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Acontecimientos vitales estresantes, perfil de personalidad y correlatos neurales en la ansiedad social

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A mis padres

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Siglas y Abreviaciones

ALE	Estimación de la Probablidad de Activación (Activation Likelihood Estimation)
AVEs	Acontecimientos Vitales Estresantes
DSM	Manual Estadístico y Diagnóstico de los Trastornos Mentales (Diagnostic and Statistical Manual of Mental Disorders)
FFA	Área Fusiforme de las Caras (Fusiform Face Area)
fMRI	Resonancia Magnética Funcional (Functional Magnetic Resonance Imaging)
HA	Evitación del Daño (Harm Avoidance)
HHA	Eje Hipotalámico-Hipofisiario-Adrenal
HAns	Alta Evitación del Daño - Baja Búsqueda de Novedad
HANS	Alta Evitación del Daño - Alta Búsqueda de Novedad
LSAS	Escala de Ansiedad Social de Liebowitz (Liebowitz Social Anxiety Scale)
MINI	Entrevista Mini-Internacional Neuropsiquiatria (Mini-International Neuropsychiatric Interview)
NS	Búsqueda de Novedad (Novelty Seeking)
OFA	Área Occipital de las Caras (Occipital Face Area)
SCID	Entrevista Clínica Estructurada para el Diagnóstico de Trastornos DSM-IV (Structured Clinical Interview for DSM-IV Disorders)

STAI	Inventario de Ansiedad Estado-Rasgo de Spielberger (State-Trait Anxiety Inventory)
STin2.VNTR	Número Variable de Repeticiones en Tándem del STin2 (Variable Number Tandem Repeat of the STin2)
TAS	Trastorno de Ansiedad Social
TCI	Inventario de Temperamento y Carácter de Cloninger (Temperament and Character Inventory)
TKS	Síndrome de Taijinkyofusho
SW	Síndrome de Williams-Beuren
5HTTLPR	Polimorfismo del gen transportador de la serotonina (Serotonin Transporter Linked Polymorphic Region)

Índice

Marco general del proyecto

A pesar de ser uno de los trastornos de ansiedad más frecuentes y de asociarse a un importante deterioro psicosocial, el Trastorno de Ansiedad Social continúa siendo en comparación con otros trastornos de ansiedad, un trastorno poco estudiado. Ello, se ha reflejado que un crecimiento más lento y en un menor número de publicaciones científicas en los últimos 20 años en comparación al resto de trastornos de ansiedad.

En este contexto, en el año 2007, se inicia un amplio proyecto de investigación sobre el Trastorno de Ansiedad Social (Estudio ANSIOS (IMIM/UAB; IP: R. Martín-Santos/S. Subirà) al que me incorporé como colaboradora mediante una beca de Colaboración otorgada por el Ministerio de Educación, Cultura y Deporte en el año 2007. El presente trabajo forma parte de esta línea de investigación. Parte de esta investigación ha sido realizada con las siguientes ayudas a la investigación: Instituto Carlos II (G03/184, IP: R. Martín-Santos; PI052565, IP: R. Martín-Santos) y el apoyo de la Generalitat de Catalunya (SGR2009/1435; IP: R. Martín-Santos).

Los resultados parciales y finales de esta tesis han sido presentados previamente en congresos nacionales e internacionales, y algunos de ellos, han recibido una distinción.

Presentaciones en congresos:

Binelli C, Batalla A, Crippa JA, Pérez-Jurado L, Subirà S, Martín-Santos R. "*Common and different neural correlates during facial emotion processing in Social Anxiety Disorder and Williams Syndrome: A systematic review and metanalysis".* Póster aceptado para el próximo "XVI World Congress of Psychiatry", Madrid (Septiembre 2014).

Ortiz A, **Binelli C**, Muñiz A, Crippa JA, Subirà S, Martín-Santos R. *Social Anxiety Disorder, Comorbidity, and Early* Life Events: A Case-Control Study. "32nd Anxiety and Depression Association of America (ADAA): Integrating Mind-Body Connections:

Advancing Science, Informing Practice for Anxiety and Related Disorders", Virginia (EEUU), (Abril de 2012).

Binelli C., Gelabert E., Ortiz A., Subirá S., Martín-Santos R. *The Role of Early Negative Life Events During Childhood on Social Anxiety In Adulthood*". "19th European Congress of Psychiatry", Viena (Marzo de 2011).

Ortiz A., **Binelli C**., Ferranz L., Langhor K., Gelabert E., Subirà S., Batalla A., Moreno J., Muñiz A., y Martín-Santos R. *¿Are stressful life events during childhood associated to the presence of social anxiety in adulhood?* XIII Congreso Nacional de Psiquiatría, Madrid (Octubre de 2009).

Binelli C., Ortiz A., Santos Filho A., Ferranz L., Langhor K., Subirà S., Crippa J., y Martín-Santos R. *Gender, negative life events and risk of social anxiety*. "Jornada Sul-Brasileira de Psiquiatría". (Brasil, Mayo de 2009).

Binelli C., Gelabert E., Plaza A., Garcia-Esteve L., Subirá S., y Martin-Santos R. *Life events during childhood and social anxiety*. Congreso Anual de la Societat Catalana de Recerca i Teràpia del Comportament (SCRiTC).(Barcelona, 2008).

Premios:

Premio al mejor póster. **Binelli C**., Gelabert E., Ortiz A., Subirá S., Martín-Santos R. *"The Role of Early Negative Life Events During Childhood on Social Anxiety In Adulthood".* 19th European Congress of Psychiatry. (Viena , Marzo de 2011).

Premio Accesit de Investigación Dr. Antonio Zuardi. **Binelli C**., Gelabert E., Ortiz A., Subirá S., Martín-Santos R. *"Gender, negative life events and risk of social anxiety"*. Jornada Sul-Brasileira de Psiquiatría (Ribeirao Preto, Brasil, Mayo de 2009).

Los resultados finales de esta tesis se encuentran en proceso o han sido sometidos a publicación en revistas de impacto:

Estudio 1: "*Social anxiety and negative early life events in university students*".
Binelli C, Ortiz A, Muñiz A, Gelabert E, Ferraz L, S Filho A, Crippa JA, Nardi AE, Subirà S, Martín-Santos R. *Social anxiety and negative early life events in university students*. Rev Bras Psiquiatr. 2012 Jun;34(1):S69-74.

Estudio 2: "*New evidence of heterogeneity in social anxiety disorder: defining two distinct personality profiles taking into account clinical, environmental and genetic risk factors".*
Estado: Sometido a publicación; en fase de revisión (*European Psychiatry*).

Estudio 3(a): "*Common and distinct neural correlates during facial emotion processing in Social Anxiety Disorder and Williams Syndrome: A systematic review and voxel-based meta-analysis of functional magnetic resonance studies*".
Estado: Sometido a publicación; en fase de revisión *(Neuropsychologia).*

Estudio 3(b): "*Facial emotion processing in Social Anxiety Disorder and Williams Syndrome: an fMRI study*".
Estado: *En preparación*.

RESUMEN

A pesar de ser uno de los trastornos de ansiedad más frecuentes y de asociarse a un importante deterioro de la vida personal, académica y profesional, el Trastorno de Ansiedad Social continúa siendo uno de los trastornos de ansiedad menos estudiados. El presente proyecto tiene como objetivo general profundizar en el estudio de tres factores que han sido asociados al inicio y/o mantenimiento de la ansiedad social en la literatura previa: los acontecimientos vitales estresantes, los rasgos temperamentales y de personalidad, y la actividad neural durante el procesamiento emocional.

Cuatro estudios fueron realizados para alcanzar estos objetivos: (i) un estudio epidemiológico en el que se estudió la asociación entre cinco acontecimientos vitales estresantes experimentados en la infancia y/o adolescencia (pérdida de una persona querida; abuso físico; abuso emocional; violencia familiar y abuso sexual) y la ansiedad social en la edad adulta en una muestra de adultos jóvenes universitarios; (ii) un estudio caso-control en sujetos con un diagnóstico clínico de Trastorno de Ansiedad Social (DSM-IV) y sujetos controles sanos en el que se estudiaron dos perfiles de personalidad heterogéneos basados en los rasgos temperamentales "*Búsqueda de Novedad*" y "*Evitación del Daño*"; (iii) una revisión sistemática con meta-análisis comparativa de los estudios de resonancia magnética funcional disponibles hasta la fecha examinando paradigmas de procesamiento emocional a través de la expresión facial en sujetos con Trastorno de Ansiedad Social y sujetos con Síndrome de Williams-Beuren, un trastorno del neurodesarrollo raro caracterizado por un fenotipo clínico de escasa ansiedad social y algunas características clínicas opuestas al las observadas en el Trastorno de Ansiedad Social, incluidas las alteraciones en el contacto visual y las alteraciones en el procesamiento de estímulos emocionales/sociales; (iv) y por último, un estudio de resonancia magnética funcional utilizando el paradigma de

procesamiento emocional a través de la expresión facial de Hariri en una muestra de sujetos con Trastorno de Ansiedad Social, una muestra de sujetos con Síndrome de Williams y un grupo de sujetos controles sanos emparejados por edad, sexo y lateralidad.

Los resultados del primer estudio demostraron que la violencia familiar experimentada durante la infancia y/o adolescencia se asocia a la presencia de ansiedad social en la vida adulta, y que un alto porcentaje de estudiantes universitarios sufre de síntomas de ansiedad social. Mediante el segundo estudio, demostramos que no todos los sujetos con un Trastorno de Ansiedad Social presentan el perfil de personalidad prototípico inhibido-evitativo, y que al menos un subgrupo de sujetos muestra alta *búsqueda de novedad* y conductas del espectro impulsivo. Y por último, mediante el tercer trabajo profundizamos en el estudio de las bases neurales del Trastorno de Ansiedad Social y del Síndrome de Williams y realizamos el primer estudio de resonancia magnética funcional comparativo entre ambos trastornos. Los resultados de la comparación directa de sujetos con Trastorno de Ansiedad Social y Síndrome de Williams mientras realizaban una tarea de procesamiento emocional a través de la expresión facial revelaron diferencias significativas entre ambos trastornos en la activación del giro temporal superior, una región involucrada en el procesamiento de la mirada. Los resultados del estudio reflejaron interesantes hallazgos para ambos grupos en la activación de regiones visuales involucradas en el procesamiento del rostro, y la implicación de regiones corticales pre-frontales involucradas en los mecanismos de regulación *top-down* de la ansiedad para sujetos con TAS. Estos resultados sugieren un modelo complejo en el que alteraciones *en* y *entre* regiones visuales, límbicas y prefrontales podrían contribuir a explicar las alteraciones en el procesamiento emocional observadas en el Trastorno de Ansiedad Social y el Síndrome de Williams, y el fenotipo social característico de cada trastorno.

ABSTRACT

Although is one of the most common anxiety disorder, Social Anxiety Disorder remains one of the least studied anxiety disorders. This project has the overall aim to deepen the study of three factors that have been associated with the onset and/or maintenance of social anxiety in the previous literature: Early Stressful Life Events, Personality and Temperamental Traits, and Neural Activity during Emotional Processing.

Four studies were conducted to achieve these goals: (i) an epidemiological study in which we tested the association of five stressful life events experienced in childhood and/or adolescence (loss of someone close, physical abuse, emotional abuse, family violence, and sexual abuse) and social anxiety in adulthood in a large sample of university students; (ii) a case-control study in subjects with a clinical diagnosis of Social Anxiety Disorder (DSM -IV) and healthy control subjects in which we studied two heterogeneous personality profiles based on temperamental traits "*Novelty Seeking*" and "*Harm Avoidance*"; (iii) a comparative systematic review and meta-analysis of functional magnetic resonance imaging (fMRI) studies available to date examining facial emotion processing paradigms in cases with Social Anxiety Disorder and cases with Williams-Beuren Syndrome, a rare neurodevelopmental disorder characterized by a clinical phenotype of low social anxiety and some opposite clinical features to those observed in Social Anxiety Disorder; such as altered processing of gaze and altered processing of emotional and social cues; (iv) and finally, a functional magnetic resonance imaging study using Hariri's facial emotion processing paradigm in a sample of subjects with Social Anxiety Disorder, a sample of subjects with Williams Syndrome and a healthy control group matched for age, sex and laterality.

The results of the first study showed that family violence is associated with the presence of social anxiety in adulthood, and that a high proportion of university students suffer from social anxiety symptoms. With the second study we demonstrated that not all cases with Social Anxiety Disorder have the prototypical inhibited-avoidant personality profile, and that a subgroup of subjects shows high *novelty seeking* and impulsive high-risk behaviors. Finally, with the third study we deepened into the study of the neural basis of Social Anxiety Disorder and Williams Syndrome and conducted the first functional magnetic resonance study comparing the two disorders. The results of the direct comparison of subjects with Social Anxiety Disorder and Williams Syndrome while performing a facial emotional processing task revealed significant differences between the two disorders in the activation of the superior temporal gyrus, a region that has been involved in gaze processing. The study reported interesting findings for both groups in the activation of visual regions involved in face processing, and the involvement of cortical prefrontal regions involved in the *top-down* regulation of anxiety in patients with SAD. These results suggest a complex model in which the alteration *within* and *between* visual, limbic, and prefrontal regions, may explain the changes observed in emotional processing in Social Anxiety Disorder and Williams Syndrome, and social phenotype characteristic of each disorder.

Introducción

‘‘Somos por naturaleza, una especie altamente afiliativa, que ansía el contacto social. Cuando la experiencia social se convierte en una fuente de ansiedad más que en una fuente de temor, hemos perdido algo fundamental. Sea como sea que le llamemos”.

Spinoza

1. Más allá de la timidez.

Ha pasado casi medio siglo desde que *Isaac Marks y Michael Gelder* publicaran los primeros manuscritos describiendo a un grupo de pacientes con ansiedades de tipo social (Marks & Gelder, 1966; Marks, 1970). A partir de las observaciones clínicas de su trabajo en el Hospital Maudsley de Londres, los autores describirían en sus manuscritos a un grupo de pacientes con temores eminentemente sociales; un grupo de personas tímidas, con temor a ruborizarse, a conocer hombres o mujeres, a ir a bailes y fiestas; *“*(…) *miedo a comer, beber, ruborizarse, hablar, escribir o vomitar en frente de otras personas” (*Marks, 1970*,* pg. 383). Un grupo de personas que representaba el 8% de los pacientes del Hospital de Maudsley, y al que los autores describieron como una categoría difusa y diferenciada de la Agorafobia y las Fobias animales (Marks, 1970). Fueron estos trabajos los que impulsarían en gran parte, que en la década de los 80 se reconociera oficialmente a la Fobia Social como una entidad psiquiátrica diferenciada, y se incluyera en la tercera edición del Manual Estadístico y Diagnóstico de los Trastornos Mentales (DSM-III) (APA, 2000).

Las personas con ansiedad social temen y evitan situaciones sociales o actuaciones en público en las que el sujeto se ve expuesto a personas que no pertenecen al ámbito familiar o a la posible evaluación por parte de los demás. El individuo teme actuar de un modo, o mostrar signos de ansiedad que puedan ser evaluados negativamente por los demás. Estas preocupaciones suelen ser tan pronunciadas que llevan al individuo a evitar muchas situaciones sociales; y si ello no es posible, las situaciones se experimentan con ansiedad y malestar intensos (APA,

2013). Al igual que la mayoría de trastornos psiquiátricos, el diagnóstico requiere que el miedo/ansiedad sea desproporcionado, -ya sea en duración y/o en frecuencia- y que los síntomas se presenten de forma persistente. A pesar de que en ediciones previas los criterios diagnósticos exigían que la persona reconociera el miedo como excesivo o irracional, con la reciente publicación de la quinta edición del DSM-V (APA, 2013), este requerimiento queda eliminado y la valoración de este aspecto queda a criterio del clínico. La nueva versión enfatiza en la relevancia de los aspectos culturales y contextuales y la importancia de tenerlos en cuenta a la hora de realizar -o no- el diagnóstico. Mientras que las ediciones previas restringían el diagnóstico a aquellas personas cuyos síntomas no podían explicarse o atribuirse a otra condición psiquiátrica/médica (ej. temor a temblar dentro de la Enfermedad de Parkinson), en la actual versión se admite el diagnóstico en presencia de otro trastorno o enfermedad, siempre y cuando, los temores, la ansiedad y la evitación, sean excesivos a lo esperable en el contexto de dicha enfermedad. El cambio, pretende reivindicar que la ansiedad social secundaria a una condición médica merece un reconocimiento clínico, y que las personas que la sufren también pueden beneficiarse de los tratamientos disponibles. Con la nueva versión desaparece una categoría presente en ediciones previas -el subtipo generalizado-, y se sustituye por el especificador de "*solo ejecución*" aplicable cuando los síntomas se restringen a situaciones en las que el sujetos debe hablar o hacer una ejecución en público. Por último, después de varios años de coexistencia de los términos "Fobia Social" y "Ansiedad Social", siendo el Trastorno de Ansiedad Social (TAS en adelante), una denominación alternativa en el DSM-IV, en la quinta edición se elimina el término Fobia Social y el trastorno pasa a denominarse TAS. El cambio, responde a la preocupación expresada por algunos expertos durante los últimos años y a la evidencia proporcionada por algunos estudios (Liebowitz, Heimberg, Fresco, Travers, & Stein, 2000), que sugieren que el término "Fobia Social" contribuía dentro de los profesionales de la salud mental y la atención primaria a impresiones erróneas y la minimización de la frecuencia y el deterioro asociado al trastorno; junto al poco reconocimiento por pacientes y profesionales como un trastorno que necesita tratamiento (Bruce, Heimberg, & Coles, 2012). Así, se ha propuesto que el término

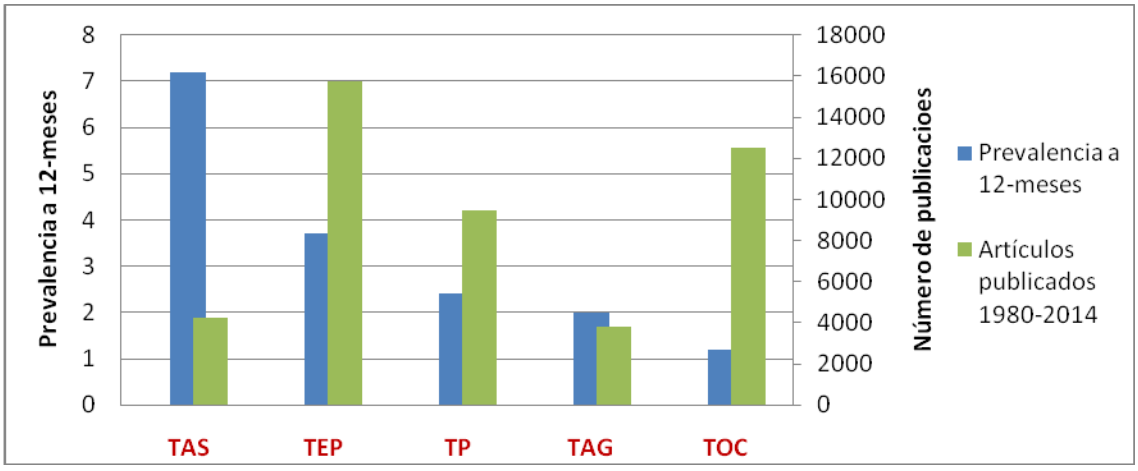
TAS, frente al de Fobia Social, transmite con más fuerza la sensación de omnipresencia y deterioro, se diferencia mejor del de fobia específica, y carece del lastre histórico que sugiere que es un trastorno poco frecuente y poco importante (Heimberg et al., 2014). Este lastre histórico es, en parte sorprendente, si tenemos en cuenta que el TAS es uno de los trastornos de ansiedad más frecuentes, se inicia a edades tempranas, tiene un curso crónico, se asocia a un considerable deterioro funcional, es un factor de riesgo para padecer trastorno depresivo mayor y abuso de sustancias, y raramente remite sin la intervención terapéutica (Crippa, 2009; M. Stein & Stein, 2008). En definitiva, un trastorno grave, con un impacto serio, que va mucho más allá que la mera timidez.

