincoln et al., 2007; Rummel-Kluge et al., 2013). Primary and unspecific therapeutic goals include the reestablishment of assertiveness and adherence to routines. The successful activation of these functional domains further unfolds therapeutic options that should specifically address the core symptoms of the distinct psychiatric disorders.

One strength of our analysis is the large, randomized sample equally representing major psychiatric diagnostic groups which allowed us to perform robust statistical analysis. To assess the scales' validity, we used two complementary methods, one approach to measure correlation, another one to measure aggregability. The results of both methods were satisfactory and corroborated each other. For the analysis of the properties of the scales, we used a network approach which allows us to estimate the influence of a single item (i.e., either a symptom or a functional domain) on the network structure of its own scale, as well as on the neighbor scale. Since network analysis is susceptible to the influence of group composition as well as condition (Bringmann & Eronen, 2018) we included a balanced number of patients with distinctive dimensions and diagnoses (Borsboom et al., 2018; Wichers et al., 2017).

Despite its strengths, our study has some limitations. We included only the main treatment diagnosis for our analysis and therefore lost sharpness regarding the degree of comorbidity. We sought to compensate for this by including the comorbidity for alcohol and substance use disorder, and comorbid

personality disorder. We did not include all proposed HiTOP dimensions, first of all because the count of patients for the "somatoform" and "detachment" dimensions was too little, second because those are less well defined and validated (Kotov et al., 2017; Kotov et al., 2021). The externalizing dimension, with its "disinhibited" and "antagonistic" spectra was joined together, although each assigned to a specific diagnostic group (Kotov et al., 2017; Kotov et al., 2021). In our sample, we only included patients requiring hospitalization for treatment, therefore the generalizability of our results may be reduced to this population group.

In our study, the BPRS and the mini-ICF-APP showed a great degree of correlation and agreement. Furthermore, they performed satisfactorily in a group of patients with heterogeneous psychiatric diagnoses. The joint psychometric properties of the BPRS and mini-ICF-APP corroborate the notion that the interplay between pivotal psychopathological symptoms and functional impairment determines the severity of the psychiatric disorder. From our results, the BPRS scale seems suitable for its use in patients with chronic or severe psychiatric disorders. Since the BPRS is a widely known and readily available psychometric scale, our results support its ongoing use as a transdiagnostic scale to assess symptomatology beyond psychotic disorders.

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Table 1
Demographic Characteristics of the Sample

		Internalizing Disorders		Externalizing Disorders		Thought Disorders		Test	*p*
Diagnostic Group	Total Sample	Anxiety	Major Depression	Alcohol Use Disorder	Personality Disorder	Bipolar Disorder	Schizophrenia		
n	600	100	100	100	100	100	100		
	M (SD)	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*		
Age	41.5 (12.8)	41.9 (12.9)	45.1 (12.9)	45.8 (12.4) *	31.1 (8.6) **	44.3 (12.3)	40.5 (11.5)*	$F(5, 594) = 21.20$	<.001
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*		
Female sex	273 (45.5)	36 (36.0)	39 (39.0)	36 (36.0)	54 (54.0) **	35 (35.0)	38 (38.0)	$\chi^2(5, 600) = 28.21$	<.001
Education								$\chi^2(20, 600) = 79.91$	<.001
Incomplete Schooling	46 (7.7)	8 (8.0)	6 (6.0)	5 (5.0)	16 (16.0)	4 (4.0)	7 (7.0)		
Regular School	264 (43.9)	31 (31.0)	37 (37.0)	28 (28.0)	43 (43.0)	61 (61.0)	64 (64.0)		
Apprenticeship	232 (38.7)	49 (49.0)	46 (46.0)	54 (54.0)	35 (35.0)	25 (25.0)	23 (23.0)		
College/University	58 (9.7)	12 (12.0)	11 (11.0)	13 (13.0)	6 (6.0)	10 (10.0)	6 (6.0)		
Marital Status								$\chi^2(20, 600) = 66.36$	<.001
Single	380 (63.4)	62 (62.0)	58 (58.0)	51 (51.0)	85 (85.0)	53 (53.0)	71 (71.0)		
Married	82 (13.7)	16 (16.0)	13 (13.0)	24 (24.0)	10 (10.0)	10 (10.0)	9 (9.0)		
Separated/Divorced	116 (19.3)	20 (20.0)	26 (26.0)	21 (21.0)	4 (4.0)	33 (33.0)	12 (12.0)		

Widowed	8 (1.3)	2 (2.0)	2 (2.0)	2 (2.0)	0 (0.0)	0 (0.0)	2 (2.0)
Unknown/Other	14 (2.3)	0 (0.0)	1 (1.0)	2 (2.0)	1 (1.0)	4 (4.0)	6 (6.0)

* Alcohol Use Disorder < Schizophrenia

** Personality Disorder > all others

Table 2
Clinical Characteristics of the Sample

		Internalizing Disorders		Externalizing Disorders		Thought Disorders		Test	*p*
Diagnostic Group	Total Sample	Anxiety	Major Depression	Alcohol Use Disorder	Personality Disorder	Bipolar Disorder	Schizophrenia		
n	600	100	100	100	100	100	100		
Comorbidity	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*		
Alcohol/Substance Use Disorder	72 (12.0)	12 (12.0)	12 (12.0)	12 (12.0)	12 (12.0)	12 (12.0)	12 (12.0)	$\chi^2(5, 600) = 0$	1
Personality Disorder	30 (5.0)	10 (10.0)	3 (3.0)	6 (6.0)	0 (0.0)	6 (6.0)	5 (5.0)	$\chi^2(5, 600) = 1.18$	.38
Rating Scales	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*		
CGI-S	5.6 (0.8)	5.5 (0.8)	5.5 (0.8)	5.6 (0.7)	5.4 (1.0)	5.7 (0.9)	5.6 (0.9)	$F(5, 594) = 1.18$	.31
BPRS	45.4 (14.4)	42.06 (13.0) *	46.4 (15.8) **	38.6 (14.5) *	40.1 (11.7)	51.2 (15.2) */**	52.5 (15.5) */**	$F(5, 594) = 14.71$	<.001
mini-ICF-APP	19.9 (8.2)	18.1 (8.8)	19.2 (8.6)	17.7 (9.6) ***	18.6 (5.8)	21.2 (8.2) ***	22.1 (8.4) ***	$F(5, 594) = 3.87$	.002
Distribution Indices									
Skewness BPRS	0.67	0.91	0.61	1.17	0.81	0.20	0.17		
Kurtosis BPRS	2.64	3.39	2.48	3.96	3.58	2.03	1.99		
Skewness mini-ICF-APP	0.05	0.15	-0.16	-0.04	0.24	0.29	-0.10		
Kurtosis mini-ICF-APP	2.49	2.16	2.82	2.11	2.96	1.81	2.49		

* Anxiety, Personality Disorder and Alcohol Use Disorder < Bipolar Disorder and Schizophrenia

** Major Depression < Bipolar Disorder and Schizophrenia

1

*** Alcohol Use Disorder < Bipolar Disorder and Schizophrenia

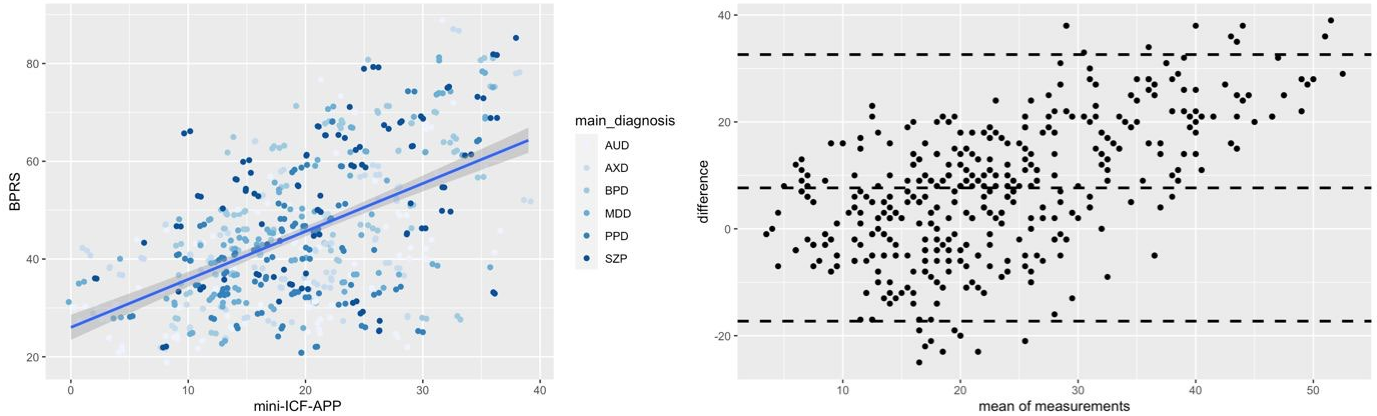
2

3

Figure 1

A. Correlation Analysis Plot modelling the BPRS and mini-ICF-APP scales, corresponding to the diagnostic group

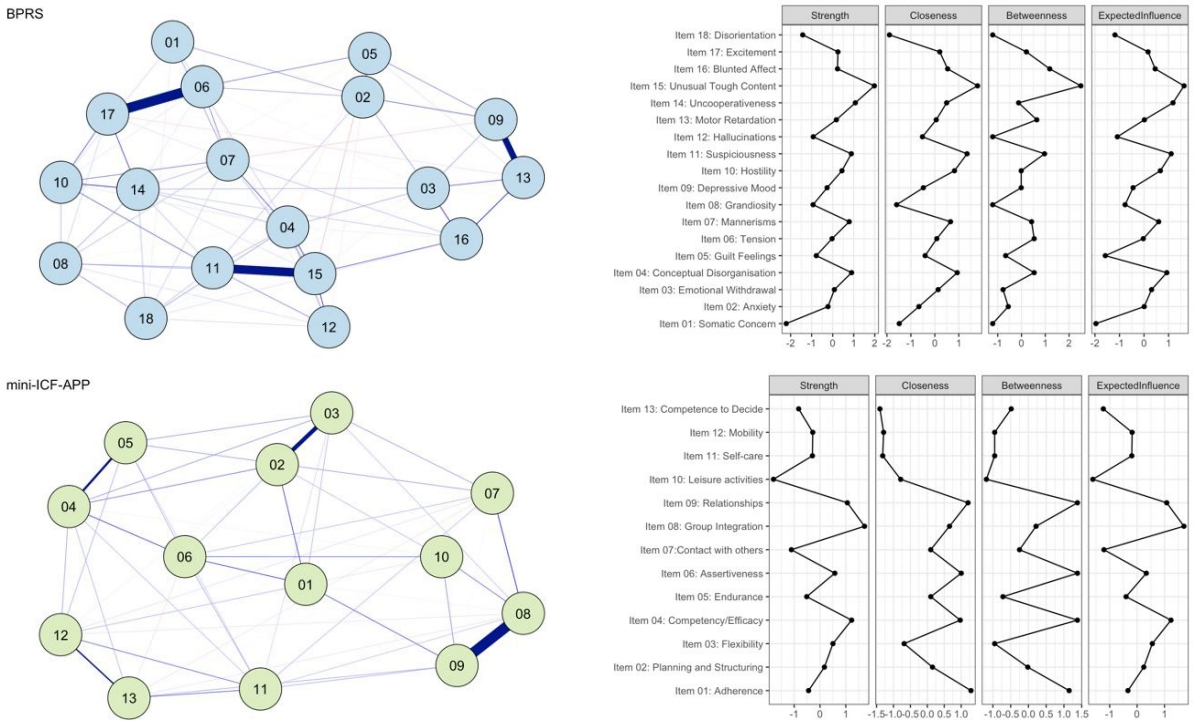
B. Bland Altman Plot using z-scores of the BPRS and mini-ICF-APP scales