1.2 El estudio del TAS en cifras.

Desde que fuera reconocido de manera oficial en los años 80, el recorrido del TAS ha estado marcado, por una cierta dificultad para hacerse un hueco en el campo de la psiquiatría. Ya en la década de los 80, *Liebowitz* y sus colaboradores, expresaban en un manuscrito titulado "*Social phobia; Review of a neglected anxiety disorder*" (Liebowitz, Gorman, Fyer, & Klein, 1985) su preocupación por la escasísima atención que recibía el trastorno en la época, en el que las publicaciones sobre el trastorno apenas sobrepasaban la decena de artículos. A mediados de los noventa, *Murray Stein* (Stein, 1996) reivindicaba en una breve nota en la prestigiosa "*The Lancet*" que esta forma de ansiedad era un trastorno, -y no mera timidez-, y remarcaba la importancia de que fuera reconocido como tal por parte de los profesionales. A finales de la década del 2000, una nota editorial (Crippa, 2009) destacaba que el número de publicaciones sobre el TAS continuaba siendo modesto, y reflexionaba sobre algunas de las causas que habrían contribuido a su poca visibilidad. Entre ellas, el autor destacaría a la propia naturaleza evitativa del trastorno, la poca atención recibida por los medios de comunicación (en comparación por ejemplo, con el trastorno obsesivo compulsivo o el trastorno de pánico), y las críticas provenientes de ciertos sectores que argumentaban que se estaba *medicalizando* algo que no era un trastorno. A pesar

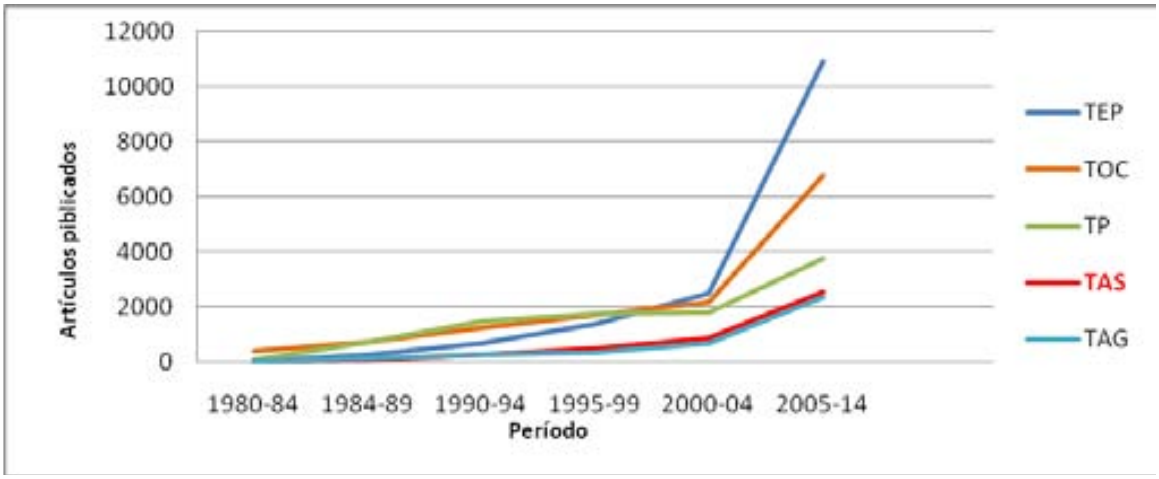
del indudable progreso alcanzado durante los últimos 30 años en nuestro conocimiento sobre la epidemiología, diagnóstico, etiología, y tratamiento del TAS, el número de publicaciones sobre el trastorno continúa estando muy por debajo que el de la mayoría de trastornos de ansiedad.

Figura 1(a). Prevalencia a 12-meses de diferentes trastornos de ansiedad y número de artículos publicados en la base de datos Medline entre el periodo 1980-2014.



TAS - Trastorno de Ansiedad Social; **TEP** - Trastorno por Estrés Post-traumático; **TP** - Trastorno de Pánico; **TAG** - Trastorno de Ansiedad Generalizada; **TOC** - Trastorno Obsesivo Compulsivo. Los datos de prevalencia corresponden a datos en población americana (Kessler et al., 2012). El número de artículos publicados corresponde a la búsqueda realizada en la base de datos MEDLINE (ver figura siguiente).

Figura 1(b). Evolución en el número de publicaciones en diferentes trastornos de ansiedad en el período 1980-2014.



Número de publicaciones entre el período 1980-2014. Fuente: MEDLINE insertando las siguientes palabras clave: TAG ("Generalized Anxiety Disorder"); TAS ("Anxiety Social Disorder" OR "Social Phobia"); TP ("Panic Disorder"); TOC (Obsessive Compulsive Disorder" OR "OCD" NOT "Osteochondritis"); TEP ("Post Traumatic Stress Disorder OR PTSD).

1.3 Epidemiología, curso, e impacto del TAS.

El TAS es un trastorno frecuente, con una prevalencia media estimada a lo largo de la vida del 6,7% (rango 3,9 al 13,75) en países europeos (Fehm, Pelissolo, Furmark, & Wittchen, 2005), y del 12,1% en EE.UU (Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012), con mayor afectación en mujeres. En España, según datos publicados por el ESEMeD (Haro et al., 2006), un proyecto europeo sobre la epidemiología de los trastornos mentales en Europa, la prevalencia en España es considerablemente menor. Datos epidemiológicos sugieren que EE.UU y Rusia presentan las tasas más altas del trastorno, mientras que las menores se encontrarían en países asiáticos, y muestras no-nativas de origen asiático, donde la manifestación del trastorno varía (Hofmann, Anu Asnaani, & Hinton, 2010). El *Taijinkyofusho (TKS)*, un síndrome frecuente en la cultura japonesa y koreana, ha sido por como algunos autores como una expresión cultural específica del TAS. Al igual que los individuos con TAS, las personas con *TKS* temen ser observados, y en consecuencia, evitan una gran variedad de situaciones sociales. Sin embargo, la diferencia con el TAS tal como se expresa en culturas occidentales, es que el individuo con TKS teme hacer algo que pueda ofender o avergonzar a *la otra persona*. En este sentido, es importante destacar como los aspectos culturales podrían contribuir a explicar las diferencias en la prevalencia y la expresión del TAS en diferentes países y culturas (Hofmann et al., 2010).

El trastorno comienza generalmente en niñez o adolescencia temprana, -una etapa particularmente importante en desarrollo de las capacidades sociales-, y se estima que antes de los 20 años el 80% de los pacientes con TAS ya habrán desarrollado el trastorno (Stein & Stein, 2008). El trastorno suele persistir en la edad adulta y raramente remite sin tratamiento. La comorbilidad psiquiátrica parece ser la regla más que la excepción, particularmente para el trastorno depresivo mayor y el abuso de sustancias (Fehm et al., 2005). En la mayoría de casos, el TAS precede al comienzo del trastorno depresivo y los problemas relacionados con sustancias, lo que ha llevado a proponer que el TAS es un factor de riesgo a padecerlos (Fehm et al.,

2005; Stein & Stein, 2008). Un gran número de sujetos con TAS es propenso a abusar de sustancias, -en especial del alcohol- lo que se ha relacionado con un intento de automedicar los síntomas de ansiedad o utilizar el alcohol como facilitador social (Stein & Stein, 2008; Stein et al., 2001). La búsqueda de ayuda profesional suele retrasarse durante años (Buckner, Heimberg, Ecker, & Vinci, 2013; Wagner, Silove, Marnane, & Rouen, 2006). En promedio, se estima que los sujetos con TAS tardan el triple de tiempo en buscar ayuda de un profesional de atención primaria en comparación a personas que sufren un trastorno de pánico/agorafobia o un trastorno de ansiedad generalizado, lo que en parte, se explicaría por el propio temor y la evitación que caracterizan al trastorno. Sin embargo, los datos sugieren que habiendo accedido a consulta de atención primaria, generalmente un médico de familia, la detección del trastorno fracasa en un alto porcentaje de casos (Crippa, 2009; Wagner et al., 2006), lo que acaba retrasando la derivación a un especialista de salud mental. Se estima que entre el comienzo de los síntomas y que la persona recibe atención especializada transcurre una media de más de 9 años, un dato relevante, si tenemos en cuenta que el trastorno raramente remite sin tratamiento (Wagner et al., 2006).

El TAS afecta la mayor parte de áreas vitales de un individuo, se asocia a un importante deterioro psicosocial, en particular de la educación, la carrera profesional, la productividad en el trabajo, así como las relaciones familiares y de pareja del individuo (Filho et al., 2010; Wittchen, Fuetsch, Sonntag, Müller, & Liebowitz, 2000). No menos relevante es el importante sufrimiento y malestar subjetivo asociado. Subjetivo, -o no tanto-, si consideramos algunos importantes avances del campo de las neurociencias que comienzan a poner de manifiesto que la experiencia del llamado “dolor social”, -incluida la percepción de rechazo social o evaluación social negativa-, también típicos del TAS, activan regiones neurales involucradas en el procesamiento del dolor físico (Eisenberger, 2012a, 2012b). La evidencia de que estos circuitos del dolor-físico/dolor-social se solapan, nos invita a pensar más detenidamente acerca de las consecuencias que pueden tener algunas experiencias sociales y ponen de relieve

que la experiencia de dolor social, es tan importante y real como la experiencia de dolor físico.

1.4 Causas y patogénesis

Dada la complejidad del comportamiento social y los trastornos psiquiátricos en general, no resulta sorprendente que la etiología del TAS sea a fecha de hoy, un enorme rompecabezas aún sin resolver. Como en la mayoría de los trastornos psiquiátricos, existe un consenso en que detrás del origen y mantenimiento del TAS subyace la interacción compleja de múltiples causas de origen biológico, psicológico y ambiental (Rapee & Spence, 2004; Stein & Stein, 2008).

La evidencia proporcionada por los estudios genéticos y familiares disponibles hasta la fecha sugieren una predisposición genética moderada para el trastorno. Esto se ha justificado en parte, por la evidencia proveniente de estudios familiares que indican que el TAS es más frecuente entre familiares afectados por el trastorno (Fyer, Mannuzza, Chapman, Liebowitz, & Klein, 1993), especialmente en aquellos casos de TAS generalizado (Stein, Chartier, Hazen, et al., 1998). Sin embargo, existe un consenso en que más que una herencia genética en concreto, son algunos rasgos temperamentales subyacentes (como son la inhibición conductual, el neuroticismo, o la evitación del daño) los que se transmitirían genéticamente, contribuyendo a aumentar la vulnerabilidad a desarrollar TAS (Stein & Stein, 2008). A pesar de que varios genes candidatos se han asociado con rasgos relevantes en la ansiedad social, hasta la fecha, la evidencia no es concluyente y los intentos de vinculación del TAS a genes específicos no han arrojado resultados fructíferos (Stein, Chartier, Kozak, King, & Kennedy, 1998). Es quizás un polimorfismo en la región promotora del gen transportador de la serotonina (5HTTLPR), uno de los posibles candidatos relevantes en la ansiedad social, ya que ha sido relacionado con constructos como la timidez y con rasgos de personalidad del espectro ansioso (Arbelle et al., 2003; Battaglia, Ogliari,

Zanoni, & Al, 2005). Lo que sí parece cierto es que algunos rasgos temperamentales configurarían un perfil de personalidad que caracteriza a un gran número de sujetos con ansiedad social, y que estos rasgos podrían estar en parte, transmitidos genéticamente (Stein, Chartier, Lizak, & Jang, 2001).

A nivel neurobiológico, se ha propuesto que varios neurotransmisores, incluídas las monoaminas, el glutamato, el GABA, y varios neuropéptidos, podrían ser revelantes en el trastorno. Sin embargo, hasta la fecha, son el sistema serotoninérgico y la transmisión dopaminérgica los que han recibido mayor atención. La implicación del sistema serotoninérgico en el TAS se ha justificado en gran parte, por la eficacia terapéutica que han demostrado los inhibidores selectivos de la receptación de la serotonina (ISRS) en el trastorno (Ipser, Kariuki, & Stein, 2008), y porque la administración de ISRS atenúa el patrón de hiperactividad neural observada en estos sujetos en regiones ricas en fibras serotoninérgicas como la amígdala (Furmark et al., 2005; Furmark, Tillfors, Marteinsdottir, & Al, 2002). Por otra parte, la elevada tasa de sujetos con Enfermedad de Parkinson que presenta el trastorno (Bolluk, Ozel-Kizil, Akbostanci, & Atbasoglu, 2010), y la disminución de dopamina en zonas del estriado que se ha observado en sujetos con TAS (Schneier et al., 2000), han llevado a que se postule que sistema dopaminérgico podría estar implicado en el trastorno. Y por último, cabe destacar los hallazgos del campo de la neuroimagen, que sugieren que alteraciones en ciertas regiones cerebrales importantes en la respuesta de miedo y ansiedad podrían subyacer al TAS. No me detendré en los mismos puesto que serán objeto de una revisión detallada a lo largo del trabajo.

En otro escenario nos encontramos a los factores ambientales, aquellas experiencias que según los modelos de diátesis-estrés, moldearían o facilitarían la expresión de una predisponían biológica. Entre estos factores encontramos a los estilos de crianza parentales y al ambiente familiar, incluida la psicopatología por parte de los progenitores y un estilo de crianza caracterizado por el rechazo o falta de soporte emocional, (Knappe et al., 2009) la influencia de las experiencias sociales y el

aprendizaje (Kearney, 2005), y los acontecimientos vitales o las experiencias adversas (Magee, 1999).

En resumen, los hallazgos disponibles hasta la fecha han puesto de manifiesto que la contribución de múltiples factores de tipo biológico y ambiental estarían implicados en el origen y mantenimiento de TAS (Tomas Furmark, 2009; Kearney, 2005; M. Stein & Stein, 2008). Entre ellos, se ha propuesto que los rasgos temperamentales y de personalidad y su posible transmisión genética, la implicación de algunos neurotransmisores, las experiencias vitales adversas, y la alteración en ciertos circuitos neurales importantes en la respuesta de miedo y ansiedad podrían ser algunas de las piezas más importantes del *puzzle*.

1.4.1 Acontecimientos vitales negativos

El estudio de los acontecimientos vitales estresantes (AVEs) ha generado gran interés en el campo de los trastornos psiquiátricos durante los últimos años. Parte de este interés se relaciona con el abandono de viejas concepciones y dicotomías dentro de la salud mental y el reconocimiento de que la combinación de diferentes factores biológicos y ambientales interactúan de forma compleja produciendo una *vulnerabilidad* (Rutter, Moffitt, & Caspi, 2006*).* Por otra parte, con la emergencia de nuevos campos como la epigenética (Tsankova, Renthal, Kumar, & Nestler, 2007), ha habido, durante los últimos años, un renovado interés entre los investigadores por el rol de los factores ambientales en los trastornos psiquiátricos (Heim & Binder, 2012).

Numerosos estudios han demostrado que la exposición temprana a AVEs está asociada a una mayor vulnerabilidad al estrés y mayor riesgo de psicopatología en la edad adulta (Brietzke et al., 2012). Aunque los mecanismos concretos que median el impacto perjudicial a largo plazo son aún inciertos, la evidencia proveniente de estudios animales y humanos sugiere que los efectos observados a largo plazo podrían estar relacionados con cambios en el eje hipotalámico-hipofisiario-adrenal (HHA) y la

liberación de glucocorticoides, y su impacto en el desarrollo cerebral, en particular, en aquellas estructuras en desarrollo en el momento de la exposición (Lupien, McEwen, Gunnar, & Heim, 2009). Sin embargo, la variabilidad en los resultados y la evidencia de que no todos los individuos expuestos al estrés desarrollen mayor riesgo de psicopatología (Brietzke et al., 2012) plantea la importante cuestión de que factores median esta respuesta. Dentro de los factores potenciales se ha propuesto que el "*timing*" o momento en el que se produce la exposición es una de las piezas claves (Heim & Binder 2012; Lupien et al., 2009). Existe un consenso en que la infancia y la adolescencia representan un período de especial vulnerabilidad a los efectos de los AVEs y el estrés, por ser una etapa clave en la maduración cerebral y el desarrollo neurocognitivo, y en la que el cerebro es particularmente vulnerable a los efectos ambientales (Heim & Binder 2012; Lupien et al., 2009). Además de esta noción de "período o ventana crítica", la interacción de estas experiencias ambientales con variaciones genotípicas individuales ha sido propuesto como un factor mediador clave (Brietzke et al., 2012; Lupien et al., 2009).

A pesar de que hallazgos recientes han puesto de manifiesto la importancia que los AVEs durante la infancia tienen en el comienzo, persistencia, y deterioro asociado los trastornos psiquiátricos (Green et al., 2010; McLaughlin et al., 2010a, 2010b), el estudio de los AVEs en el campo de la ansiedad social se ha expandido en menor medida. Los estudios disponibles en el campo del TAS sugieren una asociación entre el TAS en la edad adulta y diferentes formas de abuso durante la infancia, incluidas la agresión verbal por parte de los progenitores (Magee, 1999) , el abuso físico y sexual (Chartier, Walker, & Stein, 2001), y el abuso emocional (Gibb, Chelminski, & Zimmerman, 2007; Kuo, Goldin, Werner, Heimberg, & Gross, 2011; Simon et al., 2009; Spinhoven et al., 2010), éste último, el AVE que ha sido asociado de manera más consitente al TAS. Así, se ha propuesto que esta forma de abuso podría resultar particularmente importante en el desarrollo del trastorno, asociarse a mayor gravedad, y a una peor calidad de vida (Simon et al., 2009). Sin embargo, los estudios

en el campo de los AVEs en el TAS han sido escasos hasta la fecha y se han limitado a población con un diagnóstico clínico.

1.4.2 Factores temperamentales y de personalidad

Existe un consenso de la importancia que ciertos rasgos temperamentales y de personalidad como -la inhibición conductual, el neuroticismo o la evitación del daño- tienen en el TAS, y la noción de que podrían transmitirse genéticamente (Stein et al., 2001; Stein & Stein, 2008). Numerosos estudios en población infantil han demostrado la relación entre la inhibición conductual –un rasgo temperamental presente desde la infancia temprana- y el TAS (Clauss & Urbano-Blackford, 2012). Se trata de un rasgo con un fuerte componente hereditario, caracterizo por la tendencia a responder a personas, lugares u objetos desconocidos de forma temerosa y evitativa. Más de un 40% de los niños que presentan este rasgo durante la infancia desarrollan un TAS durante la edad adulta. Recientemente, un meetanálisis demostró que la inhibición conductual durante la infancia incrementa más de 7 veces el riesgo de padecer TAS en la vida adulta, incluso, cuando se controlan varios factores (Clauss & Urbano-Blackford, 2012).

Los estudios en población adulta realizados hasta la fecha han girado en torno a rasgos temperamentales del espectro evitativo-ansioso como el neuroticismo y la evitación del daño (Stein et al., 2001; Stein & Stein, 2008); que a pesar de tener ciertas diferencias tienen en común el núcleo del temor y la inhibición. La transmisión familiar de estos rasgos parece ser uno de los componentes fundamentales y podría explicar en parte, el componente “hereditario” del trastorno. Los familiares de primer grado de personas con TAS puntúan más alto no solo en medidas de ansiedad social y ansiedad general, sino en de estos rasgos de personalidad como la evitación del daño (Stein et al., 2001; Stein & Stein, 2008).

Uno de los modelos más utilizados para estudiar la personalidad en la ansiedad social ha sido el modelo de personalidad propuesto por Cloninger (Cloninger, Svrakic, & Przybeck, 1993) y su herramienta asociada: el Inventario de Temperamento y Carácter (TCI) (Cloninger, Przybeck, Svrakic, & Wetzel, 1994). Se trata de un modelo dimensional y psicobiológico de la personalidad que integra el papel de variables temperamentales y caracteriales en la determinación de la conducta. El autor, propone cuatro dimensiones temperamentales, heredables en un 40-60%, que se mantienen estables a lo largo de la vida, y son poco modificables por los procesos de aprendizaje: Búsqueda de Novedad, Evitación del Daño, Dependencia de la Recompensa y Persistencia. Por otra parte, forman el carácter tres dimensiones, que incluyen valores, metas, y creencias y se estructuran a lo largo del desarrollo a través del aprendizaje sociocultural: Autodirección, Cooperativismo y Autotrascendencia.