1

Figure 2

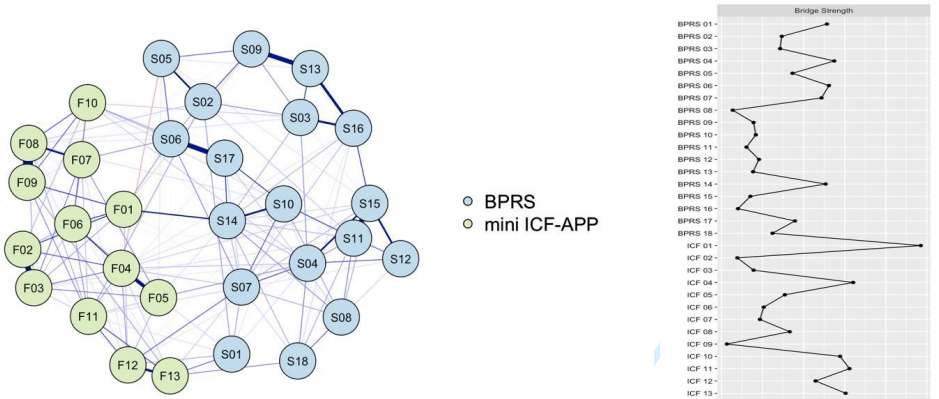
Network Analysis for the BPRS and the mini-ICF-APP



6

Figure 3

Joint Network Analysis for the BPRS and the mini-ICF-APP scales



1

5. Discusión

Empleando ultrasonido transcraneal se pudo evaluar las características hemodinámicas de las arterias cerebrales medias durante una tare cognitiva en pacientes con esquizofrenia y controles sanos. Los pacientes con esquizofrenia tardaron más que los controles sanos en completar la tarea neuropsicológica, demostrando un desempeño cognitivo inferior. Paralelamente, la medición con ultrasonido transcraneal del flujo sanguíneo en las arterias cerebrales medias expuso un patrón de flujo distintivo entre pacientes con esquizofrenia y controles sanos. Adicionalmente, entre los pacientes con esquizofrenia, una carga sintomática mayor se relaciona con una prolongación en el tiempo para completar la tarea neuropsicológica, a la vez que un patrón hemodinámico más distintivo.

5.1. Estudio 1 - Neurofisiología

5.1.1. Resultados de la Tarea Neuropsicológica

Los pacientes con esquizofrenia tardaron significativamente más en completar la tarea neuropsicológica con un nivel equiparable de fallos. Por ende, se puede afirmar que los pacientes con esquizofrenia tienen una velocidad de procesamiento menor que los controles sanos; a la vez que la carga sintomática en pacientes con esquizofrenia influye negativamente en la velocidad de procesamiento.

En los controles sanos se pudo observar una relación entre la edad de los participantes y el desempeño durante la actividad neuropsicológica. En pacientes con esquizofrenia no pudimos observar esta relación, teniendo los pacientes con esquizofrenia básicamente un bajo desempeño independientemente de la edad (109,

133, 134). La falta de relación entre la edad y el desempeño cognitivo en los pacientes con esquizofrenia puede deberse a que el deterior cognitivo es constante durante el curso de la enfermedad, por lo cual el efecto de la edad no puede ser observado (135, 136). Sugiriendo que el efecto de la edad sobre el desempeño cognitivo durante una tarea neuropsicológica obedece a mecanismos distintos en participantes sanos y en pacientes con esquizofrenia (137). El desempeñó cognitivo, durante la tarea neuropsicológica, esta inversamente relacionado con los niveles de carga sintomática y con el nivel de gravedad, un resultado intuitivo en la misma línea que resultados previos (138).

5.1.2. Resultados del Estudio Neurofisiológico

Los controles sanos en nuestro estudio demostraron durante ambas partes del “Trail Making Test” un incremento inicial en la velocidad de flujo cerebral en las arterias cerebrales medias, la cual retorna progresivamente a sus valores iniciales. Con lo cual se ha podido reproducir resultados previos (139). Esto ha sido relacionado con un resultado temporalmente limitado de la actividad cerebral en respuesta a un estímulo, un fenómeno reportado para diferentes tareas neuropsicológicas (139-141).

Los pacientes con esquizofrenia tienen un patrón de flujo en las arterias cerebrales medias que difiere en dos aspectos fundamentales al observado en controles sanos. En primer lugar, el incremento en la velocidad de flujo es diferida. En segundo lugar, la velocidad de flujo no retorna a sus valores iniciales; inclusive formando un segundo pico de incremento. Adicionalmente pudimos demostrar que los patrones de flujo difieren entre los pacientes con esquizofrenia, de acuerdo con la carga sintomática.

Las diferencias son más acentuadas en pacientes con una mayor carga sintomática; a la vez que con mayor dificultad de la tarea neuropsicológica.