De particular importancia en el estudio del TAS han sido dos de las dimensiones temperamentales: la evitación del daño (HA, *Harm Avoidance*) y la búsqueda de novedad (NS*, Novelty Seeking).* El *HA* se caracteriza por la evitación, la inhibición social y la timidez; y ha sido asociado con el sistema serotoninérgico (Cloninger et al., 1993). El *NS* se caracteriza por la tendencia a la actividad exploratoria, la toma de decisiones impulsiva y la evitación de la monotonía; y ha sido asociado al sistema dopaminérgico (Cloninger et al., 1993). Numerosos estudios han demostrado que el TAS se asocia a puntuaciones elevadas en dimensión *HA* y puntuaciones bajas en la dimensión *NS* (Dalbudak et al., 2013; Lochner et al., 2007; Marteinsdottir, Tillfors, Furmark, Anderberg, & Ekselius, 2003; Mörtberg, Bejerot, & Aberg Wistedt, 2007) una combinación que parece encajar bien con el perfil prototípico del *ansioso social*. Sin embargo, aunque tradicionalmente el TAS se ha asociado a rasgos de personalidad del espectro evitativo-ansioso, existe evidencia de que al menos un subgrupo de sujetos con TAS muestra un perfil atípico (Kachin, Newman, & Pincus, 2001; Kashdan, Collins, & Elhai, 2006; Kashdan, McKnight, Richey, & Hofmann, 2009; Kashdan & Hofmann, 2008). Este perfil estaría caracterizado por conductas típicamente impulsivas y de riesgo, como los contactos sexuales sin protección, la búsqueda de novedad, y mayor

uso de sustancias. Es decir, un grupo de fóbicos que a pesar de tener elevada ansiedad social, no hacen un uso mayoritario de estrategias típicamente evitativas. Aunque a primera instancia la deshinibición, la impulsividad o la búsqueda de novedad son características que parecerían no encajar con el perfil prototípico del ansioso, se ha propuesto que al menos para algunos sujetos, podría representar una estrategia alternativa para enfrentar los temores sociales y hacer frente al patrón de evitación (Kashdan & Hofmann, 2008; Kashdan et al. 2009). En 2008, Kashdan y sus colaboradores (Kashdan & Hofmann, 2008) utilizaron la técnica del análisis de clusters para estudiar los perfiles de personalidad en el TAS en base a la dimensión de temperamento *NS*. Los autores encontraron evidencia para 2 grupos heterogéneos basándose en la tendencia de la dimensión *NS* (alta/baja). Aunque los grupos no demostraron diferencias en cuanto a la gravedad de la ansiedad social o el deterioro asociado, el grupo con *NS*-alto se asoció a mayor gravedad en la comorbilidad para trastornos relacionados con el consumo de sustancias.

A pesar de que la noción de heterogeneidad en el TAS comienza a hacerse un hueco a nivel conceptual (Miskovic & Schmidt, 2012), existen escasas evidencias y estudios en este campo. Las propuestas de Kashdan y colaboradores sobre perfiles heterogéneos en base a la dimensión temperamental *NS* parece un buen punto de partida (Kashdan & Hofmann, 2008; Kashdan et al., 2009) aunque hasta el momento, no ha sido replicada por otros autores. Por otra parte, la propuesta tampoco ha tenido en cuenta el rol de uno de los rasgos temperamentales con mayor peso en el TAS: el *HA*.

1.4.3 Correlatos neurales en el TAS

Teniendo cuenta que una de las características nucleares del TAS es *la respuesta anormal o exagerada de miedo* ante los estímulos sociales, la mayoría de estudios y modelos fisiopatológicos del TAS han propuesto que una alteración en los

mecanismos implicados en la respuesta de miedo podría subyacer al trastorno (Phan & Klumpp, 2010). Numerosos estudios han puesto de manifiesto que las personas que sufren ansiedad social presentan alteraciones en la percepción, atención y respuesta de miedo ante estímulos sociales (Machado-de-Sousa et al., 2010). Así, en comparación con sujetos controles, los individuos con TAS muestran un patrón de hipervigilancia ante estímulos negativos o potencialmente amenazantes, como las expresiones faciales negativas (Machado-de-Sousa et al., 2010), prestan más atención a estímulos que expresan temor (Amir, Elias, Klumpp, & Przeworski, 2003), y tienden a interpretar estímulos ambiguos como amenazantes (Amir, Beard, & Przeworski, 2005). Como consecuencia, se ha propuesto que la disregulación de regiones involucradas en la percepción, reconocimiento y respuesta del miedo, -en el que la amígdala y otras regiones límbicas juegan un rol central- podría subyacer detrás de estas alteraciones, ya sea a través de una *hipersensibilidad* a las señales potencialmente amenazantes, o bien, a través de una *hiperreactidad* en la respuesta frente a estímulos o situaciones temidos (Phan & Klumpp, 2010). La alteración de los mecanismos corticales que regulan esta respuesta de miedo -a través de zonas corticales prefrontales- también podría jugar un papel fundamental y estar alterada en el trastorno (Goldin, Manber, Hakimi, Canli, & Gross, 2009; Goldin, Manber-Ball, Werner, Heimberg, & Gross, 2009; Ziv, Goldin, Jazaieri, Hahn, & Gross, 2013a, 2013b). El interés por los mecanismos neurales que subyacen a los trastornos de ansiedad en general, y al TAS en particular, ha generado gran interés y un gran número de publicaciones en el campo de la neuroimagen durante la última década (Freitas-Ferrari et al., 2010). Hasta la fecha, la mayor parte de nuestro conocimiento sobre las bases neurales del tratorno proviene de estudios de resonancia magnética funcional (RMf) que han utilizado principalmente dos paradigmas: el paradigma de procesamiento emocional a través de la expresión facial, seguido por los paradigmas de provocación de síntomas (Freitas-Ferrari et al., 2010). El uso de paradigmas de procesamiento emocional a través de la expresión facial es una aproximación particularmente válida en el estudio de la ansiedad social, si tenemos en cuenta que la cara es en sí misma un potente estímulo social, y que los

sujetos con TAS presentan una respuesta anormal ante estímulos que expresan temor, incluidas las expresiones faciales (Machado-de-Sousa et al., 2010).

1.4.4 Entendiendo las bases neurales del TAS desde otra perspectiva.

Aunque tradicionalmente la gran mayoría de estudios de neuroimagen han comparado a sujetos con TAS con sujetos sanos como grupo control, existe un síndrome de enorme interés en el estudio de la ansiedad social: el Sindrome Williams-Beuren, o más comunemente llamado, Síndrome de Williams (SW). Se trata de un trastorno raro del neurodesarrollo causado por una delección de aproximadamente 26 genes en el cromosoma 7q11.23 (Pérez Jurado, 2003). El SW se asocia a un fenotipo social único típicamente descrito como *hipersociable* (Järvinen, Korenberg, & Bellugi, 2013). Las personas con SW muestran un elevado interés social, incluso por personas desconocidas y presentan baja ansiedad social en situaciones sociales en las que típicamente la mayoría de personas presentarían algún grado de ansiedad o temor (Bellugi, Adolphs, Cassady, & Chiles, 1999; Doyle, Bellugi, Korenberg, & Graham, 2004; Järvinen-Pasley et al., 2010; Klein-Tasman & Mervis, 2003). Mientras que las sujetos con TAS suelen ser tímidos y evitan personas y situaciones no-familiares, (Stein & Stein, 2008), las personas con SW suelen mostrar una actitud abierta y sociable, y tienden a acercarse a personas desconocidas (Bellugi, Adolphs, Cassady, & Chiles, 1999; Doyle et al., 2004; Järvinen-Pasley et al., 2010; Klein-Tasman & Mervis, 2003). Sin embargo, son personas que presentan fobias simples no-sociales y ansiedad generalizada con mayor prevalencia que personas de igual edad cronológica (Dykens, 2003; Leyfer, Woodruff-Borden, Klein-Tasman, Fricke, & Mervis, 2006). Aunque puede transmitirse de forma autosómica dominante, la mayoría de los casos son esporádicos, con una prevalencia estimada de la enfermedad de 1 entre 7,500 a 20,000 habitantes. Afecta por igual a hombres y mujeres, no demuestra preferencia étnica, y el diagnóstico suele ser obvio a partir de los 2 o 3 años (Strømme, Bjømstad, & Ramstad, 2002). El diagnóstico se asocia a alteraciones cardiovasculares, y otras condiciones

médicas asociadas como la hipercalcemia (Antonell, Del Campo, Flores, Campuzano, & Perez-Jurado, 2006; Del Campo et al., 2006; Pérez Jurado, 2003). El perfil cognitivo suele ser asímetrico y se asocia generalmente a un déficit intelectual moderado, con un CI promedio de 55, mejor ejecución en aspectos verbales y grave afectación del área visuo-espacial (Järvinen et al., 2013a). Suelen presentar hipersensibilidad al sonido (Blomberg, Rosander, & Andersson, 2006) y gran interés por el área musical (Levitin, 2005).

Además del patrón de hipersociabilidad y escaso temor social, los individuos con SW muestran un gran interés por las caras y otros estímulos relacionados como la mirada (Porter, Shaw, & Marsh, 2010; Riby & Hancock, 2009; Riby & Hancock, 2008; Riby et al., 2011; Riby & Hancock, 2009); un aspecto esencial de la interacción social en los humanos. En contra del patrón de evitación de la mirada que típicamente se observa en sujetos con TAS (Weeks, Howell, & Goldin, 2013), las personas con SW presentan una atracción especial hacia el rostro y suelen fijar la mirada durante más tiempo en la cara y los ojos cuando se les compara con sujetos controles (Porter, Shaw, & Marsh, 2010; Riby & Hancock, 2009; Riby & Hancock, 2008; Riby et al., 2011; Riby & Hancock, 2009). La evidencia sugiere que el procesamiento emocional está alterado y podría explicar en parte, algunas características del fenotipo social (Järvinen et al., 2013). Estudios previos han puesto de manifiesto que las personas con SW muestran dificultades para detectar estímulos potencialmente amenazantes, incluida la dificultad para percibir emociones negativas a través de la expresión facial o la voz (Plesa-Skwerer, Faja, Schofield, Verbalis, & Tager-Flusberg, 2006), y para detectar expresiones faciales de enfado (Santos, Silva, Rosset, & Deruelle, 2010). En cambio, suelen mostrar mayor atención e interés hacia rostros que expresan alegría (Bellugi et al., 1999; Dodd & Porter, 2010) y suelen percibir rostros desconocidos como anormalmente positivos (Frigerio et al., 2006). En base a esta evidencia, se ha hipotetizado que estas alteraciones en el procesamiento emocional podrían contribuir al fenotipo social de escaso temor social, al carácter hipersociable y a la tendencia a aproximarse a los extraños característica de estos sujetos; unas alteraciones que

podrían explicarse en parte, por una respuesta anormal en el funcionamiento de la amígdala frente a estímulos sociales que expresan temor (Haas & Reiss, 2012).

En conjunto, la evidencia sugiere que a pesar de que existen evidentes diferencias en cuanto al perfil cognitivo y en relación a aspectos neuroevolutivos, las similitudes clínicas existentes entre ambos trastornos posicionan al fenotipo social del SW como un modelo opuesto al observado en el TAS, y por tanto, una oportunidad única para estudiar las bases neurofisiológicas del TAS.

En este proyecto proponemos una aproximación al estudio de la ansiedad social desde tres perspectivas: la primera de ellas, el estudio de los AVEs, un área que ha resurgido en la literatura psiquiátrica en los últimos años pero que ha sido relativamente poco estudiada en la ansiedad social. La segunda, los perfiles de personalidad y la heterogeneidad en el TAS, un campo emergente y de creciente interés, pero que hasta la fecha, cuenta con escasas evidencias. Y por último, proponemos el estudio de las bases neurales del TAS desde una perspectiva novedosa y original no realizada hasta la fecha, la comparación con “su opuesto”: el SW.

Objetivos e hipótesis

2. OBJETIVOS E HIPÓTESIS

2.1 Objetivo general

El objetivo general del proyecto es profundizar en el estudio de tres factores que han sido asociados al inicio y/o mantenimiento de la ansiedad social en la literatura previa: los acontecimientos vitales estresantes, los rasgos temperamentales y de personalidad, y la actividad neural durante el procesamiento de emocional.

2.2 Objetivos específicos

Estudio 1: Acontecimientos vitales estresantes

- Estudiar la asociación entre cinco acontecimientos vitales estresantes experimentados en la infancia y/o adolescencia (pérdida de una persona querida; abuso físico; abuso emocional; violencia familiar; abuso sexual) y la ansiedad social en la edad adulta en una muestra epidemiológica de adultos jóvenes universitarios.

Estudio 2: Perfil de Personalidad

- Estudiar dos perfiles de personalidad heterogéneos basados en las dimensiones del temperamento del TCI "Evitación del Daño" (*HA*) y "Búsqueda de novedad" (*NS*) en un estudio caso-control de sujetos con diagnóstico de trastorno de ansiedad social y sujetos controles sanos.

Estudio 3: Correlatos neurales del Trastorno de Ansiedad Social incorporando la perspectiva del Síndrome de Williams.

- Realizar una revisión sistemática (y metaanálisis cuando sea posible), de los estudios de resonancia magnética funcional (RMf) disponibles hasta la fecha

examinando el procesamiento emocional a través de la expresión facial en el Trastorno de Ansiedad Social y el Síndrome de Williams.

- Estudiar la actividad cerebral mediante RMf durante la realización de la tarea procesamiento emocional a través de la expresión facial de Hariri en sujetos diagnosticados de Trastorno de Ansiedad Social según el DSM-IV-R, sujetos con Síndrome de Williams y un grupo de sujetos controles sanos.

2.3 Hipótesis

2.3.1. Hipótesis general

- La ansiedad social en la edad adulta estará asociada a la presencia de acontecimientos vitales estresantes durante la infancia/adolescencia y a dos perfiles de personalidad heterogéneos. La comparación de la actividad cerebral mediante RMf durante la realización de un paradigma de procesamiento emocional a través de la expresión facial en sujetos con Trastorno de Ansiedad Social y sujetos con Síndrome de Williams nos permitirá delimitar las regiones implicadas en el procesamiento emocional en cada trastorno, e inferir acerca de los correlatos comunes y específicos entre ambos.

2.3.1. Hipótesis específicas

Estudio 1: Acontecimientos vitales negativos

- La ansiedad social en la edad adulta estará asociada a la presencia de acontecimientos vitales estresantes durante la infancia.

Estudio 2: Perfil de Personalidad

- El TAS estará asociado a dos perfiles de personalidad heterogéneos basados en las dimensiones *HA* y *NS*: **HAns** (*HA*-alto/*NS*-bajo) un perfil que caracterizará a la mayoría de sujetos y al perfil prototípico inhibido-evitativo del TAS; y un

segundo perfil, **HANS** (*HA*-alto y *NS*-alto) que caracterizará a un subgrupo de sujetos que no muestran el patrón de evitación prototípico, sino la tendencia a explorar y a presentar conductas del espectro impulsivo.

Estudio 3: Correlatos neurales del TAS desde la perspectiva del SW.

- El TAS y el SW mostrarán similitudes y diferencias en los correlatos neurales durante el procesamiento emocional. Se espera encontrar diferencias en la activación cerebreal de regiones implicadas en la percepción y respuesta de miedo entre ambos trastornos, incluida la amígdala y el área límbica, y en regiones corticales prefrontales importantes para regular la respuesta de temor. Estas diferencias podrían ser más evidentes frente a expresiones faciales que expresen temor.

Estudio 1

Acontecimientos vitales estresantes en la ansiedad social

OBJETIVO: Estudiar la asociación entre cinco AVEs experimentados antes de los 18 años (pérdida de una persona querida; abuso físico; abuso emocional; violencia familiar; y abuso sexual) y la ansiedad social en una muestra epidemiológica de adultos jóvenes universitarios.

MÉTODO: Se trata de un estudio transversal epidemiológico realizado en el año 2007 en la Universidad Autónoma de Barcelona. Los participantes fueron seleccionados mediante carteles distribuidos en diferentes puntos del campus universitario en el que se invitaba a participar a aquellos sujetos que se sintieran identificados -o no- con las características clínicas de la ansiedad social. La muestra final estuvo formada por 571 estudiantes (581 iniciales de los cuales 10 fueron descartados por no contestar adecuadamente los instrumentos). Los sujetos rellenaron un cuestionario semi-estructurado que incluía variables sociodemográficas y la historia familiar psiquiátrica. Cinco AVEs fueron evaluados de forma retrospectiva mediante cinco preguntas cerradas en el que la persona contestaba de forma dicotómica (SI/NO) si había sufrido alguno de los siguientes AVEs antes de los 18 años: (i) pérdida de una persona querida; (ii) abuso físico; (iii) abuso emocional; (iv) violencia familiar; y (v) abuso sexual. Una breve definición para cada AVE fue incluida. La ansiedad social se evaluó mediante la versión española de la escala de ansiedad social de Liebowitz (LSAS) (Bobes, Badía, Luque, García, González, & Dal-Ré, 1999). Se realizó un análisis descriptivo de la muestra (frecuencias absolutas/relativas y cálculo de medias y desviación estándar (DS) para las variables cualitativas y cuantitativas respectivamente). Para examinar la asociación entre los AVEs y la ansiedad social (puntuación total LSAS), se realizó una regresión líneal ajustando por el efecto de la edad, el sexo, y los antecedentes familiares psiquiátricos.

RESULTADOS: La edad media de la muestra fue de 21 años. El 75% de la muestra eran mujeres. La media de la puntuación en la escala LSAS fue de 40 puntos (DS=22; mediana=35; rango =1-116). Un 19,6% (n=112) de estudiantes obtuvo una puntuación

en el cuestionario LSAS mayor de 60, una puntuación que ha demostrado buena sensibilidad/especificidad para discriminar a sujetos con un diagnóstico clínico de TAS (Rytwinski et al., 2009). Un 50,6% de estudiantes había sufrido algún AVEs antes de los 18 años. La frecuencia de todos los AVEs fue más alta entre los estudiantes con las puntuaciones más elevadas de ansiedad social (LSAS>60). Para éste último grupo, el abuso emocional y la violencia familiar fueron los AVEs más frecuentes. El análisis de regresión lineal reveló una asociación positiva entre la violencia familiar y la ansiedad social después de ajustar por el efecto del resto de AVEs, la edad, el sexo, y la historia familiar psiquiátrica. Los sujetos que habían experimentado violencia familiar antes de los 18 años mostraron un incremento de 12 puntos en la escala LSAS (p= 0,03; 95% CI = 1,97–21,3). Ninguno de los restantes AVEs se asoció a un incremento en las puntuaciones de ansiedad social.

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ARTICLE

Social anxiety and negative early life events in university students

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Abstract
Introduction: There is substantial evidence regarding the impact of negative life events during childhood on the aetiology of psychiatric disorders. We examined the association between negative early life events and social anxiety in a sample of 571 Spanish University students. *Methods*: In a cross-sectional survey conducted in 2007, we collected data through a semi-structured questionnaire of sociodemographic variables, personal and family psychiatric history. We assessed the five early negative life events: (i) the loss of someone close, (ii) emotional abuse, (iii) physical abuse, (iv) family violence, and (v) sexual abuse. All participants completed the Liebowitz Social Anxiety Scale. *Results*: Mean (SD) age was 21 (4.5), 75% female, LSAS score was 40 (DP = 22), 14.2% had a psychiatric family history and 50.6% had negative life events during childhood. Linear regression analyses, after controlling for age, gender, and family psychiatric history, showed a positive association between family violence and social anxiety score ($p = 0.03$). None of the remaining stressors produced a significant increase in LSAS score ($p > 0.05$). *Conclusion*: University students with high levels of social anxiety presented higher prevalence of negative early life events. Childhood family violence could be a risk factor for social anxiety in such a population.

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Introduction

In the past decade, a growing number of studies had proposed negative life events during childhood as risk factors that induce psychopathology in adulthood.[1-3] Traditionally, traumatic events, such as sexual abuse, have been studied in patients with post-traumatic stress disorder.[4] Previous research has yielded considerable evidence of an association between affective/anxiety disorders and childhood adversities.[5-8] Moreover, recent publications have focused on the impact of childhood adversities on the onset, persistence, and functional impairment of psychiatric disorders.[9-11] Despite the growing interest in this phenomenon, little is known about the effect of negative childhood events on social anxiety.

The psychiatric impact of adversities seems to begin during childhood.[12] Recently, one study[13] found an association between exposure to violence and preschool psychopathology symptoms even when other key factors, including economic disadvantage, parenteral mood and anxiety symptoms, were statistically controlled. A study of 1,364 adoptees found that children who suffered adversities prior to adoption had an increased risk of anxiety, mood, and substance use disorders in adulthood.[14] This result suggests that, even when adversities occur over a short period of time, the risk persists into adulthood. In agreement with this finding, a 45-year prospective study that collected data on a wide range of adversities in subjects' lives at 7, 11, and 16 years of age and evaluated adult and mid-life psychopathologies suggested that this risk association does not decrease throughout the life course.[15] Although the mechanisms and pathways linking negative life events and psychopathology are still unclear, there is increasing evidence that neurobiological factors may play a pivotal role.[16] The hypothalamic-pituitary-adrenal axis and corticotrophin-releasing factor are hypothesised to be deregulated following traumatic childhood events.[17,18] These data highlight the importance of identifying such risk factors and investigating how they are related to the aetiology of psychiatric disorders.

Social anxiety is characterised by a marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or possible scrutiny by others. In the more severe form, social anxiety disorder is one of the most common anxiety disorders, with a prevalence ranging from 7% to 10%.[7,19-21] There is some evidence that negative life events may play a role in the development of social anxiety disorder. For instance, in a representative sample of the US population,[22] the relationship between chronic traumatic experiences during childhood and the onset of agoraphobia, specific phobia, and social phobia was investigated. It was observed that sexual assault by a relative and verbal aggression have unique effects on social phobia. In addition, in a Canadian population-based community study,[23] a positive relationship between social anxiety disorder and a wide range of childhood adversities was observed, including a parental history of mental disorders and childhood physical and sexual abuse. More recently, using data from the Netherlands Study of Depression and Anxiety,[24] one study examined the specificity of childhood adversities and negative life events across anxiety and depressive disorders. The authors observed that emotional neglect was specifically associated with social anxiety disorder, depressive disorders, and dysthymia, supporting previous data recorded from psychiatric outpatients.[25]

The present study investigated the association between social anxiety symptoms measured using the Liebowitz Social Anxiety Scale (LSAS)[26] and early negative life events -(i) the loss of someone close, (ii) emotional abuse, (iii) physical abuse, (iv) family violence, and (v) sexual abuse – in a cross-sectional survey of university students. We specifically focused on the university student population because it is composed of young adults with an age range by which social anxiety has developed in 80% of the cases.[27] We hypothesised that early negative life events would be associated with social anxiety in university students.

Methods

Sample and procedure

The study was a cross-sectional survey of university students conducted in 2007. We selected 581 university students of both genders from the Universidat Autonòma de Barcelona (UAB). Ten participants were excluded because they did not complete the instruments correctly. Thus, the final sample consisted of 571 participants. The students were recruited through an advertisement that was distributed at different locations on the university campus. Subjects received a small payment for participating. The study was approved by the university's Research Ethics Committee.

After being informed of the nature of the study, all participants provided written informed consent. A sociodemographic questionnaire, an assessment of family history of psychiatric disorders, a negative life event questionnaire, and the LSAS were administered to all participants.

Measures

A semi-structured questionnaire that included sociodemographic variables was designed *ad hoc* by the research team using questions that were coded dichotomously as "absent" or "present". A family history of psychiatric disorders was specifically assessed for each first-degree family member (0 = absent; 1 = probable; 2 = present; 4 = unknown). Only the "present" categories were considered evidence of a positive family history of psychiatric disorders.

Negative life events were assessed retrospectively using five closed questions regarding early adverse life events. Subjects were asked whether they had experienced one of the following life events before 18 years of age: (i) the loss of someone close, (ii) emotional abuse (verbal communication with the intention of humiliating or degrading the victim), (iii) physical abuse (physical contact, constraint, or confinement, with the intention to hurt or injure), (iv) family violence, or (v) sexual abuse (unwanted sexual contact performed solely for the gratification of the perpetrator or for the purposes of dominating or degrading the victim). These events were coded dichotomously as absent or present. The total number of early adverse life events was also registered. We did a test-retest reliability study of the five closed questions in a sample of 186 university students who were

re-evaluated between one and two months and the results showed that kappa statistics ranged between 0.80 and 1.00.
Social anxiety was assessed using the validated Spanish version of the LSAS.[26,28] It consists of 24 items, each describing a different social situation. The LSAS evaluates the severity of anxiety and social avoidance in a wide range of typical social situations. The fear ratings are based on how much fear or anxiety the patient experiences in such social situations, measured by a Likert scale (0 = never; 1 = occasionally; 2 = often; 3 = usually). It is one of the most commonly used anxiety disorder rating instruments and demonstrates satisfactory psychometric properties for research and clinical purposes. The Spanish validated version of LSAS showed good level of internal consistency (r = 0.61-0.93), the ROC analysis between social phobia subjects and healthy controls was AAC = 0.95-0.99), and intra-class correlation showed a good level of reproducibility (ICC = 0.63).[28] To describe the sample we used the cut-off proposed by RR for positive screening for social anxiety disorder (LSAS score > 60).[29]

Statistical analysis

Absolute and relative frequencies were used to describe the qualitative variables. For the quantitative variables, we calculated means and standard deviations. For the univariate analyses, we used the chi-square test and Student's *t*-test for the qualitative and quantitative variables, respectively. Pearson correlation analysis was used to explore whether the five negative early life events were associated with one another. To examine the association between negative life events and social anxiety scores, a linear regression analysis, adjusted according to age, gender, and family psychiatric history, was conducted.
The data analyses were carried out using the SPSS 17 (SPSS Inc., Chicago, IL, USA) statistical software package.

Results

Descriptive and univariate analysis

The mean age of the sample was 21 years (SD 4.5); 75% were women. The frequency of family psychiatric history was 14%. Ninety-eight percent of participants were Caucasian. The mean (SD) LSAS score was 40 (SD = 22; median = 35; range = 1 to 116). In the total sample, 50.6% of the students had a negative life event during childhood. The frequency for each negative life events in described in Table 1.
Table 2 shows the relationship between each negative life event. Most of the statistically significant correlation coefficients showed either a weak positive association (r = 0.3 to 0.7) or little to no association (r = -0.3 to 0.3).[30]

Association between LSAS total score and negative life events

The linear regression analyses to determine the association between negative life events and social anxiety score are presented in Table 3. There was a positive association between family violence and social anxiety score after we statistically controlled for other negative life events, such as age, gender, and family psychiatric history. Subjects who have experienced family violence had a 12-point increase in LSAS total score (p = 0.03; 95% CI = 1.97 to 21.3). None of the remaining stressors produced a significant increase in LSAS score.

Discussion

The primary goal of this study was to investigate the association between negative life events during childhood and social anxiety disorder in adulthood, using a social anxiety scale. We found that only family violence was associated

Table 1 Characteristics and comparison of the university sample (N = 571)

	Total sample N = 571	LSAS > 60 * N = 112	LSAS = 0-30** N = 231	p value
Age: mean (SD)	21 (4.5)	21.3 (3.9)	22.5 (5.6)	0.069
Female: N (%)	427 (74.8)	88 (78.6)	166 (71.9)	0.052
Male: N (%)	144 (25.2)	24 (21.4)	65 (28.1)	0.052
Family psychiatric history: N (%)	81 (14.2)	19 (16.9)	23 (9.9)	0.001
LSAS score: Mean (SD)	40 (22)	77.4 (13.4)	20.2 (6.9)	0.000
N# of early life events: mean (SD)	0.64 (0.79)	0.84 (1)	0.45 (0.58)	0.001
Loss of someone close: N (%)	226 (39.5)	46 (41)	75 (32)	0.118
Emotional abuse: N (%)	77 (13.5)	23 (20.5)	19 (8.2)	0.000
Physical abuse: N (%)	20 (3.5)	8 (7)	3 (1.2)	0.004
Family violence: N (%)	23 (4)	11 (10)	3 (1.2)	0.000
Sexual abuse: N (%)	22 (3.9)	6 (5.3)	4 (1.7)	0.061

LSAS: Liebowitz Social Anxiety Scale; * LSAS > 60: positive scrennning for social anxiety disorder; **LSAS = 0-30: positive screening for absent of social anxiety disorder.[29]

Table 2 Correlations among five negative life events

	Loss of someone close	Emotional abuse	Physical abuse	Family violence	Sexual abuse
Loss of someone close	---	0.005	0.119**	-0.002	0.043
Emotional abuse	0.005	---	0.371**	0.232**	0.134**
Physical abuse	0.119**	0.371**	---	0.349**	0.011
Family violence	-0.002	0.232**	0.349**	---	0.098*
Sexual abuse	0.043	0.134**	0.011	0.098*	---

*p < 0.05; **p < 0.01.

Table 3 Association between negative early life events and Liebowitz Social Anxiety Scale Total Score

	Regression coefficient	â*	p value	95% CI	
Loss of someone close	2.164	1.124	0.261	-1.61	5.94
Emotional abuse	7.718	1.338	0.181	-3.61	19.0
Physical abuse	3.653	1.221	0.223	-2.22	9.52
Family violence	12.03	2.17	0.030	1.97	21.3
Sexual abuse	3.314	0.673	0.502	-6.36	12.9

* Adjusted for the variables: age, gender and a positive family psychiatric history.

with social anxiety, even after controlling for age, gender and family psychiatric history. The loss of someone close, emotional abuse, physical abuse and sexual abuse before 18 years of age were not associated with the presence of social anxiety in our sample of university students.

Previous studies have shown that family violence is associated with the onset, persistence, and functional impairment of psychiatric outcomes (in the National Comorbidity Survey in the USA), with a particularly strong impact on anxiety disorders.[9-11] Moreover, it was recently found that family dysfunction is a strong predictor of the onset of psychopathology throughout the lifetime of a Mexican population sample.[31] This study found an association between family violence and social anxiety. A previous study[22] demonstrated that verbal aggression between parents, which is a subtype of family violence, has negative effects on social anxiety. In contrast with previous literature,[21,22] the present results did not show that emotional abuse is associated with social anxiety. One possible explanation for the lack of such an association is the fact that the present study did not consider the persistence, recurrence, severity, and subjective impact of emotional abuse, which may play a crucial role in this association. In the present sample, family violence had weak positive correlations with emotional, physical and sexual abuse. However, this study cannot answer whether this early life negative event is or is not specifically associated with social anxiety or general psychopathology in adulthood. Thus, some authors have suggested that specific adversities might contribute to specific psychiatric disorders,[24] whereas others have suggested that childhood adversities are nonspecific risk factors for adult psychopathology.[25,32]

This study has some methodological limitations that must be considered. The results cannot be generalised to the general population, as the sample was only composed of university students. The retrospective nature of assessing negative life events may be affected by recall bias. However, there is some evidence that the under-reporting of childhood maltreatment is more likely to occur than over-reporting.[33] Moreover, it would be interesting to explore childhood emotional neglect.[24,34] Because we measured social anxiety using a rating scale (LSAS), a clinical diagnosis (DSM-IV) would have been a second necessary step to extrapolate the results to people with full-blown social anxiety disorder and control for other psychiatric disorders. However, the LSAS cut-off for social phobia has been shown to have considerable psychometric properties for identifying subjects with social anxiety disorder.[29] Finally, it should be acknowledged that, given the cross-sectional design of this study, we cannot make any conclusions about the causal effect of negative life events on social anxiety. It is evident that not all children who suffer negative life events develop mental health problems later in life. Unmeasured confounding variables, such as genetic features, personality traits, and resilience factors, may influence and/or mediate this association.[35-37]

These results may have clinical and epidemiological implications. On the one hand, considering that family violence is unacceptable, but real in many countries,[38] it is clear that future research needs to focus on childhood prevention and intervention programmes to prevent adulthood psychopathologies, such as social anxiety disorder. The first step in determining where to focus our efforts is to conduct epidemiological studies. On the other hand, a considerable number of university students have social anxiety problems.[39] This makes the university population an important source for early detection and treatment of social anxiety disorder. It is necessary to emphasise that, despite the disability and impairment associated with social anxiety,[40] individuals with this disorder usually only seek for treatment after 15 years of symptoms.[41] Finally, it

is known that the rates of psychiatric comorbidities and the impairment of psychosocial function increase progressively over the course of social anxiety disorder.[42]

In summary, the present results highlight the importance of including family violence when studying the childhood risk factors for social anxiety in university students. Future studies addressing these issues are still necessary and desirable.

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Estudio 2

Perfiles de personalidad en el TAS

RESUMEN ESTUDIO 2

OBJETIVO: Estudiar los perfiles de personalidad y la heterogeneidad en base a las dimensiones de temperamento del Inventario de Carácter y Temperamento de Cloninger (TCI) *HA* (*Harm Avoidance*) y *NS* (*Novelty Seeking*) en una muestra caso-control de sujetos diagnosticados de TAS y sujetos controles sanos.

MÉTODO: Ciento-cuarenta-y-dos estudiantes con TAS (DSM-IV) reclutados mediante carteles distribuidos en el campus de la UAB, que habían presentado un screening positivo en la escala de ansiedad de Liebowitz (LSAS>50) (Liebowitz, 1987) fueron evaluados con la Entrevista Semi-estructurada para el Diagnóstico de los Trastornos Mentales (SCID DSM-IV) (First, Spitzer & Gibbon, 2007) para confirmar el diagnóstico de TAS. Ciento-sesenta y cinco sujetos controles sanos (LSAS<30) fueron evaluados con el SCID para confirmar ausencia de trastorno mental. La evaluación para todos los sujetos incluyó las versiones españolas de los siguientes intrumentos: Inventario TCI de Cloninger (Gutiérrez, Torrens, Boget, Martín-Santos, Sangorrín, Pérez, & Salamero, 2001) la Escala de Ansiedad Social de Liebowitz (LSAS) (Bobes et al. 1999); y un cuestionario sociodemográfico que incluía la historia personal y familiar psiquiátrica, la historia de tentativas autolíticas y de autolesiones, el uso de sustancias, y los AVEs. Se extrajo una muestra de sangre de todos los sujetos para estudiar dos transportadores en el polimorfismo de la serotonina (5-HTTLPR y STin2.VNTR).

Para estudiar la personalidad se crearon los siguientes perfiles en base a las puntuaciones en las dimensiones del TCI *HA* y *NS*: (i) *HA*-alto/*NS*-bajo (HAns), representando al perfil prototípico tímido-inhibido; (ii) *HA*-alto/*NS*-alto (HANS), representando a sujetos con un perfil atípico caracterizado por elevada ansiedad social aunque alta búsqueda de novedad y conductas del espectro impulsivo; (iii) y una tercera categoría (Otros) representando a sujetos con cualquier otra combinación. Puntos de corte de 45 y 55 fueron utilizados para determinar puntuaciones bajas y altas respectivamente en cada dimensión (Castellvi et al., 2009).

Se estudió la frecuencia de los 3 perfiles (HAns; HANS y Otros) para el grupo de casos con TAS y para el grupo de sujetos controles. A continuación, se estudió la frecuencia

para cada una de las variables clínicas y de los dos transportadores de la serotonina en cada grupo. Por último, se realizó una regresión logística con el TAS como variables dependiente y los perfiles HAns y HANS como variables independientes. Como variables de control se incluyeron la edad; el sexo, la historia familiar psiquiátrica; los AVEs y los polimorfismos de la serotonina 5-HTTLPR y STin2.VNTR**.**

RESULTADOS: Los perfiles HAns y HANS caracterizaron al 62% (n=88) de casos con TAS, frente a un 12% (n=21) de sujetos controles sanos (p<0.001). Tal como fue hipotetizado, la mayoría de casos con un diagnóstico de TAS mostraron el perfil prototípico inhibido (HAns) (n=71; 50%); mientras que un subgrupo de casos con TAS mostró un perfil caracterizado por la alta búsqueda de novedad (12% (n=17) de casos con HANS). Los perfiles no se diferenciaron en la gravedad de la ansiedad social aunque si mostraron diferencias significativas en variables clínicas. Mientras que los casos con un perfil HAns mostraron un mayor consumo de alcohol, los casos con un perfil HANS mostraron un mayor consumo de sustancias con perfil estimulante (cocaína, anfetaminas, éxtasis, y alucinógenos), y una tasa de más alta de tentativas autolíticas previas. El perfil HAns mostró la tendencia a presentar mayor frecuencia del genotipo 5HTTLPR SS/SL. Ambos perfiles se asociaron al TAS en el modelo de regresión, incluso después de controlar por el efecto de múltiples variables [(HAns: B=3,04; OR=20,92; IC 95%: 8,49-51,58; p<0,01) y (HANS: B=1,07, OR=3.26; IC 95%: 1,11-7,73; p=0,02)]. Los resultados del modelo de regresión revelaron que otras variables de control incluidas en el modelo también se asociaron al TAS: edad (B=0,84; OR=1,08; IC 95: 1,0-1-17; p=0,02); historia familiar psiquiátrica (B=1,70; OR=5,48; IC 95%: 2,35-12,80); AVEs (B=0,98; OR=2,68; IC 95% 1,45-4,94); y STin2.VNTR 1212 (B=0,81; OR=2,26; IC 95% 1,21-4,21).

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New evidence of heterogeneity in social anxiety disorder: defining two distinct personality profiles taking into account clinical, environmental and genetic risk factors

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Abstract

Purpose: To study personality profiles in Social Anxiety Disorder (SAD) based on high-harm-avoidance (HHA) and high/low novelty-seeking (HNS/LNS) dimensions and their clinical/genetic correlates.

Method: One-hundred and forty-two university students with SAD (SCID-DSM-IV) and 165 healthy controls were evaluated with Cloninger's Temperament and Character Inventory. Sociodemographic variables, SAD severity, substance use, history of suicide and self-harm attempts, early life events, and two serotonin-transporter-gene-polymorphisms (5-HTTLPR and STin2.VNTR) were studied. Univariate and logistic regression analyses were performed.

Results: The two profiles explained 62% of SAD cases, compared with 12.7% of controls ($p<0.001$). Twelve per cent of SAD patients showed a pattern of HHA/HNS. The HHA/LNS profile increased the odds of SAD twenty times (OR=20.92; 95%CI:8.49-51.58); HHA/HNS profile more than three times (OR=3.26; 95%CI:1.11-7.73) after adjustment for age, gender, family psychiatric history, early life events and 5-HTTLPR and Stin2VNTR.The HHA/HNS profile showed higher frequency of suicide attempts ($p=0.039$), less use of alcohol ($p=0.017$), and greater use substances with a high-sensation-seeking-profile ($p=0.005$). The HHA/LNS profile showed a trend towards a higher frequency of SS/SL genotype ($p=0.063$).

Conclusions: SAD was associated with two personality profiles based on HHA and HNS/LNS dimensions. Both profiles had a specific clinical phenotype and may have a different genetic background.

Key Words: Social Anxiety Disorder; Personality; Temperament and Character Inventory; Harm Avoidance; Novelty Seeking; STin2 VNTR

1. Introduction

Social anxiety disorder (SAD) is a disabling chronic disorder characterized by fear of humiliation in social performance and/or interactional situations. Epidemiological studies show that SAD is a common disorder, with an estimated 12-month prevalence of 7.4% [1] and with onset in early adolescence in more than half of individuals [2]. SAD is associated with significant psychosocial impairment and high rates of comorbidity [3] and has been reported to be a risk factor for subsequent depressive and substance abuse disorders [2].