La relación entre el patrón hemodinámico, la gravedad de la carga sintomática, y la demanda cognitiva de la tarea neuropsicológica está vinculada a la velocidad de procesamiento. Nuestros resultados refuerzan la noción que la activada neuronal y el flujo sanguíneo cerebral están estrechamente ligadas entre si (90, 142). Los cambios hemodinámicos en las arterias cerebral medias durante una tarea neuropsicológica son por ende resultado de la activación (o la falta de desactivación) de las áreas corticales en su área de irrigación (90, 95, 112, 143, 144). Los pacientes con esquizofrenia demuestran una actividad cerebral incrementada, que se refleja en un incremento en la velocidad de flujo de mayor duración, a la vez que tienen un desempeño pobre en comparación con los controles sanos (92).

Las distintas actividades visuales y motoras que conllevan a la resolución satisfactoria de cada uno de los componentes del “Trail Making Test” pueden estar relacionadas con las diferencias en el flujo cerebral en las arterias cerebrales medias. Esta observación es compartida con estudios previos empleando distintos métodos de examinación, donde también se pudo observar patrones de activación distintivos para el “Trail Making Test” parte A y parte B (93, 145). En este estudio, los pacientes con esquizofrenia demostraron una mayor aberración en el “Trail Making Test”, siendo esta mayor para la parte B que para la parte A.

En los pacientes con esquizofrenia que tuvieron un desempeño similar durante el “Trail Making Test” parte B que los controles sanos, el flujo cerebral seguía mostrando

un patrón distintivo, básicamente con la persistencia del flujo cerebral elevado. En estudios previos de neuroimagen, con paradigmas de memoria funcional, el nivel de desempeño no constituyó un factor de confusión con respecto a los resultados de la resonancia magnética funcional. Es más, en dicho estudio el control de la variable de desempeño no alteró las diferencias encontradas en pacientes con esquizofrenia con respecto a los controles sanos (146). Empleando un diseño similar, con un paradigma para evaluar la función ejecutiva se pudo demostrar que los pacientes con esquizofrenia tienen una actividad cerebral elevada en comparación con los controles sanos, para alcanzar niveles similares de desempeño (147).

Estos resultados convergen con respecto al desempeño pobre en el "Trail Making Test" de pacientes con esquizofrenia en comparación con controles sanos. Sin embargo, el incremento en flujo cerebral contrasta con resultados previos empleando el "Trail Making Test", en los cuales se reporta una diminución en la activada prefrontal por medio del método Near-infrared spectroscopy NIRS (112, 148). Esta discrepancia, puede deberse a varios factores. En primer lugar, el ultrasonido transcraneal y el método NIRS no evalúan el mismo fenómeno hemodinámico, el uno mide velocidad de flujo mientras que la otra la relación de hemoglobina oxigenada/desoxigenada: la velocidad de flujo se corresponde con la cantidad de hemoglobina desoxigenada (94). En segundo lugar, las regiones analizadas por ambos métodos son diferentes. El ultrasonido transcraneal evalúa las características hemodinámicas de la arteria cerebral media, la cual irriga a la parte lateral de los hemisferios cerebrales, incluyendo estructuras subcorticales como el tálamo (149, 150). Existe evidencia de que el "Trail Making Test" involucra a varias redes neuroanatómicas y neurofuncionales, localizadas en áreas frontales, ganglios basales y estructuras

talámicas (113); es decir, que no solo involucra estructuras corticales. El método NIRS, por otro lado, permite una localización neuroanatómica más precisa, con la limitación de que tan solo puede evaluar áreas corticales (112). Finalmente, el estudio involucrado NIRS, no empleaba como parámetro el tiempo para completar la tarea, además de que permitía la repetición múltiple de la prueba. Tomando en cuenta que para el "Trail Making Test" se han reportado efectos de aprendizaje (151), nuestro estudio solo permitió un prueba por participante precisamente para evitar el efecto de aprendizaje.

La evidencia derivada de estudios con resonancia magnética funcional es indicativa de que los pacientes con esquizofrenia no son capaces de desactivar regiones cerebrales durante una tarea neuropsicológica, con una activación incrementada en los núcleos caudados, el área témporo-parietal, el córtex rostral prefrontal, el giro inferior frontal, la ínsula, el claustro, y el cíngulo (152, 153). El incremento del flujo cerebral en pacientes con esquizofrenia puede deberse a una desregulación de la modulación cerebral (154) con una respuesta neurovascular exagerada, o bien al fallo de desactivación de regiones cerebrales en el territorio de irrigación de la arteria cerebral media.

La actividad cerebral necesaria para completar satisfactoriamente el "Trail Making Test" difiere para la parte A de la parte B. En el caso de la parte A, están involucradas áreas relacionadas con la velocidad grafomotora, el escaneo visual, y la atención selectiva. Mientras que en la parte B están involucradas áreas relacionadas con la flexibilidad mental y las funciones ejecutivas (111). Estudios previos muestran una relación mayor entre el flujo cerebral en la arteria cerebral media y el Trail Making

Test parte B. Esto puede deberse a la activación del córtex dorsolateral prefrontal, los ganglios basales y el tálamo (93, 94). Algunas de estas áreas están involucradas en la psicopatología y el déficit cognitivo presente en los pacientes con esquizofrenia (96, 146). Estudios previos muestran una correlación entre el desempeño neurocognitivo y los patrones hemodinámicos de las arterias cerebrales (91, 92, 96). Esto soporta la visión de que hay factores hemodinámicos inherentes a la esquizofrenia, como son: la disfunción de la integridad neuronal, la aceleración del envejecimiento de la substancia blanca, la hipoperfusión frontal y el incremento en la resistencia cerebral (155-158).