The evidence of dysfunctional personality traits and high rates of comorbidity with certain personality disorders [4] suggests a link between SAD and the personality domain. Based on Cloninger's psychobiological model of personality [5], the Temperament and Character Inventory (TCI) [6] provides a description of seven basic dimensions of temperament and character. The temperament aspects of personality are believed to be highly hereditary, independent, and stable throughout life, while the character aspects of personality involve individual goals, values, and self-conscious emotions that are believed to be influenced by maturity and social learning. Previous studies indicate that SAD is associated with an increase in Harm Avoidance (HA) [7-14] and a decrease in the Novelty-Seeking (NS) temperament dimensions [7, 9, 12-14]. It should be noted that both dimensions assess differences in automatic emotional responses to stimuli defining personality style, and have their corresponding neurobiological substrate [15]. HA is defined as a heritable bias in the inhibition of behaviors and the tendency to respond intensely to aversive stimuli, and is believed to be regulated by the serotonin system. NS is defined as a tendency to respond actively to novel stimuli with frequent exploratory activity in response to novelty, and is believed to be regulated by the dopamine system [15]. Genes related to the serotonin or dopamine pathways may contribute to the genetic liability to both temperamental dimensions and psychiatric disorders such as SAD [16-17]**.** In this regard, functional genetic variants of the serotonin transporter have been associated with affective and anxiety disorders and with anxiety-related personality traits [18]. The combination of both high-HA and low-NS may well represent the prototypical SAD pattern

characterized by shyness, behavioral inhibition, and risk aversive patterns. However, there is evidence that, at least in a subgroup of subjects, SAD is not associated with the prototypical behaviorally-inhibited profile and the use of avoidant strategies. Thus, a subset of socially anxious people may exhibit risk-prone activities including high-NS and impulsive tendencies, unsafe sexual practices, and other risk-taking behaviors when exposed to a high-stress condition [19-22]. Using cluster analysis, Kashdan et al. (2008)[19] found evidence for two heterogeneous subgroups of subjects with generalized SAD based on high/low NS tendencies. The two groups did not differ in terms of social anxiety severity and impairment; but clinicians' severity ratings for comorbid substance-use-disorders were greater in the high-NS group. However, Kashdan's study focused exclusively on the NS domain and did not consider the role of the HA dimension, which has been consistently associated with SAD in previous studies [7-14].

In the present study, we hypothesized that two heterogeneous profiles based on the HA and NS temperament dimensions would characterize individuals with SAD: a larger subgroup representing the prototypical SAD profile (HAns: high-HA and low-NS), and a smaller subgroup representing individuals with high social anxiety but atypical strategies for coping with social anxiety symptoms (HANS: high-HA and high-NS).

Based on this approach, the aims of the study were: 1) To study the personality profile based on HA and NS tendencies among individuals with a clinical diagnosis of SAD and healthy controls, controlling for the effect of other clinical and genetic variables; 2) to explore differences in clinical variables and functional genetic variants of the serotonin transporter between the two different SAD personality profiles.

2. Material and methods

2.1 Sample and Procedure

A case-control study was performed in a sample of Caucasian university students from the Universidad Autonoma de Barcelona, Spain. Cases and controls were recruited by advertisements distributed throughout the university campus.

Written informed consent was obtained from all the participants. The study was approved by the local Ethics Committee (CEIC-IMAS and CEIC-UAB).

One hundred and forty-two university students (both genders, aged over 18) with DSM-IV criteria for SAD [23] and aLiebowitz Social Anxiety Scale (LSAS) [24] score greater than 60 [25] and for whom social anxiety was the primary mental health problem were included in the study. Exclusion criteria included lifetime diagnoses of psychotic disorders and mental disorders due to a medical condition.

One hundred and sixty-five healthy students were evaluated under the same protocol to ensure the absence of mental/medical disorders. Moreover, all controls had a LSAS score below 30 [25].

2.2 Measures

An *ad hoc* categorical questionnaire designed by the team was administered to all participants. It included sociodemographic data, first-degree family psychiatric history, as well as personal history of medical and psychiatric conditions and drug-use. The questionnaire also included the assessment of history of self-harm and suicide attempts, and early negative life events (loss of someone close, family violence, and emotional, physical and sexual abuse).

Social anxiety was assessed by the validated Spanish version of the LSAS [26] comprising 24 items, each describing different social situations. The LSAS evaluates the severity of anxiety and/or social avoidance in a wide range of social situations.The fear ratings are based on how much fear/anxiety the patient experiences in these situations using a Likert scale (ranging from 0 = never; to 3 = usually).

Two trained clinical researchers administered the Structured Clinical Interview for DSM-IV (SCID) [27] to establish the psychiatric diagnosis of SAD and the presence of other psychiatric comorbidities. Researchers applying the psychiatric interview were blind to the results of self-administered scales. Inter-rater reliability (kappa) for psychiatric diagnoses ranged between 0.65 and 1.00.

Personality traits were assessed with the Spanish version of the TCI [28], a self-administered questionnaire with 240 dichotomous items (True/False). It assesses four basic temperament dimensions with their subscales: 1) Novelty Seeking; 2) Harm Avoidance; 3) Reward Dependence; 4) Persistence; and three character dimensions: 1) Self-Directedness; 2) Cooperation; 3) Self-Transcendence. The sample was divided into three groups based on HA and NS tendencies: 1) High-HA and low-NS (HAns); 2) High-HA and high-NS (HANS); 3) Other Personalityincluding all subjects with profiles other than HAns/HANS. For the TCI dimension scores we used T-scores. Cut-off points of 45 and 55 on HA and NS scores were used to establish low or high scores respectively [29].

2.3. Genotyping

Blood samples (5–10 mL) were collected for genotype analyses from all participants. The Puregene-DNA-purification-kit (Gentra Systems®) was used to extract genomic DNA from blood samples. Two polymorphisms in SLC6A4 (5-HTT) that affect 5-HTT expression were analysed: 5-HTTLPR, a 44-base pair insertion/deletion in the promoter region, and STin2, a multi-allelic 17-base pair variable number of tandem repeats (VNTR) within intron 2 [30]. Alleles of the 5-HTTLPR were termed S (short allele with the deletion) and L (long allele with the insertion). 5-HTTLPR and 5-HTTVNTR genotyping was performed using PCR. Each reaction mixture contained: 1 × PCR Amplification buffer and 1 × PCREnhancer solution (Invitrogen, Carlsbad, CA), 1.5 mM MgSO4, 300 ìMdNTPs, 0.5 pmol of each primer, 0.5 U of Taq DNA polymerase (Invitrogen) and 50ng of genomic DNA as template. PCRs were performed using the next pair of primers: FAM-5′-GGCGTTGCCGCTCTGAATGC-3′ and 5′ GAGGACTGAGCTGGACAACAACCAC-3′ and FAM-5′-GTCAGTAT- CACAGG-CTGCGAG-3′ and 5′-TGTTCCTAGTCTTACGCCAGT-3′ for 35 cycles at 58°C and at 60°C as annealing temperatures for 5-HTTLPR and 5-HTTVNTR amplification respectively. A 10-ìL total reaction volume was used and after PCR, the products of allelic specific amplifications (allele L, 528bp; allele S, 484 bp for 5-HTTLPR; and allele 9, 250 bp; allele 10, 267 bp; and allele 12, 300 bp for 5-HTTVNTR) were detected on an automatic ABI 3730XL

capillary sequencer and analysedby GeneMapper Software v3.5 (Applied Biosystem, Foster City, CA, USA).

2.4 Statistical Analysis

Variables were described independently for cases and controls and between cases with personality profiles based on HA/NS. Means (SD), absolute and relative frequencies were obtained for descriptive analyses. Comparisons between groups were analysed using the chi-square-test or t-test for independent samples.

Logistic regression analysis was applied to identify relevant factors associated with SAD. A backward selection strategy was used, including variables with a probability of entering the model of 0.1 or less, and establishing a probability model of 0.05 or less for not exiting. Variables included in the analysis were: age, gender, family psychiatric history, early negative life events and functional polymorphisms 5-HTTLPR (SS/SL; LL genotypes) and STin2.VNTR (1010/1012; 1212 genotypes). Adjusted odds-ratios and the corresponding Wald confidence intervals were calculated using regression coefficients. The Hosmer-Lemeshow test was applied to test the goodness-of-fit of the model. All statistical analyses were 2-sided with an alpha-error set at 0.5 and were conducted using 95% CI. Statistical significance was set at $p<0.05$. All analyses were performed using the Statistical Package for Social Sciences (SPSS version 21.0 for Windows; SPSS Inc, Chicago, Il).

3. Results

3.1. Characteristics of the sample and bivariate analysis.

Table 1 shows the characteristics of SAD cases and controls. The mean age of cases was 23.6 (SD 5.8) and 21.8 (SD 5.1) for controls ($p=0.007$). Compared to controls, cases had a higher proportion of females (83.8% vs. 73.3%; $p=0.025$). Cases showed significantly higher scores on the LSAS ($p<0.001$). The prevalence of family psychiatric history, early negative life events, and history of self-harm and suicide attempts was

higher in SAD cases than in controls (p<0.001). Prevalence of use of alcohol, cannabis and other drugs was higher among the control group (p<0.005). Both polymorphisms were in Hardy–Weinberg equilibrium in cases (5-HTTLPR; p= 0.4894, Stin2 VNTR; p=0.3156) and controls (5-HTTLPR; p= 0.4454, Stin2.VNTR; p=0.3980). The genotype frequency of the Stin2.VNTR differed between groups (p=0.010). Cases showed a higher frequency of the 1212 genotype, while controls showed a higher frequency of the 1010/1012 genotype. There were no differences in the 5-HTTLPR genotype frequency between cases and controls. The prevalence of the HAns and HANS profiles was higher in the SAD group than in controls (50% vs. 4.2%, p<0.001, and 12% vs 8.5%, p<0.001 respectively). The prevalence of Other personality profiles (neither HAns nor HANS) was higher in controls (87.3% vs. 38%, p<0.001).

Table 1.Characteristics of cases and controls.

	Cases N=142	Controls N=165		
	N(%) x (SD)	N(%) x (SD)	X^2/F	P
Personality Profiles				
HAns	71 (50)	7 (4.2)	92.50	*<0.001*
HANS	17 (12)	14 (8.5)		
Other Personality	54 (38)	144 (87.3)		
Age	23.6 (5.8)	21.8 (5.1)	6.72	0.007
Gender (Female)	119 (83.8)	121 (73.3)	5.501	0.025
Family Psychiatric History	48 (33.8)	16 (9.6)	29.802	*<0.001*
Early Negative Life Events	84 (59.1)	55 (33.3)	17.001	*<0.001*
History of suicide attempts	9 (6.3)	0 (0)	11.016	*<0.001*
History of self-harm	18 (12.6)	0 (0)	23.875	*<0.001*
Use of substances				
Alcohol	49 (34.5)	80 (48.5)	6.120	*0.009*
Cannabis	11 (7.7)	37 (22.4)	12.465	*<0.001*
Other drugs	7 (4.9)	20 (12.5)	5.296	*0.017*
5-HTT Polymorphisms				
5-HTTLPR SS/SL	114(69.1)	105(73.9)	0.377	0.209
5-HTTLPR LL	51(30.9)	37(26.1)		
STin2 VNTR 1010/1012	69(48.9)	102(65)	0.019	0.010
STin2 VNTR 1212	72 (51.1)	55(35)		

3.2. Multivariate analysis

Table 2 shows the results of the logistic regression analysis, with SAD as dependent variable. HAns/HANS profiles were associated with the presence of SAD after controlling for 5-HTTLPR, Stin2.VNTR, age, gender, family psychiatric history, and early negative life events. The HAns profile increased the odds of having SAD (OR=20.92; 95% CI 8.49-51.58) more than twenty times. The HANS profile increased the odds of having SAD (OR 3.26; 95% CI 1.11-7.73) more than three times. The Hosmer–Lemeshow test showed the goodness-fit of the model (p> 0.05).

Table 2.Logistic regression analysis of SAD including the TCI personality profiles and controlling by age, gender, family psychiatric history, early negative life events and 5-HTTLPR and Stin2 VNTR polymorphisms.

	B	SE	Wald	P	OR	95% CI
Personality Profile						
HAns	3.041	0.460	43.653	*<0.001*	20.927	8.490-51.581
HANS	1.078	0.493	4.781	0.029	3.260	1.118-7.730
Age	0.084	0.038	4.810	0.028	1.088	1.009-1.173
Family Psychiatric History	1.703	0.432	15.153	*<0.001*	5.489	2.352-12.808
Negative Life Events	0.987	0.312	10.042	0.002	2.684	1.458-4.944
Stin2.VNTR-1212	0.818	0.317	6.641	0.010	2.265	1.216-4.218
Constant	-4.650	1.145	16.488	*<0.001*	0.010	

*5-HTTLPR and gender did not enter in the final model p>0.05

3.3 Personality profiles based on HA and NS tendencies on cases.

Table 3 shows differences between cases with personality profiles based on HA and NS tendencies. There were no differences between groups in terms of age or gender (p>0.05). In comparison to the HAns profile, SAD cases with a HANS profile showed an increase in all TCI-NS-subscales (p<0.001), but no differences in the TCI-HA-dimension and LSAS scores (Figures 1 and 2). The HANS profile showed an increase in all TCI-NS-subscales (p<0.001), but no differences in the TCI-HA-dimension and LSAS scores (Figures 1 and 2). The HANS profile showed higher frequency of suicide attempts (p=0.039), less use of alcohol (p=0.017), and greater use of other substances (p=0.005). The prevalence of family psychiatric history, early negative life events,

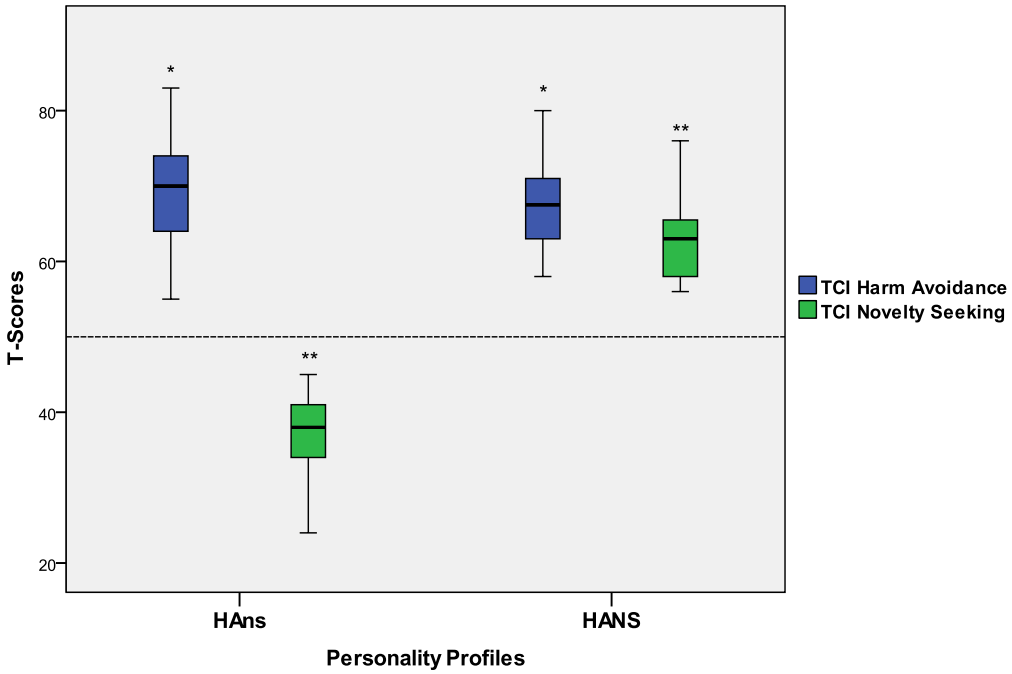
history of self-harm and comorbidity did not show differences between groups. When HAns+HANS were compared to the Other Personality group, the HAns+HANS groups showed higher scores on the shyness (p=0.01) and risk avoidance subscales (p=0.005), and decreases on all NS subscale scores (p<0.001). There were no differences in clinical variables between these groups. When functional genetic polymorphisms were compared between HAns/HANS profiles, the HAns profile showed a trend towards a higher frequency of the 5-HTTLPR-SS/SL genotype frequency (p=0.063). There were no differences in the frequency of the STin2.VNTR genotype between profiles.

Table 3. Comparison between cases with personality profiles based on HA and NS tendencies.

	HAns N=71	**HANS N=17**			**HAns + HANS N=88**	**Other N=54**		
	N (%) / x (SD)		**F/x²**	**P**	**N (%) / x (SD)**		**F/x²**	**P**
Age	24.3	22.5	1.551	0.313	23.9	23.1	1.448	0.371
Gender (Female)	59 (83.3)	14 (82.3)	0.323	0.746	73 (82.9)	46 (85.1)	0.040	0.511
LSAS (Total)	75.2 (18.9)	71.1 (17.0)	0.318	0.444	74.1 (18.7)	74.7 (17.3)	0.556	0.864
Family Psychiatric History	23 (33)	8 (50)	1.557	0.168	31 (35.2)	17 (31.4)	0.364	0.369
Early Negative Life Events	41(59.4)	11 (68.8)	0.476	0.347	52 (59.1)	32 (59.2)	0.008	0.535
History of suicide attempts	4 (5.9)	4 (25)	4.968	0.039	8 (9.1)	1 (1.8)	3.173	0.071
History of self-harm	7 (10.1)	4 (25)	2.544	0.121	11 (12.5)	7 (12.9)	0.029	0.532
Comorbidity	37 (52.1)	9 (52.9)	0.090	0.493	45 (51.1)	29 (53.7)	0.014	0.522
H. psychiatric treatment	29 (40.8)	7 (43.7)	0.016	0.558	36 (40.1)	23 (42.5)	0.004	0.546
Use of substances								
Alcohol	25 (32.2)	1 (6.3)	5.127	0.017	26 (29.5)	23 (42.5)	2.123	0.101
Cannabis	4 (5.6)	1 (6.3)	0.009	0.648	5 (5.6)	6 (11.1)	1.256	0.211
Other drugs	0 (0)	3 (18.8)	13.788	0.005	3 (3.4)	4 (7.4)	1.052	0.261
5-HTT Polymorphisms								
5-HTTLPR SS/SL	56(78.9)	7(41.1)	0.107	0.063	66 (75)	39 (72.2)	0.846	0.471
5-HTTLPR LL	15(21.1)	10(58.8)			22 (25)	15 (27.8)		
STin21010/1012	41 (57.7)	6 (35.3)	0.176	0.127	47 (53.5)	26 (48.1)	0.494	0.292
STin21212	30 (42.3)	11 (64.7)			41 (46.5)	28 (51.9)		

HAns: High Harm Avoidance - Low Novelty Seeking / HANS: High Harm Avoidance - High Novelty Seeking
LSAS-Liebowitz Social Anxiety Scale

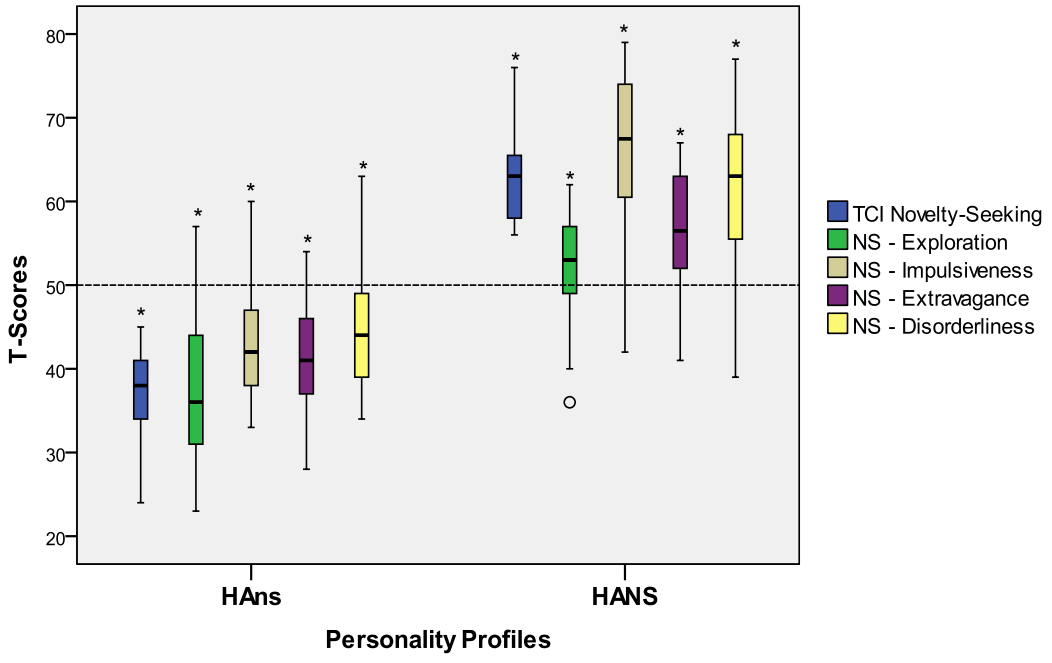
Figure 1 .Comparison of HA and NS dimensions on cases with HAns/HANS personality



*p>0.05 ns; **p<0.001

profile.

Figure 2. Comparison of NS dimension and its subscales in SAD cases with HAns/HANS profiles.



*p<0.001

4. Discussion

To our knowledge, this is the first study to explore personality profiles based on HA and NS tendencies using a control group. We found evidence of heterogeneous personality profiles among SAD based on HA and NS tendencies compared to healthy controls. As hypothesized, the high-HA and low-NS profile (HAns) was the most prevalent profile among subjects with SAD, while the high-HA and high-NS profile (HANS) defined a smaller subgroup of SAD subjects. The two groups did not differ in social anxiety severity, but did differ in history of suicide attempts and pattern of substance abuse. Moreover, both profiles were highly associated with the presence of SAD after controlling for age, gender, family psychiatric history, early negative life events, and 5-HTTLPR and STin.2 VNTR polymorphisms.

In the present sample, HAns/HANS profiles defined most individuals with SAD: (i) a larger group representing the prototypical SAD profile characterized by elevated social fears and avoidance patterns, and (ii) a smaller subgroup of subjects exhibiting elevated social fears and exploratory and impulsive tendencies. In contrast to the SAD group, the Other-Personality-Profile characterized the majority of individuals in the control group. Moreover, we reported that both HAns/HANS profiles were strongly associated with the presence of SAD, even after controlling for the effect of other clinical and biological factors. These findings support previous evidence in clinical samples showing increases in HA and decreases in NS [7, 9, 12-14] and is in agreement with the initial evidence of the presence of heterogeneous SAD subgroups based on NS tendencies [19]. However, it should be noted that alterations in these temperament domains are not exclusive to SAD, since high levels of HA also appear in other anxiety, affective and other psychiatric disorders [31]. Moreover, it is evident that not all individuals with high-HA manifest SAD or another psychiatric disorder. In SAD, pronounced levels of HA may suggest the presence of a more stable trait with stronger association with comorbid conditions, early shyness, and an earlier onset of the disorder [11].

Additionally, our results support previous evidence of the association of SAD with age [4], family psychiatric history [32], and early negative life events [33], and provide initial evidence of the Stin2.VNTR polymorphism in SAD. The STin2.12/12

homozygous genotype was associated with the presence of SAD in our study. To our knowledge, only one previous study, in a Japanese sample, found an association between the Stin2.12 allele and anxiety disorders, including SAD [34]. The Stin2.12 allele has also been associated with obsessive-compulsive disorder [35], bipolar disorder [36-37], and schizophrenia [38]. However, the biological function of STin2.VNTR polymorphisms has not been clearly elucidated. In vitro [39] and in vivo [40] studies have shown differential regulatory effects on transcription between alleles. Moreover, a study in an embryonic stem cell model suggested that individual repeat elements within the STin2.VNTR domain differ in their enhancer activity [41]. In contrast to previous evidence [42-43], we did not find an association between 5-HTTLPR and SAD. However, differences between studies regarding sample characteristics (age) and allele approach (biallelic/triallelic) may contribute to the discrepancies with previous studies.

The second aim of the study was to explore differences in clinical and genetic variables between SAD individuals with HAns and HANS profiles. In agreement with previous research [19] we did not observe differences in social anxiety severity between personality profiles. However, we found that the HANS profile was associated with a higher prevalence of history of suicide attempts and a different pattern of substance abuse. Interestingly, while the HAns profile was associated with a greater use of alcohol, the HANS profile was associated with a greater use of other substances (this category included the use of cocaine, amphetamines, ecstasy and/or hallucinogens). Cannabis use did not show differences between profiles. Two previous studies using cluster analysis to study heterogeneous SAD subgroups based on novelty-seeking tendencies [19] and risk prone-behaviors [20] found evidence of greater substance abuse problems and higher clinician's severity ratings for substance abuse disorders among SAD subjects with high impulsive tendencies than in subjects with prototypical inhibited profiles. Although our results do not fully support these findings, the fact that HANS was associated with a greater use of cocaine, amphetamines, ecstasy and/or hallucinogens may suggest the influence of the high-NS domain on the propensity to experiment with substances with a high-sensation-seeking profile. However, in view of the small sample size, these conclusions should be interpreted

with caution. Interestingly, compared to SAD subjects, controls showed a higher prevalence of substance-use in our study -a surprising finding-, perhaps, since SAD has been associated with increased risk and high rates of substance use disorders (See [44] for a review). However, it should be noted that our sample consisted of young adults in their twenties; it is probable that substance abuse-related problems occur later in life, in the context of a chronic disorder where the use of a substance may act as a strategy to cope with SAD symptoms and as a social facilitator [44]. No evidence of history of suicide attempts among socially anxious individuals with high impulsive tendencies is available for comparison, but our results are in accordance with previous research linking high NS with suicide attempts in other populations [45-46]. In contrast to Kashdan's study [19], we did not report gender differences between personality profiles, perhaps due to the large proportion of women in our sample. Moreover, comorbidity, history of psychiatric treatment, family psychiatric history and early negative life events did not differ between groups.

It should be stressed that high-risk behaviors may not be influenced only by temperamental traits. Other contextual variables such as situation expectations [47] and high-stress conditions [22] have been shown to influence high risk-taking behaviors in SAD. Genetic factors may influence both high risk behaviors and personality traits [16, 48]. We observed a trend toward a higher frequency of the 5-HTTLPR SS/SL genotype among SAD cases with the HAns profile. Possibly, the two profiles have a different genetic background. In particular, DRD4, another polymorphism within the dopamine gene, seems of particular interest, since other studies have proposed an association between this polymorphism and the NS domain [49]. Moreover, the interaction between neurotransmitters may underlie the neurobiological correlates of personality. Susuki et al., (2008) [50] reported that the interaction between the serotonin transporter (5HTT) and the norepinephrine transporter (NET) function, but not their independent effects had a significant impact on HA and NS in healthy females. Future studies examining the role of serotonin and dopamine activity and its interaction with other neurotransmitters would help to further define endophenotypes of HAns/HANS profiles in SAD.

This study has some other limitations that should be noted. Despite the intense association observed between SAD and HAns/HANS profiles, the cross-sectional design prevents us from determining the direction of the association and the overlapping effect of SAD symptoms and personality traits. Furthermore, temperament and character dimensions other than HA/NS were not considered for analyses and may also play a role,-particularly the self-directedness character dimension- , which has previously been associated with SAD [7, 9, 11-12, 14]. Lastly, our sample was composed by university students, which may limit the generalization of our findings to other populations. On the other hand, the study also presents some important strengths such as the case-control design, the use of a semi-structured diagnostic interview to assess psychiatric diagnosis, and the assessment of several variables to control for confounding effects.

5. Conclusion

This study provides evidence for the presence of heterogeneous SAD subgroups and the propensity of a subset of people with high social anxiety to exhibit impulsive tendencies and high risk behaviors. The two personality profiles may have different genetic backgrounds. From a clinical point of view, the division of SAD into two subgroups based on heterogeneous personality profiles may improve the approach to treatment. Studies with larger samples, recruited from longitudinal cohort subjects, are now required in order to investigate these findings further.

Conflict of interest

Conflict of interest: none

Acknowledgments

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Estudio 3

Correlatos neurales del TAS desde la perspectiva del SW

Estudio 3(a) "Common and distinct neural correlates during facial emotion processing in Social Anxiety Disorder and Williams Syndrome: a systematic review and metaanalysis".

RESUMEN

OBJETIVO: Realizar una revisión sistemática con metaanálsis de los estudios de resonancia magnética funcional disponibles hasta la fecha utilizando paradigmas de procesamiento emocional a través de la expresión facial en el TAS y el SW con el objetivo de: (a) identificar regiones implicadas en el procesamiento emocional en el TAS y el SW; y (b) realizar inferencias acerca de los correlatos neurales comunes y diferenciales durante esta tarea en ambos trastornos.

MÉTODO: Se realizó una búsqueda sistematizada utilizando las bases de datos Pubmed y Medline. Todos los estudios publicados hasta diciembre de 2013 fueron incluidos. Las siguientes palabras clave fueron utilizadas para la búsqueda: "facial emotion"; "emotion processing"; "fear"; "happy"; "sad", "angry"; "disgust" "social anxiety"; "social phobia"; "Williams syndrome"; "neuroimaging"; "functional magnetic resonance"; "fMRI"; en sus diferentes combinaciones. Con el fin de homogeneizar la selección y facilitar las comparaciones, sólo se incluyeron los estudios que cumplieran los siguientes criterios: (i) estudios de procesamiento emocional a través de expresión facial comparando sujetos adultos (edad > 18) con un diagnóstico clínico de SAD o WS y un grupo de sujetos controles; (ii) uso de resonancia magnética funcional. Para la realización del metaanálisis se consideraron los siguientes criterios: (iii) utilización de sustracción de imágenes que identificaran cambios en la actividad neural durante la realización de una tarea activa y una tarea control (iv) presentar los resultados en coordenadas de un espacio estereotáctico estándar (Talairach ò Montreal Neurological Institute, MNI). Todos aquellos estudios investigando otros procesos más allá del procesamiento emocional (ej. ensayos clínicos) que no publicaran los resultados basales del análisis entre-grupos fueron excluidos. De los artículos incluidos se extrajo la siguiente información: (i) datos sociodemográficos; (ii) tipo de tarea y diseño; (iii) contrastes realizados entre estímulos (ej: *fear* > *neutral; fear* > *happy*) (iv) resultados para cada contraste (v) correlación de la actividad neural con medidas clínicas

(cuestionarios). Para realizar el metaanálisis se extrajeron las coordenadadas de cada estudio y se analizaron de forma independiente (un metanálisis para el TAS; uno para el SW) con la técnica "*Activation Likelihood Estimation" (ALE),* implementada en GingerALE 2.1 (http://brainmap.org/ale).

RESULTADOS: Ciento-sesenta y dos estudios fueron inicialmente identificados, de los cuales 133 fueron eliminados tras criba mediante lectura de "*abstract".* De los restantes 41 estudios *a priori* seleccionados, 19 no cumplieron criterios de inclusión. Finalmente, 22 estudios fueron incluidos en la revisión; 17 de TAS y 5 de SW. La mayoría de los estudios en el TAS incluían la presentación de expresiones faciales negativas. Más de un 70% de los estudios utilizaron paradigmas explícitos/implícitos, mientras que una minoría utilizó paradigmas libres (17,6%) o combinados (11,7%). Las expresiones faciales de la colección de Ekman y Friesen (Ekman & Friesen, 1978) presentadas en bloque fueron el método más utilizado por los estudios. La mayoría de estudios incluyó muestras de casos/controles en edad adulta joven, con cierta heterogeneidad en la distribución por sexos. La entrevista diagnóstica estructurada para los trastornos mentales del DSM-IV (SCID) (First et al., 2007) fue el método mayormente utilizado para realizar el diagnóstico clínico y la mayoría de estudios apareó a los sujetos por lateralidad. Un 58% de los estudios incluía casos con comorbilidad y en la mayoría de estudios se incluyó a sujetos libres de tratamiento farmacológico. El análisis cualitativo de los estudios disponibles hasta la fecha reflejó que para el TAS, el hallazgo más consistente y replicado ha sido la hiperactividad de la amígdala (aunque también de otras regiones paralímbicas como la ínsula y el giro parahipocampal) durante el procesamiento emocional, en particular -aunque no limitado a- las caras que expresan temor. La ampliación del foco de estudio a regiones no-límbicas que se observa en estudios más recientes reflejaron la posible alteración en la activación de otras regiones importantes en el procesamiento del miedo y la *facies*, como algunas estructuras temporales, la corteza prefrontal y la corteza cingulada anterior, aunque la evidencia para estas regiones es aun escasa. La importancia en la elección del estímulo de contraste utilizado y como distintas condiciones experimentales pueden afectar los resultados queda reflejada en la revisión. Desde la perspectiva del SW, el análisis de los estudios disponibles hasta la

fecha reflejó que una doble disociación en la activación de la amígdala, -hipoactivación frente a caras de temor e hiperactivación frente a caras que expresan alegría- caracterizaría las alteraciones en el procesamiento emocional presentes en estos sujetos. A pesar de los escasos estudios sobre procesamiento emocional a través de la expresión facial disponibles en el campo del WS, puede apreciarse una cuidadosa elección en los diseños, estímulos y muestras seleccionadas para cada estudio, que han permitido extender la evidencia disponible. Los resultados del metaanálisis confirman y extienden los resultados de la revisión y reflejan la implicación de regiones límbicas para ambos trastornos, aunque con un patrón de activación opuesto. Así, en comparación a sujetos controles sanos, los casos con TAS mostraron un patrón de hiperactivación en la amígdala, el giro parahipocampal y el globo pálido. En comparación a sujetos controles, los casos con SW mostraron un patrón de hipoactivación en las mismas regiones; un hallazgo que probablemente refleje el componente de temor que comparten ambos trastornos. Para el TAS se observó además la hiperactivación de varias regiones, incluidas la ínsula, el putámen y áreas temporales (giro temporal superior), frontales (frontal medio/superior) y occipitales (cúneo), mientras que para el SW se observó una hipoactivación de la región parietal inferior.

(Manuscrito sometido a publicación; en fase de revisión en *"Neuropsychologia"*)

Common and distinct neural correlates of facial emotion processing in Social Anxiety Disorder and Williams Syndrome: a systematic review and voxel-based meta-analysis of functional resonance imaging studies.

Binelli C, Subirà S, Batalla A, Muñiz A, Sugranyes G, Crippa JA, Farré M, Perez-Jurado L, Martín-Santos R.

Background: Social Anxiety Disorder (SAD) and Williams-Beuren Syndrome (WS) are two disorders that are on opposite extremes in the continuum of social fear and have some opposite clinical features, including gaze contact and atypical processing of emotional cues. Although an increasing number of neuroimaging studies have greatly expanded our knowledge of the neural bases of facial emotion processing in both disorders, to date, SAD and WS have not been directly compared.

Methods: We conducted a systematic review of functional magnetic resonance imaging (fMRI) studies comparing SAD and WS cases to healthy control participants (HC) using facial emotion processing paradigms. Two researchers conducted comprehensive PubMed/Medline searches to identify all fMRI studies of facial emotion processing in SAD and WS. The following search key-words were used: "emotion processing"; "facial emotion"; "social anxiety"; "social phobia"; "Williams syndrome"; "neuroimaging"; "functional magnetic resonance"; "fMRI" and their combinations, as well as terms specifying individual facial emotions (fear, happy, sad, angry, disgust). We extracted spatial coordinates from each study and conducted two separate voxel-wise activation likelihood estimation meta-analyses, one for SAD and one for WS.

Results: Twenty-two studies met inclusion criteria: 17 of SAD and five of WS. We found evidence for common and distinct patterns of neural activation. Limbic engagement was common to SAD and WS during facial emotion processing, although we observed opposite patterns of activation for each disorder. Compared to HC, SAD cases showed *hyperactivation* of the amygdala, the parahippocampal gyrus and the globus pallidus. Compared to controls subjects, participants with WS showed *hypoactivation* of these regions. Differential activation in a number of regions specific to either condition was also identified: SAD cases exhibited greater activation of the insula, putamen, the superior temporal gyrus, medial frontal regions and the cuneus, while WS subjects showed decreased activation in the inferior region of the parietal lobule.

Conclusions: The identification of limbic structures as a shared correlate may reflect the neural substrate of the fear component. The pattern of hyper/hypo activation observed within limbic structures may explain the pattern of exaggerated/diminished fear response to social cues that characterizes SAD and WS respectively. We believe that insights from WS and the inclusion of this syndrome as a control group in future experimental studies may improve our understanding of the neurobiology of social behaviour in general and of SAD in particular.

1. Introduction

Social fear is part of the adaptive human psychological repertoire and is expressed along a continuum of severity from moderate-adaptive distress to incapacitating fear that exceeds the adaptive threshold (1). The best example of this spectrum is probably Social Anxiety Disorder (SAD), a highly prevalent (2) psychiatric disorder characterized by fear and avoidance of interpersonal situations that exceeds the adaptive threshold and interferes with daily life (3). Individuals with SAD frequently present intense fear, distress, and avoidant behaviors in specific social situations. However, some cases fear and avoid most social situations; in this case they are diagnosed with the generalized subtype.

A condition of particular interest in the study of social fear is Williams-Beuren-Syndrome, also known as Williams Syndrome (WS), a rare neurodevelopment disorder caused by a hemizygous delection of 26-28 genes on chromosome band 7q11.23 (4). Williams-Syndrome is associated with a markedly uneven neurocognitive profile and a distinctive social phenotype (5). Individuals with WS are socially fearless and typically engage in social interactions, even with strangers (6). Whereas people with SAD are typically shy, avoid meeting new people, and are withdrawn in unfamiliar social settings (7), people with WS typically display outgoing, friendly, hypersocial behaviour and exhibit an unusual attraction to unfamiliar people (6,8-10). Interestingly, this pattern of social fearlessness coexists with high levels of non-social anxiety, as evidenced by high rates of generalized anxiety disorder and specific phobia (11,12).

Another core characteristic of the WS phenotype is the unusual attention and fixation to faces and other social cues such as gaze (13,14). While people with SAD fear and avoid eye contact (15) people with WS tend to fixate on faces (16) and eyes (17) longer than controls, and, once fixated, they show delays in disengaging (18).

Atypical emotion processing is another feature shared by WS and SAD. Specifically, individuals with WS are less able to detect social threat signals, as evidenced by difficulties in perceiving negative emotions through facial expressions and voices (19) and in detecting angry faces (20). Indeed, they show greater attention bias towards

processing happy faces (21), a tendency to perceive unfamiliar faces as more positive (8) and to rate happy facial expressions as more approachable (22). These findings contrast to those reported in SAD subjects who are typically hypervigilant to facial expressions, tend to judge neutral faces as negative (23), and rapidly avoid facial stimuli perceived as threatening (24). Taken together, findings suggest that SAD and WS differ not only in their social behaviour, but in other related core features such as the processing of emotional cues.

During the last decade, neuroimaging studies have greatly expanded our knowledge of the neural bases of facial emotion processing in both SAD and WS. These findings suggest that atypical response in regions involved in the threat-detection-system and the fear response, particularly, in the amygdala, may underlie the neural basis of emotion processing in both disorders and contribute to explain the neurobiology of the social phenotype (25,26). Although previous systematic reviews (25,26) and meta-analyses (27-28) have independently summarized some of these findings, to date, SAD and WS have not been directly compared.

In the present study we conduct a systematic review and meta-analysis of existing functional magnetic resonance (fMRI) findings on facial emotion processing in SAD and WS with two aims in mind (a) to identify regions implicated in facial emotion processing in SAD and WS, and (b) to draw inferences about common and distinct neural correlates of facial emotion processing between the two disorders.

This review offers an original approach to the study of the neural basis of emotion processing in SAD. Although the main interest in WS has come from the neuroscience field, we believe that insights from this syndrome could also contribute to understand the neural bases of SAD and how the fear component impacts this response.