5.1.3. Resultados de la Evaluación de los Métodos Estadísticos

Los métodos estadísticos paramétricos se emplean en la mayor parte de áreas de investigación, incluyendo la biología, medicina y psicología (85, 86, 88). La mayoría de los estudios que emplean ultrasonido transcraneal analizan los resultados obtenidos agrupando los datos de los participantes, siendo el análisis de regresión y el análisis de variación los métodos estadísticos aplicados con mayor frecuencia (85, 89). El modelo lineal general es capaz de incluir variables cualitativas y cuantitativas en el análisis matemático, siendo el análisis de regresión y el análisis de variación instancias particulares del modelo lineal general (159). A pesar de su versatilidad, el modelo lineal general tiene limitaciones, en particular cuando analiza variables dinámicas e interdependientes como son el flujo y la velocidad, siendo su análisis y representación en ocasiones contraintuitiva. En contraste, análisis no paramétricos,

como el modelo adicional general, permiten una representación superior y de interpretación intuitiva de variables dinámicas e interdependientes; sin embargo, su análisis e interpretación estadística son más complejas (159, 160).

El modelo aditivo general se empleó para la evaluación estadística y la representación gráfica de los resultados de la medición hemodinámica; incluyendo variables cualitativas y cuantitativas (161). En la comparación directa entre el modelo lineal general y el modelo aditivo general, fue este último el que demostró su superioridad. Este modelo permite un análisis robusto de los datos obtenidos, con gran flexibilidad en cuanto a los prerrequisitos y las sumisiones de los datos (159, 161, 162), a la vez que incorpora los cambios dinámicos y la interdependencia presente entre estos (163, 164). Todo ello, permite una representación gráfica del flujo cerebral de fácil interpretación clínica. Sin embargo, la comparación matemática y estadística de los modelos obtenidos a través del modelo adicional general es mucho más compleja (159, 160). Por lo cual, en un segundo paso, se compararon entre sí los modelos obtenidos empleando un análisis de covarianza. Este proceso permite discernir puntualmente las diferencias estadísticas entre las curvas hemodinámicas.

5.1.4. Influencia de los Efectos Secundarios de la Medicación

Los psicofármacos, en particular los antipsicóticos, pueden interferir en el desempeño neurocognitivo, ya sea de manera directa por medio de los efectos adversos y secundarios sobre el sistema neuronal de neurotransmisión, o indirecta atreves de su actividad vascular y por ende hemodinámica (165-169). Adicionalmente, la

medicación también puede influenciar la hemodinámica cerebral (166). La relación entre la medicación antipsicótica, el desempeño cognitivo y el flujo cerebral es compleja, donde tienen que ser considerados como factores determinantes: la indicación médica, es decir el trastorno en si, su gravedad y su evolución clínica; a la vez que la medicación, su dosificación, duración del tratamiento, efectos secundarios y adversos (170). En el diseño de este estudio estos factores no fueron controlados directamente. Sin embargo, en los diferentes grupos de pacientes con esquizofrenia no se encontraron diferencias significativas entre la medicación y los efectos adversos. La carga sintomática, la duración de la enfermedad y el número de hospitalizaciones están relacionadas entre sí; siendo todos factores indicativos de gravedad que se relaciona con un desempeño cognitivo bajo (171, 172).

En pacientes con acatisia encontramos una disminución en la actividad de control visomotora, especialmente al inicio. La acatisia es una forma especial de los síntomas extrapiramidales que aparece debido a la acción anti-dopaminérgica de los antipsicóticos. Sin embargo las diferencia fisiopatológicas entre los síntomas extrapiramidales y la acatisia es elusiva (173), siendo el estriado una región neuroanatómica afectada, principalmente por su alta densidad de receptores D2 (174). En términos clínicos, la acatisia es un trastorno del movimiento con intranquilidad que implica síntomas subjetivos tanto como objetivos. La acatisia aparece con una frecuencia de hasta dos tercios en pacientes con tratamiento antipsicótico (175), por lo que tiene una importancia clínica, siendo en ocasiones una causa de deterioro cognitivo, discapacidad y sufrimiento (147, 176).

5.1.5. Limitaciones y Fortalezas del Estudio 1

Las limitaciones de este estudio y por ende de sus resultados son inherentes al estudio por ultrasonido. En primer lugar, en contraste con otros métodos no se obtuvo una imagen neuroanatomía directa, limitando los resultados al territorio de irrigación de las arterias cerebrales medias. A pesar de esta limitación, el estudio por ultrasonido está capacitado para detectar la relación entre actividad cerebral y función cognitiva, siendo su mayor fortaleza la alta resolución temporal (141, 177, 178).

La influencia de los cambios en la circulación sistémica sobre el flujo sanguíneo cerebral no fue controlada directamente. La circulación sistémica, en especial la frecuencia cardiaca y la presión sanguínea, podrían contribuir a un incremento en flujo el cerebral durante una activad motriz (88, 179, 180). En este estudio estos efectos fueron controlados al incluir una tarea de control visomotor y al usar valores de flujo relativos a un nivel de base previo y posterior a la tarea. Sin embargo, la condición de control visomotor, con movimientos aleatorios tiene el potencial de activar áreas neurocognitivas (181), por lo cual esta no puede ser considerada perfecta. La actividad de control visomotor tiene el potencial de nivelar los efectos comunes, como es el caso de la circulación sistémica, y compensar factores inespecíficos y sutiles de confusión permitiendo resaltar las diferencias en las áreas de activación cortical (97, 182).