2. Methods

2.1 *Search strategy and selection criteria*

Electronic searches for published reports were performed using Medline and PubMed, without any language restriction. All studies published up to December 2013 were included. The following search key words were used: “emotion processing”; “facial emotion”; “social anxiety”; “social phobia”; “Williams syndrome”; “neuroimaging”; “functional magnetic resonance”; “fMRI”, and their combinations, as well as terms specifying individual facial emotions (fear, happy, sad, angry, disgust). The reference lists of the selected papers were also searched for relevant articles. First, a general review of all abstracts was performed. In order to homogenize the selection and facilitate comparisons, studies were only included if they met the following inclusion criteria: (i) studies of facial emotion processing reporting comparisons between adult (age>18) subjects with clinical diagnoses of SAD or WS and healthy control subjects (ii) use of functional magnetic resonance imaging (fMRI). For Activation Likelihood Estimation (ALE), the following criteria were considered: (iii) the use of image subtraction methodology to identify foci of task-related neural changes during an active/control condition, and (iv) the reporting of their results in standard stereotactic coordinates (either Talairach or Montreal Neurological Institute space). All studies investigating processes other than brain reactivity to facial emotion processing (e.g. clinical trials, studies of emotion regulation strategies) that did not provide between-group basal results of brain reactivity to a facial emotion processing task were excluded.

2.2 Data extraction

Data were extracted by one of the authors and were subsequently reviewed by a second author. From the included articles, we recorded: (i) socio-demographic information; (ii) type of task and design; (iii) contrasts performed between stimuli (e.g. fear > neutral; fear > happy); (iv) results for each contrast, and (v) correlation of brain activity results with clinical measures.

2.3 Activation Likelihood Estimation Meta-Analysis

Coordinates from SAD and WS studies were analyzed separately following the ALE technique implemented in GingerALE 2.1 (http://brainmap.org/ale). For each study, statistically significant foci of activation from a selected contrast were included (Table 1). Coordinates of the *foci* of activation reported in the original studies were transformed into Talairach space using the Lancaster transform (icbm2tal tool) in GingerALE (29). For each study, peaks were modelled as the centre of a 3D Gaussian distribution and a modeled activation (MA) map was then computed. ALE scores from the convergent MA maps were then calculated on a voxel-by-voxel basis to test for convergent (random-effects) rather than study specific foci (fixed-effects). All ALE data processing was performed using the BrainMap Search and View software (http://brainmap.org). The threshold of statistical significance was set at p=0.05, with False Discovery Rate (FDR) correction for multiple comparisons and a minimum cluster size of 160 mm3. Each ALE map was imported into Mango (http://rii.uthscsa.edu/mango) and overlaid on an anatomical Template (http://www.brainmap.org/ale/colin_tlrc_1x1x1.nii) for representation purposes. Significant clusters were manually localized and Brodmann areas (BA) were identified using the Talairach and Tournoux stereotactic anatomic brain atlas (30).

3. Results

Figure 1 shows the flow-chart of the selection strategy followed. From the 162 studies identified, 133 were excluded after review of abstract. From the 41 remaining articles selected *a priori*, 19 did not meet inclusion criteria. Thus, 22 studies were finally included in the review: seventeen of SAD and 5 of WS (for detailed information of the studies included, see Table 1).

Figure 1. Flow-chart

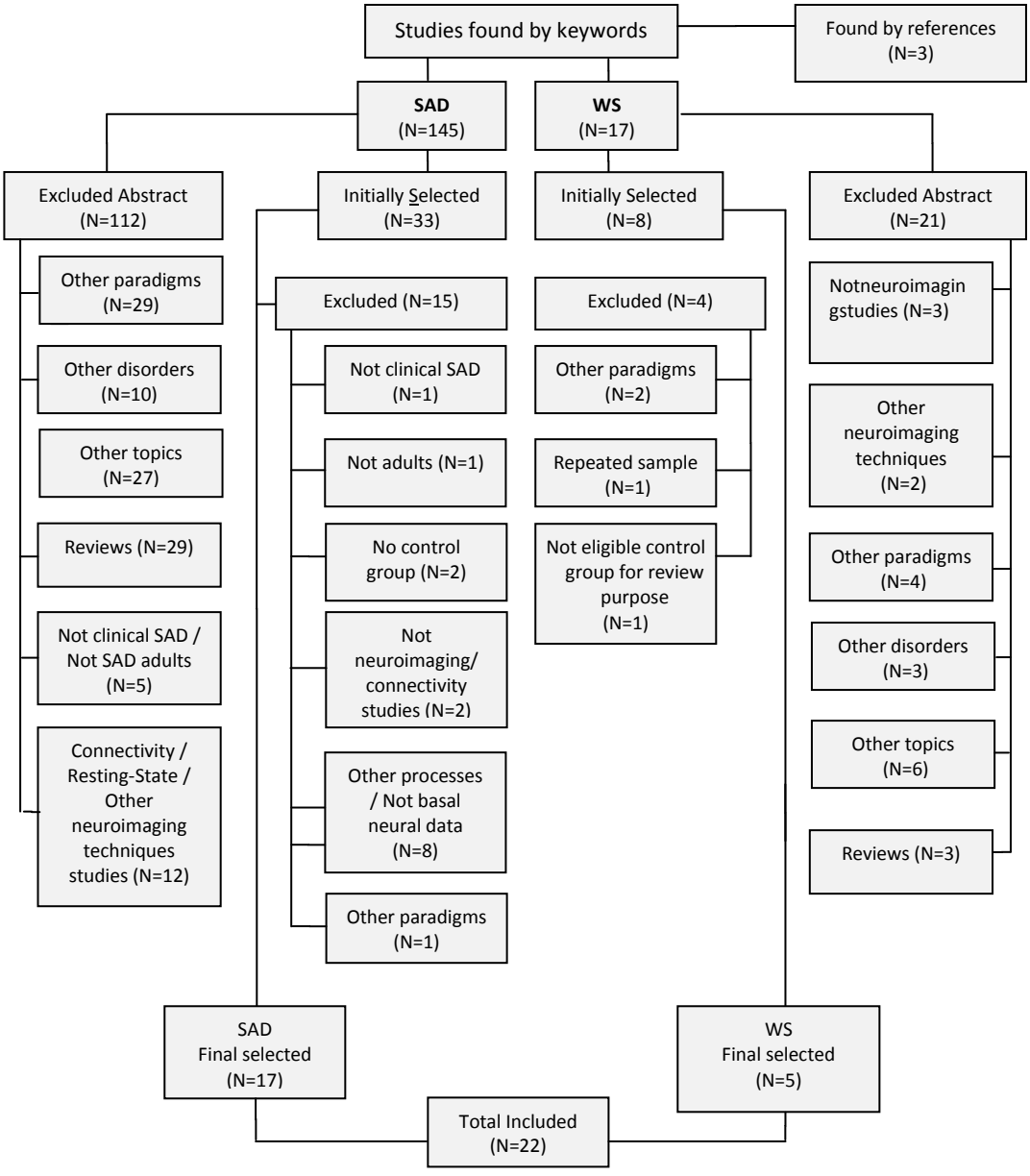


Table 1. Studies of facial emotion processing in SAD and WS.

Author (yr.)	*Subjects*	*Mean (SD) age*	*M/F*	*Hand-edness / Match*	*Diagnoses Comorbidity Current medication IQ (WS)*	*Task*	*Contrast*	*Results (SAD > HC; SAD < HC)* **Brain area**							***Detailed results***	***Correlations with clinical variables***
								FL	***PL***	***OL***	***TL***	***Am***	***In***	***ACC***		
Social Anxiety Disorder																
Stein et al. (2002)	*15 SAD 15 HC*	*39.1±14.3 39.3±12.3*	*10/5 10/5*	*RH Match*	*SCID Comordibidy: Yes (n=8) No Medication*	*Implicit: Gender Classification*	*Harsh > Happy* [a]	⬆	--	--	⬆	⬆	○	--	*↑activation amygdala, uncus, PHG, bilateral DMPFC, inferior frontal gyrus , and superior frontal gyrus*	*No correlation analysis*
						Block design	*Angry / Contemptuous >Happy*	○	--	--	⬆	⬆	○	--	*↑ activation of amygdala, uncus and PHG*	
							Fear / Neutral > Happy	○	--	--	○	○	○	--	*Ns*	
Straube et al. (2004)	*10 SAD 10 HC*	*25.0±3.3 23.2 ±3.9*	*5/5 4/6*	*RH Match*	*SCID None*	*Explicit: Emotion classification*	*Photographic angry > Neutral (Explicit)* [a]	○	○	--	○	○	⬆	--	*↑activation of insula*	*No correlation analysis*
						Implicit: Picture classification	*Photographic angry > Neutral (Implicit)*	○	⬆	--	⬆	⬆	⬆	--	*↑activation amygdala, insula , PHG, fusyform gyrus, STS*	
						Event-related design	*Schematic angry > Neutral (Explicit)*	○	○	--	⬆	○	○	--	*↑activation STS*	
							Schematic angry > Neutral (Implict)	⬆	○	--	⬆	○	○	--	*↑activation DMPFC and fusiform gyrus*	
Straube et al. (2005)	*9 SAD 9 HC*	*25.7±3.4 22.7±2.6*	*4/5 4/5*	*NS NS*	*SCID None*	*Free viewing Block design*	*Angry* [a]	--	--	--	⬆	⬆	⬆	--	*- ↑ activation amygdala, insula, and fusyform gyrus.*	*No correlation analysis*
							Happy	--	--	--	⬆	⬆	○	--	*↑ activation amygdala, fusyform gyrus*	
							Neutral	--	--	--	⬆	○	○	--	*↑ activation fusyform gyrus*	
Amir et al. (2005)	*11 SAD 11 HC*	*24.1 ±5.2 23.9±5.7*	*3/8 3/8*	*RH Match*	*SCID Comordibidy: Yes (n=3) Medication: (n=4)*	*Explicit: Valence Judgment Block design*	*Disgust > Neutral* [a]	⬆	⬆	⬆	⬆	⬆	⬆	⬆	*↑ activation ACC , insula, inferior/medial frontal gyrus , PHG, STS, caudate, thalamus and other parietal/occipital depending on run.*	*No correlation analysis*
Cooney et al. (2006)	*10 SAD 10 HC*	*28.7±8.4 28.8±5.3*	*4/6 3/7*	*19 RH NS*	*SCID Comordibidy: Lifetime Axia-I Medication: (n=5)*	*Explicit: Valence Judgment Event-related design*	*Neutral > Shapes* [a]	--	--	--	--	↑↓	--	--	*↑ activation right amígdala, ↓ activation lerft amígdala*	*SAD group: mean percent signal change in right amygdala was correlated with STAI-S /STAI-T scores.*
							Happy > Shapes	--	--	--	--	○	--	--	*Ns*	

								FL	PL	OL	TL	Am	In	ACC		
Phan et al. (2006)	*10 SAD* *10 HC*	*26.7± 6.8* *26.6±6.8*	*5/5* *5/5*	*RH* *Match*	*SCID* *None*	*Explicit: Emotion classification* *Block design*	*Harsh > Happy* [a]	○	⬆	○	⬆	⬆	○	⬆	*↑ activation amygdala, post-central sulcus, PHG, ACC.*	*Activation to fearful faces within right amygdala correlated to LSAS scores (but not BDI or STAI).*
							Harsh > Neutral	○	○	○	○	⬆	○	○	*↑ activation amygdala*	
							Neutral > Happy	○	○	○	○	○	○	○	*Ns*	
Yoon et al. (2006)	*11 SAD* *11 HC*	*27.0±6.0* *26.9±6.1*	*5/6* *5/6*	*RH* *Match*	*SCID* *Comordibidy: Yes (n=1)* *No Medication*	*Explicit: Emotion classification* *Block design*	*Harsh x High >Low intensity* [a]	⬆	⬆	⬆	○	⬆	⬆	○	*↑ activation amygdala, insula, middle frontal gyrus , superior P, lingual gyrus, cuneus.*	*No correlation analysis*
Blair et al. (2008)	*17 SAD* *17 HC* *17 GAD*	*29.0±8.7* *35.0±10.6* *31.2±9.1.9*	*9/8* *6/11* *9/8*	*NS* *Match*	*SCID* *Comordibidy: Yes (n=1)* *No Medication*	*Implicit: Gender Classification* *Event-related design*	*Fear > Neutral* [a]	⬆	○	○	⬆	⬆	○	⬆	*↑ activation amygdala, middle frontal gyrus, lateral frontal cortex, ACC, temporal cortex.*	*Amygdala ↑ associated to anxiety symptoms (BAI) in SAD (but not to LSAS or BDI).*
							Angry > Neutral	⬆	○	○	⬆	○	○	○	*↑ activation lateral region middle frontal gyrus, inferior temporal cortex and the culmen.*	
Evans et al. (2008)	*11 SAD* *1 HC*	*29.0±7.5* *27.9±10.6*	*4/7* *4/7*	*RH* *Match*	*SCID* *Comordibidy: Yes (n=5)* *No Medication*	*Free viewing* *Block design*	*Schematic angry > Neutral* [a]	⬆	⬆	○	⬆	⬆	○	⬇	*↑ activation amygdala, superior frontal cortex, and supramarginal gyrus, ↓ activation ACC.*	*Amygdala activation associated to LSAS scores (but not to BAI or BDI).*
							Schematic angry > Happy	⬇	⬆	⬆	⬆	○	○	○	*↑ activation middle/superior temporal, fusiform gyrus, posterior cingulate, precentral gyrus, lingual gyrus, cerebellum and ↓ middle frontal gyrus*	
Gentili et al. (2008)	*8 SAD* *7 HC*	*39±7* *30±7*	*4/4* *4/3*	*RH* *NS*	*DSM* *None*	*Implicit: Face identity detection* *Event-related design*	*Faces > Scrambled-Images* [a]	⬆	↑↓	○	↑↓	⬆	⬆	⬆	*↑ activation amygdala, insula, inferior frontal gyrus , STS, parietal, cuneus, and ↓activation intraparietal sulcus, fusiform gyrus.*	*No correlation analysis*
Goldin et al. (2009)	*15 SAD* *15 HC*	*31.6±9.7* *32.1±9.3*	*6/9* *6/9*	*RH* *NS*	*DSM* *Comordibidy: NS* *No Medication*	*Free viewing* *Block design*	*Threat faces> Neutral scenes* [a]	⬆	↑↓	↑↓	⬆	○	○	⬆	*↑activation of OFC, ACC , PHG, postcentral gyrus, superior parietal, middle/inferior occipital gyrus, lingual gyrus, cuneus and ↓activation precuneus, inferior parietal, supramarginal gyus.*	*LSAS associated to ↑BOLD in response to social threat in amygdala,PCC, occipital gyrus and dLPFC*
							Physical-Threat Scenes > Neutral scenes	○	○	○	○	○	○	○	*- NS*	
Klumpp et al. (2010)	*12 SAD* *12 HC*	*28.2± 8.6* *33.6±9.6*	*NS* *NS*	*RH* *NS*	*SCID* *Comordibidy: Yes (n=1)* *No Medication*	*Explicit: Valence Judgment Event-related design*	*High Threat* [a]	⬆	○	○	⬆	⬆	○	○	*↑ activation of amygdala, PHG, inferior frontal gyrus , OFC*	*No association between amygdala activation and LSAS scores.*
							Medium Threat [a]	○	○	○	○	⬆	⬆	○	*↑ activation of amygdala, insula, cerebellum, midbrain, putamen*	
							Low Threat	⬇	○	⬆	⬆	○	⬆	○	*↑ activation insula, PHG, thalamus, cuneus and ↓activation middle frontal gyrus .*	

								FL	PL	OL	TL	Am	In	ACC		
Blair et al. (2011)	*39 SAD* *39 HC* *Both adults adoles-cents*	*32.2±9.14* *13.3±3.42* *29.7±8.30* *14.9±2.03*	*23/16* *21/18*	*NS* *Match*	*SCID* *None*	*Implicit: Gender Classification Event-related design*	*Fear x Diagnoses*[a]	○	○	○	○	⬆	○	⬆	*↑ activation amygdala, rostral ACC*	*SAD adults: positive correlation between BOLD response to both angry and fear faces and LSAS scores in ACC.*
							Angry x Diagnose	○	○	○	○	○	○	⬆	*↑ activation rostral ACC*	
							Neutral x Diagnoses	○	○	○	○	○	○	○	*NS*	
							Diagnoses> Age > Emotion	○	○	○	○	○	○	○	*NS*	
Klumpp et al. (2012)	*29 SAD* *26 HC*	*24.7±5.9* *26.2± 6.3*	*12/17* *10/16*	*RH* *NS*	*SCID* *Comordibidy: Yes (n=5)* *No Medication*	*Explicit: Emotion matching* *Block design*	*Fear> Happy*[a]	⬆	⬆	○	⬆	⬆	⬆	○	*↑ activation insula, amygdala, inferior frontal gyrus, DMFC, PHG, inferior temporal gyrus, postcentral gyrus, superior parietal gyrus, caudate*	*No correlation analysis*
							Angry > Happy	--	--	--	--	--	⬆	--	*↑ activation insula*	
Frick et al. (2013)	*14 SAD* *12 HC*	*32.4±8.8* *28.0±8.2*	*14/0* *14/0*	*RH* *NS*	*SCID* *Comordibidy: Yes (n=3)* *Medication (n=1)*	*Implicit: Gender Classification* *Block design*	*Fear > Neutral*[a]	↑↓	⬆	○	⬆	○	○	○	*↑ activation fusyform gyrus, precentral gyrus, superior frontal gyrus and ↓ activation of vmPFC.*	*Positive correlation between amygdala activation and LSAS scores to fearful faces.*
Klumpp et al. (2013)	*29 SAD* *27 HC*	*24.9± 6.3* *24.9±5.9*	*11/18* *8/19*	*RH* *NS*	*SCID* *Comordibidy: NS* *Medication (n=2)*	*Implicit/ Explicit* *Emotion matching* *Block design*	*Faces> Shapes*[a] *(Match faces/match shapes presented in the same field view)*	--	--	--	--	--	⬆	⬇	*↑ activation anterior insula when attending faces.* *When attention was directed away from faces, HC (but no SAD) exhibited ACC recruitment*	*Positive correlation between insula activation and LSAS scores (but not STAI-T or BDI).*
Ziv et al. (2013)	*67 SAD* *28 HC*	*33.0±8.8* *32.6±9.5*	*35/32* *15/13*	*RH* *NS*	*ADIS-IV-L* *Comordibidy: Yes (n=24)* *No Medication*	*Explicit: Emotion rating* *Block design*	*Threat faces > Asterisk-Count*[a]	⬆	○	○	⬆	○	○	○	*↑ activation middle/ superior frontal gyrus , superior temporal gyrus, and middle temporal gyrus/inferior frontal gyrus*	*LSAS associated with left insula activation during the faces task.*
Williams Syndrome																
Meyer-Linderberg et al. (2005)	*13 WS* *13 HC*	*28.3±9.6* *28.3±9.6*	*6/7* *6/7*	*RH* *Match*	*NS* *IQ WS: 92.1± 9.6*	*Explicit: Emotion matching* *Block design*	*Threat faces > shapes*[a]	*	*	○	○	⬇	○	○	*↓ activation amygdala*	*No correlation analysis*
							Threat Scenes > shapes	*	*	○	○	⬆	○	○	*↑ activation amygdala* ** Detailed in results section.*	
Haas et al. (2009)	*14 WS* *13 TD*	*31.01±8.8* *29.71±9.5*	*7/7* *5/8*	*NS*	*FISH* *IQ WS: 65 ± 6.8*	*Implicit: Gender Classification* *Event-related design*	*Happy > Neutral*[a]	--	--	--	--	⬆	--	--	*↑ activation amygdala*	*No correlations between IQ, reaction time or accuracy and amygdala activation to happy/ fearful faces*
							Fear > Neutral[a]	--	--	--	--	⬇	--	--	*↓ activation amygdala*	

Paul et al. (2009)	*17 WS* *17 CA* *17 DA*	*30.6±NS* *31.1± 11.2* *8.8 SD 0.7*	*7/10* *7/10* *8/9*	*NS* *Match*	*FISH* *IQ WS:* *67.5 ± 10.0*	*Implicit:* *Identity matching* *Block design*	*Neutral faces> Scrambled Images*[a]	*	*	*	*	⬇	*	*	*No activation amygdala* ** Detailed in results section.*
Haas et al. (2010)	*12 WS* *Subset of Haas et al. (2009)*	*29.46±8.07*	*4/8*		*FISH*		*Fear > Neutral*	--	--	--	--	⬇	--	--	*Higher scores on social approach towards strangers associated with ↓ amygdala response to fearful vs neutral faces*
Mimura et al. (2010)	*9 WS* *9 HC*	*33.8±12.* *34.8±10.3*	*1/8* *1/8*	*RH* *---*	*FISH* *IQ WS:* *68±8.7*	*Explicit:* *Emotion matching* *Event-related design*	*Negative > Positive*[a]	↑↓	--	--	--	⬇	--	--	*↓activation of amygdala* *↓activation lateral OFC and ↑activation of medial OFC*

Note: Yr. = years; M = male; F = female; SD = standard deviation; FL = frontal lobe; PL = parietal lobe; OL = occipital lobe; TL = temporal lobe; Am = amygdale; In = insula; CC= cingulated cortex; (L) = left hemisphere; (R) = right hemisphere; PHG=parahippocampal gyrus; STS= Superior temporal sulcus; DMPFC= Dorsomedial prefrontal cortex; OFC= Orbito-frontal cortex.; NS = not stated; RH = right-handed; SCID = Structured Clinical Interview for DSM Disorders; FISH = Fluorescence In Situ Hybridization; LSAS = Liebowitz Social Anxiety Scale; STAI-S = State- Anxiety Inventory; STAI-T = Trait Anxiety Inventory; BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory;

ns = non-significant result. ⬆ = increased activation; ⬇ = decreased activation; ↑↓ = both increased/decreased activation depending on area; O = non-significant difference; -- = not examined. [a] Included contrast on ALE.