Existen otros factores capaces de alterar el flujo cerebral, particularmente la ansiedad por medio de la hipo o hiperventilación (183, 184). En este estudio no se pudo observar signos de ansiedad previa o durante el examen. Todos los participantes del

estudio tenían una condición cardiocirculatoria estable, estando los valores de pulso, presión arterial y frecuencia respiratoria dentro de los rangos fisiológicos de normalidad; por lo cual descartamos un efecto de estos sobre los resultados.

Por otra parte, la falta de otras pruebas neuropsicológicos limita la interpretación de los resultados a los medidos por el “Trail Making Test”. Tomando en consideración que los controles sanos y los pacientes tenían un mismo nivel de errores (es decir ambos tuvieron un nivel de exactitud similar), la diferencia entre ambos se da básicamente al nivel de la velocidad de procesamiento. Limitando por ende la generalización de nuestros resultados a otros aspectos de la enfermedad o de la función neurofisiológica.

El sexo es un factor modificante en la neurofisiología (97, 178), pero debido al bajo número de participantes mujeres no pudimos conducir un análisis comparativo. Sin embargo, la distribución de hombres y mujeres, tanto en pacientes con esquizofrenia como en controles sanos fue similar; por cual cabe especular que los efectos del sexo serán cancelados a nivel global.

La edad de los participantes también constituye un factor modificante, tanto para el desempeño neurocognitivo como para la función neurofisiológica. En nuestros resultados se pudo observar un efecto de la edad en los controles sanos, mas no en los pacientes con esquizofrenia. Al igual que con el sexo, el número de participantes fue reducido para realizar un análisis estratificado por edad: por lo cual no podemos discernir este efecto. Sin embargo, el emparejamiento por edad nos permite controlar para esta variable y limitar sus efectos.

5.1.6. Aplicación Clínica, Líneas futuras de Investigación

Estudio 1

Los resultados obtenidos en el presente estudio deben ser considerados preliminares, al momento se cuenta con los datos y el análisis de controles sanos y pacientes con esquizofrenia. Los resultados y las conclusiones publicadas por ende se limitan a este colectivo. En función de expender el uso y la utilidad del ultrasonido transcraneal, esta previsto el reclutamiento de pacientes con cuadros psiquiátricos distintivos, como son la depresión, la dependencia de alcohol y los trastornos de personalidad. Sin embargo a día de hoy, no existen instrumentos psicométricos que puedan ser aplicados utilitariamente a estos trastornos, por lo cual se dificulta la comparación de los resultados.

La relevancia de los resultados obtenidos está supeditada a su utilidad para comprender la enfermedad en sí, los mecanismos neurofisiológicos y neuroanatómicos subyacentes. Desde un punto de vista clínico, la importancia de los resultados se deriva de su utilidad como instrumentos de diagnóstico, evaluación o pronóstico. Teniendo en cuenta estos aspectos, más allá de mejorar la comprensión neurofisiológica de la esquizofrenia, estos resultados aportan poco a la práctica clínica de la psiquiatría y la neuroimagen. De cara a incrementar la utilidad de los resultados y su divulgación, resulta imprescindible determinar su empleo clínico. Para ello, es necesario establecer parámetros de referencia con respecto a los niveles de sintomatología, funcionalidad, discapacidad y calidad de vida de los pacientes; a la vez que su valor diagnóstico y pronóstico.

El emplear ambas escalas en conjunto posibilita la aplicación clínica de los resultados obtenidos mediante ultrasonido transcraneal. Futuros estudios podrían incorporar el ultrasonido transcraneal como método de evaluación en distintos trastornos mentales. Por medio de las escalas podemos determinar las capacidades de este método para mejorar el diagnóstico, a la vez que evaluar el tratamiento. El empleo del ultrasonido transcraneal, como método de neuroimagen resulta particularmente útil puesto que permite un fácil acceso con bajos costos; a la vez que es capaz de medir con alta resolución temporal cambios en la neurofisiología cerebral.

5.2. Estudio 2 - Psicometría

5.2.1. Resultados del Estudio para la Evaluación Psicométrica

Actualmente no existen parámetros aceptados para determinar y comparar la gravedad de un trastorno mental con otros trastornos, a la vez que no es posible comparar la gravedad en el transcurso de la enfermedad, si existe un cambio de diagnóstico o la presencia de nuevos síntomas o una comorbilidad psiquiátrica (107, 108, 185-187). Casi independientemente de la carga sintomática, es la capacidad funcional, o el grado de discapacidad, es fundamental para determinar la gravedad de un trastorno (188, 189). En este respecto, sin embargo, casi no existen

instrumentos de diagnóstico universalmente válidos y aceptados. La escala Mini-ICF-APP fue creado con el objetivo de cerrar esta brecha (56, 99).

La escala de funcionalidad Mini-ICF-APP, posee buenas características psicométricas y ha sida validado en varios trastornos psiquiátricos (52, 99, 190-192). Sin embargo, su utilidad como instrumento transdiagnóstico no ha sido investigada sistemáticamente (121, 190). Nuestros resultados demuestran que la mini-ICF-APP es un instrumento capaz de determinar el nivel de discapacidad independientemente del trastorno mental. Así, se han identificado perfiles distintivos para los diferentes grupos diagnósticos, que comparten afectación común de varias áreas de funcionalidad, a la vez que problemas específicos de cada uno de ellos. Esto permite, determinar el grado de severidad y discapacidad de un trastorno mental, así como su evolución clínica.

La determinación transdiagnóstica de la discapacidad y las limitaciones en la participación, es necesaria pero no suficiente. Sobre todo, en el momento de seleccionar un tratamiento, el enfoque se dirige a los síntomas presentes (185, 189). En la actualidad prácticamente no existen instrumentos capaces de ser empleados para determinar la sintomatología en todo el espectro diagnóstico. Tomando en cuenta la progresión de ciertos trastornos, esto dificulta la evaluación efectiva del tratamiento (107, 188), especialmente considerando que las escalas específicas tienen efectos suelo o techo cuando son aplicadas a pacientes con un diagnóstico distinto para el que fueron diseñadas (24).

La Escala Breve de Evaluación Psiquiátrica, BPRS, fue diseñada originalmente como una escala de aplicación transdiagnóstica para los trastornos mentales graves, como son la esquizofrenia, el trastorno bipolar y la depresión con síntomas psicóticos (25). Por este motivo en la escala no se esperan efectos techo, sin embargo, no se ha investigado su desempeño en trastornos menos graves. Tomando en consideración que la escala fue diseñada para medir no solo gravedad sino también mejoría, no caben esperar efectos suelo. De hecho, la Escala Breve de Evaluación Psiquiátrica, BPRS, se emplea sistemáticamente en estudios clínicos que involucran a pacientes con distintos trastornos o comorbilidad psiquiátrica (31-33).

La Escala Breve de Evaluación Psiquiátrica, BPRS, fue capaz de capturar el aspecto dimensional de la psicopatología de varios trastornos psiquiátricos, a la vez que delimitando los síntomas y agrupaciones de síntomas característicos para cada diagnóstico. Corroborando, resultados previos obtenidos principalmente por el análisis factorial de la escala en varias populaciones clínicas (193). Por lo que la BPRS parece ser útil como instrumento capaz de determinar la psicopatología en su aspecto dimensional, atreves del espectro de diagnósticos psiquiátricos (194). El nivel de centralidad de los distintos síntomas psicopatológicos (BPRS) y dominios funcionales (Mini-ICF-APP) refleja su importancia dentro de la red. En el caso de los síntomas psicopatológicos, son los trastornos del pensamiento (desorganización conceptual, suspicacia y contenido inusual del pensamiento) aquellos que juegan un rol central. En el caso de los dominios funcionales son la capacidad socializar (interacción grupal y relaciones familiar e intimas), a la vez que la competencia las que tienen un rol pivotal (195-198).

En nuestro estudio incluimos varios trastornos psiquiátricos distintos, con una muestra equilibrada con respecto al diagnóstico principal y comorbilidad, para evitar que las peculiaridades de un determinado trastorno determinen el análisis final. Por lo cual podemos concluir que existe un factor psicopatológico general, presente en varios trastornos psiquiátricos (199-201). La presencia de estos síntomas y déficits funcionales parece determinante para la severidad y auto manutención de los síntomas psiquiátricos (107, 202), donde distintos trastornos psiquiátricos pueden (al menos temporalmente) tener niveles similares de discapacidad (189).

5.2.2. Limitaciones y Fortalezas del Estudio 2

Una fortaleza de nuestro estudio es el tamaño de la muestra clínica, en la que se incluye la mayor parte del espectro diagnóstico psiquiátrico. Lo que permite un análisis estadístico robusto, así como la generalización de los resultados para la escala Mini-ICF-APP. Para el análisis de las propiedades de la escala Mini-ICF-APP utilizamos la aproximación por medio del análisis factorial, lo que permite un aproximamiento a las propiedades de un instrumento psicométrico (123, 203).

Para el análisis psicométrico y comparativo de las escalas de carga psicopatológica y funcionalidad-discapacidad incluimos grupos balanceados por diagnóstico; lo cual limita los posibles efectos de sobrerrepresentación por parte de un grupo de pacientes en los resultados. La validez de ambas escalas fue analizada por métodos estadísticos distintos, el primero por medio de un análisis de correlación, el segundo por el análisis de concordancia. Para el análisis psicométrico de las escalas BPRS y Mini-ICF-APP escogimos un aproximamiento a través del análisis de redes. En

primera instancia, tomando en cuenta de que para ambas escalas ya existían trabajos publicados empleando el análisis factorial (incluyendo el nuestro) (191, 193, 204). En segundo lugar, porque el análisis de redes permite evaluar la influencia de un síntoma o dominio funcional sobre la red formada por su propia escala, a la vez que sobre la escala complementaria. Puesto que el análisis de redes es susceptible de ser alterado por la composición de la muestra (205) incluimos un número equilibrado de pacientes para cada dimensión diagnóstica (206, 207).

A pesar de sus fortalezas, nuestro estudio tiene limitaciones. En primer lugar, incluimos tan solo el diagnóstico de tratamiento para el análisis, por lo cual se pierde en el análisis la influencia de la comorbilidad psiquiátrica. Esta limitación buscamos compensarla incluyendo la comorbilidad de trastornos de personalidad, y dependencia de alcohol y substancias (208, 209). Nuestra muestra incluyó exclusivamente pacientes que requerían un tratamiento hospitalario, por lo cual la generalización de nuestros resultados se puede reducir a este grupo de pacientes, los cuales por lo general tienen un mayor grado de discapacidad. En esta línea tenemos que mencionar que nuestra muestra deriva de la práctica clínica diaria, y tiene por consiguiente ciertas limitaciones con respecto a los detalles diagnósticos y psicopatológicos que puede proveer (210).

5.2.3. Aplicación Clínica, Líneas futuras de Investigación del Estudio 2

Nuestros resultados refuerzan la noción de que los trastornos psiquiátricos afectan principalmente al pensamiento y al lenguaje (211, 212), por lo cual requieren para su diagnóstico y tratamiento una aproximación a través del habla y la comunicación. De hecho, estos síntomas son los objetivos de una intervención psiquiátrica-psicoterapéutica. En primer lugar, el establecer confianza y una alianza terapéutica, por medio de un lenguaje común, así como la comprensión del concepto médico y alcance de la enfermedad mental por parte de la persona afectada (198, 213, 214). En segundo lugar, fomentar y en algunos casos reestablecer la asertividad, la cooperación y la adherencia a rutinas. El éxito de estas medidas abre el abanico de alternativas terapéuticas dirigidas a los síntomas característicos para cada uno de los diferentes trastornos psiquiátricos.

En el presente análisis se pudo demostrar que la sintomatología medida por medio de la Escala Breve de Evaluación Psiquiátrica, BPRS, y la discapacidad funcional y participación medida por la Mini-ICF-APP se solapan en un alto grado, pudiendo considerarse que miden la gravedad de un trastorno psiquiátrico desde dos ángulos distintos (215, 216). Ambas escalas muestran un buen desempeño a lo largo del espectro diagnóstico; por lo cual las consideramos aptas para evaluar la carga sintomática y el nivel de funcionalidad-discapacidad en pacientes con un trastorno mental. Asimismo son aptas para comparar pacientes con diferente diagnóstico, así como para documentar la evolución de los cuadros clínicos. Por estos motivos consideramos que ambas escalas se complementan en la práctica clínica, siendo la una determinante para realizar el diagnóstico y orientar el tratamiento adecuado, mientras que la otra es determinante para establecer la mejoría funcional y, por ende, el efecto del tratamiento más allá de la reducción sintomática (107, 188).

El empleo de escalas comunes en diferentes trastornos y diagnósticos psiquiátricos facilita la comparación de resultados clínicos y experimentales a lo largo del espectro diagnóstico (208, 209). Nuestros resultados muestran que tanto la Escala Breve de Evaluación Psiquiátrica, BPRS, como la Mini-ICF-APP son aptas para su uso conjunto en diferentes trastornos mentales (194). Sin embargo, su implementación como instrumentos transdiagnósticos y de comparación en la práctica clínica y de investigación aún no está suficientemente generalizada y en la actualidad se limita a varios estudios con un impacto limitado (32, 217, 218).

6. Conclusiones

Tomando en consideración los resultados obtenidos, así como su valoración con el actual estado del conocimiento, hemos de concluir:

1. Por medio del desarrollo del “Trail Making Test”, como tarea neuropsicológica, se ha podido comprobar que:
    - Los pacientes con esquizofrenia tienen un desempeño cognitivo inferior al de los controles sanos.
    - El desempeño cognitivo en pacientes con esquizofrenia se deteriora en relación con un aumento en la carga sintomática y una mayor complejidad de la tarea.
    - En controles sanos se pudo determinar un deterioro en el desempeño cognitivo en relación directa con la edad; mientras que en pacientes con esquizofrenia no se pudo determinar un deterioro en el desempeño cognitivo en relación con la edad.

2. Por medio de la medición continua del flujo cerebral en las arterias cerebrales medias con ultrasonido transcraneal, durante una tarea neuropsicológica se ha podido comprobar que:
    - Pacientes con esquizofrenia tienen un patrón de flujo cerebral diferente al de los controles sanos, caracterizado por un incremento diferido y mantenido en la velocidad de flujo cerebral en las arterias cerebrales medias.
    - El patrón de flujo en pacientes con esquizofrenia muestra un mayor grado de aberración en relación con un aumento en la carga sintomática y con una mayor complejidad de la tarea.

3. Por medio de la comparación de varios métodos y modelos estadísticos de análisis se ha comprobado la utilidad y superioridad de métodos no paramétricos para analizar la velocidad de flujo cerebral en las arterias cerebrales medias durante una actividad visomotora de control.

4. Por medio del análisis factorial de la escala para evaluar funcionalidad-discapacidad Mini-ICF-APP se ha podido comprobar que:
   - El nivel de discapacidad funcional en trastornos mentales puede ser determinado por medio de la escala Mini-ICF-APP; teniendo esta un desempeño similar a lo largo del espectro diagnóstico.
   - El nivel de funcionalidad-discapacidad de un paciente es independiente de su diagnóstico psiquiátrico.
   - Los diferentes trastornos psiquiátricos afectan a dominios funcionales generales, así como a otros particulares para cada trastorno.

5. Por medio del análisis de correlación y concordancia, así como por el análisis de red entre las escalas Escala Breve de Evaluación Psiquiátrica, BPRS, y Mini-ICF-APP se ha podido comprobar que:
   - La Escala Breve de Evaluación Psiquiátrica, BPRS puede ser empleada genéricamente para diferentes trastornos mentales.
   - La Escala Breve de Evaluación Psiquiátrica, BPRS es capaz de evaluar síntomas psicopatológicos comunes entre los diferentes trastornos mentales, a la vez que es capaz de discernir síntomas y agrupaciones de síntomas específicos de cada diagnóstico psiquiátrico.

- La discapacidad funcional está relacionada con la carga sintomática del trastorno mental.
- Diferentes trastornos mentales tienen diferentes patrones de relación entre los síntomas y la discapacidad funcional.
- Existen síntomas psicopatológicos determinantes para el nivel de funcionalidad- discapacidad, presentes a lo largo del espectro diagnóstico.

6. Por medio del análisis de correlación y concordancia se ha podido comprobar que:
   - La evaluación de la psicopatología por medio de la Escala Breve de Evaluación Psiquiátrica, BPRS, y la evaluación de funcionalidad-discapacidad por medio de la escala Mini-ICF-APP pueden usarse de manera complementaria.
   - El emplear ambas escalas en conjunto posibilita la comparación y eventual aplicación clínica de los resultados obtenidos mediante ultrasonido transcraneal.
   - Sin embargo, es necesario tener en cuenta que estos resultados no son todavía suficientemente concluyentes.

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