3.1 SAD studies

Studies of facial emotion processing in SAD included mostly the presentation of negative facial emotions. Seventy per cent of the studies used explicit or implicit paradigms, while a minority used free-viewing (17.6%) or combined (11.7%) paradigms. Photographs of faces from the Ekman and Friesen face collection (31) presented in block design was the most commonly used procedure. The majority of studies included both SAD and healthy control (HC) samples of young adults, with some heterogeneity in gender distribution. Handedness matching was performed in most studies. The Structured Clinical Interview for the DSM-IV Axis I (SCID) (32) was the most commonly used method to establish the SAD clinical diagnoses. Fifty-eight per cent of studies included subjects with comorbidity, and most studies included subjects free of psychotropic medication.

In general, most of the evidence indicated greater response of the amygdala to threat-related facial expressions in SAD individuals compared to HC (33–44; but see 45,46). However, other paralimbic regions such as the insula and the parahippocampal gyrus also appear to exhibit greater activation in social phobics (37–45,47,48). Increased activation of limbic/paralimbic regions is the most replicated finding, and has been observed independently of task design (implicit (33,39,41,44), explicit (36–38,42,43,47), or combined (34,48) paradigms) at different levels of emotion intensity (38,42), and even when simple-drawing schematic faces are presented (40). Using an event-related design, Klumpp et al (2010) (42) found SAD patients showed increased amygdala activation at both high and moderate threat intensities in comparison to matched controls. Although the study did not find differences in amygdala activation for threatening faces at low-intensity, SAD patients showed increased activation in other relevant paralimbic areas such as the insula and the parahippocampal gyrus, and were more accurate than controls at identifying moderately intense threatening expressions. Similary, Yoon et al., (38) found greater bilateral amygdala and insula activation to high (vs. low) intensity harsh faces. Together, these findings suggest that the amygdala activates at a relatively lower threshold in SAD patients, and supports

the notion that amygdala reactivity can be modulated by the intensity of the affect as expressed on faces (49).

Increased amygdala activation in response to angry faces has been observed even when non-photographic faces are used (40). Using simple line-drawing schematic faces, Evans et al., (2008), (40) found greater amygdala activation for angry *vs.* neutral faces, -but not when angry *vs.* happy faces were contrasted-. Although the *a priori* hypothesis focused on amygdala response, between-group differences were also found at several other *post-hoc loci* in the prefrontal, fusiform, insular, and temporal cortices even for the angry *vs.* happy contrast. In fact, the study findings presented on Table 1 reflect both inter- and intra- inconsistencies, depending on the control condition and the contrast performed. Moreover, a pattern of neural hyperactivation does not seem to be restricted to threat-related facial expressions in all cases, since some positive findings are reported for neutral and happy faces as well (35,36). This is a significant point, since the majority of studies used neutral and happy faces as a control condition. In addition to the selection of the control stimuli, differences in experimental design are also of great importance. Straube et al., (2004) (34) demonstrated this, with a well-designed study that combined different stimuli (photographic/schematic faces) and task instructions (implicit/explicit task): the study found that compared to control subjects, SAD patients showed greater responses to angry (*vs.* neutral) photographic faces in the insula regardless of task, whereas amygdala, parahippocampal gyrus, and extrastriate visual cortex were more strongly activated only during the implicit task. When schematic faces were presented SAD subjects also responded sensitively, with significant activation in the insula and extrastriate cortex, although phobics` responses were significantly increased only in the extrastriate cortex compared to control subjects. Together, these findings highlight the importance on the selection of stimuli and the experimental design, which may partially account for the discrepancies observed between studies and results.

Although neuroimaging studies of facial emotion processing have focused on the amygdala and insula as key regions, abnormalities in other areas relevant for face and fear processing have also emerged. Studying the neural response to the

presentation of faces (*vs.* scrambled-pictures) Gentili et al., (2008) (41) found that compared to HC, SAD patients showed stronger activity not only in limbic regions, but also in other key regions of the face-perception-system such as the superior temporal sulcus, -which has been involved in the evaluation of expression and personal traits-, and weaker activity in the fusiform gyrus. In another study, Amir et al., (2005) (47) used a region of interest (ROI) approach to study the involvement of the ACC in brain response to disgust (*vs.* neutral) faces, and found that compared to non-anxious controls, SAD cases exhibited significantly increased activation in the insula, the ACC and other frontal regions. To study the neural bases of emotional reactivity in SAD, Goldin et al., (2009) (45) included both threatening faces and physical threat scenes to determine relative specificity of the effect of the threat-content on emotional reactivity in SAD. The study observed significantly increased activation in several brain regions when attending threat faces (*vs.* neutral scenes), including frontal, occipital and temporal cortices, but not in the amygdala, where both SAD and HC subjects had increased activity. In contrast, when physical threat scenes were compared, no between-group differences emerged for cases and controls, a finding that supports the notion of specificity of the neural responses to relevant social threat stimuli in SAD. In a similar line, Ziv et al., (2013) (46) found no evidence of greater amygdala or insula response when attending harsh faces, but increased activity in frontal and temporal regions involved in the processing and regulation of emotions. Recently, Klumpp et al., (2013) (48), evaluated attention control in SAD subjects and HC while performing a matching task, in which a trio of faces alongside a trio of geometrical shapes was presented simultaneously within the same field of vision. Participants were instructed to match faces or match shapes, directing attention towards or away from emotional information. The authors found that participants with SAD exhibited greater insula activation compared to controls when attending to emotional faces. In contrast, when attention was directed away from faces, controls exhibited ACC recruitment, while SAD did not. Interestingly, across participants, greater ACC activation was associated with lower insula activation.

Finally, 58.8% of studies analyzed correlations of brain activation to clinical measures and most found a positive correlation between brain activation (mostly in

limbic regions) and social anxiety severity, measured with the Liebowitz Social Anxiety Scale (LSAS).

The study of the neural correlates of facial emotion processing in SAD has made important steps forward in the last decade. The clear focus of most of these studies on limbic regions (and the use of an ROI approach in most cases) has meant that the participation of these regions is the most consistently replicated finding. However, alteration on pre-frontal regions, the ACC and other temporal and parietal areas has also emerged and suggest that SAD patients differ from HC not only in the reactivity in limbic regions, but also in other regions implicated in fear-processing and the face-perception network.

3.2 WS studies

The first functional magnetic resonance study to examine facial emotion processing in WS (50) found reduced amygdala activation to threatening faces (vs. neutral scenes) but increased amygdala activation to non-social threat-scenes in a normal-IQ sample of WS subjects. Moreover, a different pattern in brain reactivity was found when face *vs*. scene matching were compared, in which normal controls differentially activated dorsolateral-prefrontal (DLPFC), medial-prefrontal (MPFC) and orbitofrontal cortex (OFC) in the more difficult condition (face matching). In contrast, participants with WS showed no activation of OFC, and both MPFC and DLPFC were activated to similar degrees in both tasks. In a different line, Haas et al., (2009) (51) studied amygdala response to both happy and fearful faces and found that WS subjects showed decreased amygdala activation to fearful faces but increased activation to happy faces in comparison with typically developing controls (TD). Moreover, amygdala activation was not correlated to IQ, reaction time or accuracy on the task.

Between-group differences in brain reactivity are not restricted to faces with emotional valence. Paul et al., (2009) (52) compared neural response to neutral faces in subjects with WS and two control groups, one of chronologically age-matched subjects (CA) and another of developmental age-matched individuals (DA). Compared

to both control groups, subjects with WS showed no activation of amygdala to neutral faces (vs. scrambled-images). In addition to the amygdala, WS showed increased activation in the ventral occipito-temporal regions and in the right superior parietal lobule during the face matching task compared to both control groups. However, neural responses in these regions were similar in WS participants and DA controls, suggesting that the WS responses resembled an immature profile.

In order to study how amygdala response in response to fear modulates social behavior in WS, Haas et al., (2010) (53) tested three models of abnormal social behavior (social approach; emotional/empathic sociability; social approach toward strangers) and abnormal amygdala function. This study found that decreased amygdala response to fearful facial expressions was related to an increased tendency to approach strangers.

Finally, based on the proposal of a differential role of the medial/lateral regions of the OFC in reward/punishment processing respectively (54), Mimura et al., (2010) (55) evaluated the neural response to positive and negative facial expressions in the amygdala and the medial/lateral OFC. The study found that relative to TD controls, participants with WS exhibited reduced amygdala activation during presentation of negative faces, as previous studies had found, as well as a different pattern of OFC activation. While TD controls showed medial OFC activation in response to positive expressions and lateral OFC activation to negative ones, WS showed the opposite pattern.

The study of the neural correlates of facial emotion processing in WS has yielded relevant findings. It should be noted that authors have taken particular care to select samples and stimuli in order to extend the existing findings. The available evidence suggests the involvement of the amygdala when processing both positive and negative faces, with decreased amygdala activation to the presentation of fearful, but increased amygdala activation to the presentation of happy ones. These findings are complemented by evidence of increased amygdala activation to non-social threat scenes and absence of recruitment of this region in response to neutral faces. Alterations in other regions, particularly pre-frontal and parietal regions, have also been observed when WS subjects were compared to both TD and DA controls,

suggesting that the altered brain response of some regions such as the amygdala is not merely a consequence of an immature brain profile.

3.3 ALE results

3.3.1 SAD vs. HC

Between-group comparisons during facial emotion processing (SAD=306; HC=269; *foci*=139) revealed several regions, with significantly increased activation in SAD compared to HC (Table 2, Figure 2). These regions included: left amygdala and parahippocampal gyrus, (x= -26; y= -4; z= -18), left entorhinal cortex (x= -18, y= -6, z= -22, BA 28), right globus pallidus (x= 20; y= -4; z= -6) right insula (x= 34; y= 20; z= 4, BA 13), left medial frontal regions, extending to the anterior cingulate cortex (x=0; y=54; z=36; BA 9 / x=-10; y=50; z=0; BA 10 / x=-44; y=42; z=16; BA 46), left putamen (x= 16; y= -8; z= 2), left superior temporal gyrus (x=-42; y=-36; z=8; BA 41) and left cuneus (x= -2; y= -82; z= 8; BA 17).

3.3.2 WS vs. HC

Between-group comparisons during facial emotion processing (WS=36; HC=35; *foci*= 30) revealed two main regions showing less activation in WS compared to HC (Table 2, Figure 2). These regions were: the right inferior parietal lobule (x=36; y=-56; z=42; BA 40) the right parahippocampal gyrus (x=16; y= -8; z=-12; BA 28) centered at the amygdala (x= 16; y= -5; z= -10) and the right globus pallidus (x= 18; y= -2; z= -8).

Table 2. Activation likelihood estimation results for facial emotion recognition in patients with SAD and Williams Syndrome compared to healthy controls.

Cluster	Area	BA	Hemisphere	Talairach x	Talairach y	Talairach Z	Volume (mm3)	Extreme Value
SAD> HC								
1	Amygdala/ Parahypocampal gyrus		Left	-26	-4	-18	2136	0.0280
	Entorhinal cortex	28	Left	-18	-6	-22		0.0230
2	Globus Pallidus		Right	20	-4	-6	1080	0.0217
	Subcallosalgyrus	34	Right	12	2	-14		0.0105
3	Insula	13	Right	34	20	4	624	0.0104
4	Medial Frontal gyrus.	9	Right	0	54	36	304	0.0160
5	Medial Frontal gyrus.	10	Left	-10	50	0	232	0.0120
6	Middle frontal gyrus	46	Left	-44	42	16	208	0.0145
7	Putamen		Left	-16	8	-2	216	0.0152
8	Superior temporal gyrus	41	Left	-42	-36	8	256	0.0136
9	Cuneus.	17	Left	-2	-82	8	192	0.0139
SAD < HC								
	No significant clusters							
WS > HC								
	No significant clusters							
WS < HC								
1	Inferior Parietal lobe	40	Right	36	-56	42	312	0.0114
2	Amygdala		Right	16	-5	-10*	200	0.0097
	Parahippocampal gyrus	28	Right	16	-8	-12		0.0097
	Globus Pallidus		Right	18	-2	8		0.0093

Social Anxiety Disorder; WS, Williams Syndrome; HC Healthy Control. x = sagittal, y = coronal, z = axial coordinates according to Talairach and Tournoux of the extreme value for each cluster. ; BA = Brodmann Area; ALE = Activation Likelihood Estimation p 0.05 False RateDiscovery corrected for multiple comparisons. *Shows coordinates of the weighted center for cluster two.

Figure 2. Activation likelihood estimation maps comparing SAD and WS.

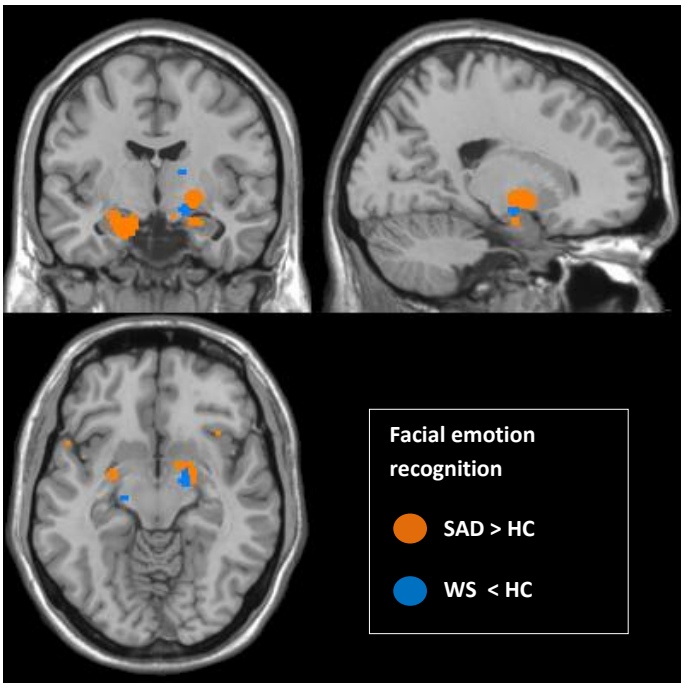
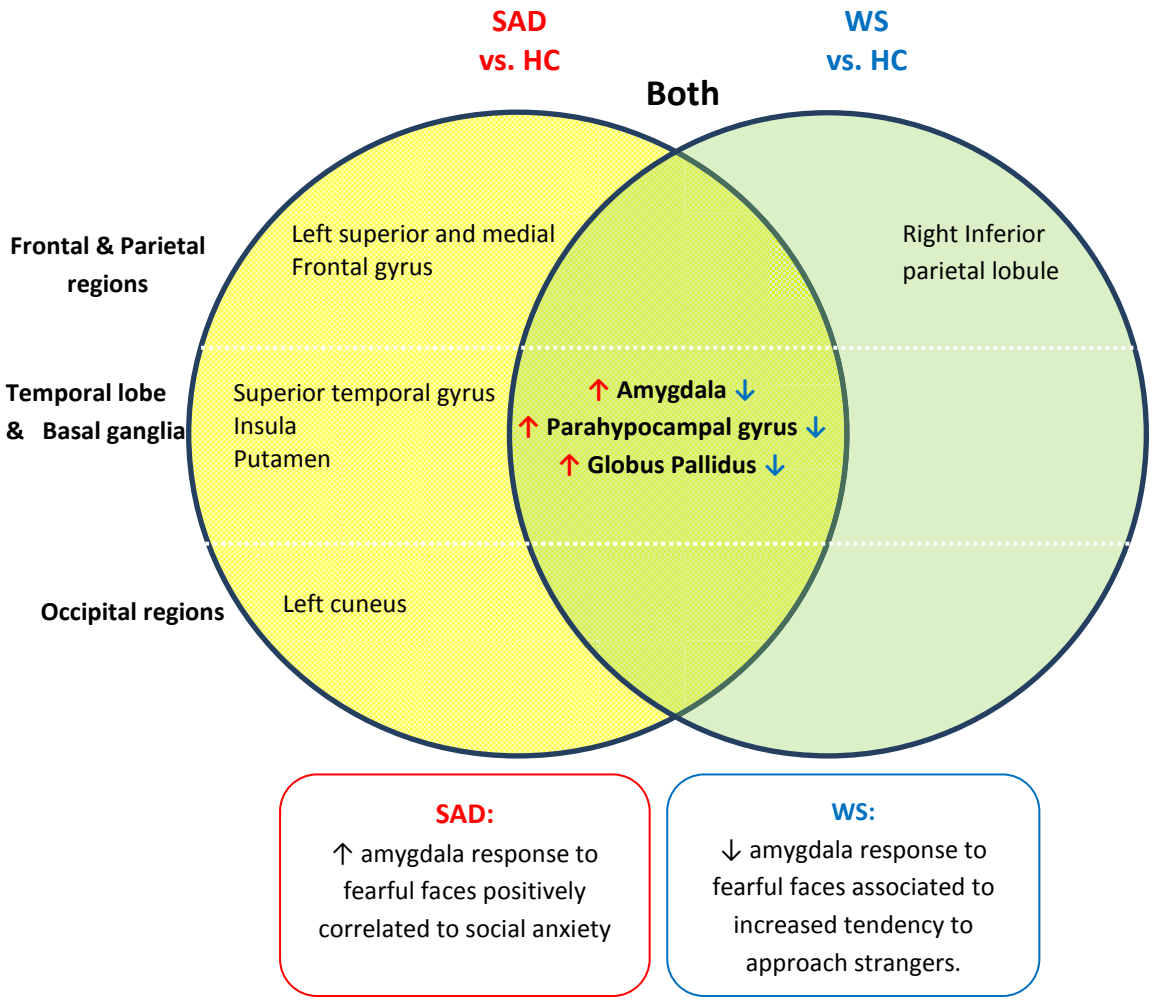


Figure 2. Activation likelihood estimation maps comparing subjects with SAD and WS with HC. ALE maps were computed at a false discover rate (FDR) corrected threshold of p< 0.05, with a minimum cluster size of K> 160mm3. Clusters shown in orange reflect brain regions where SAD subjects showed increased activation in comparison to HC. Clusters shown in blue reflect brain regions where subjects with WS showed decreased activation relative to HC. SAD=Social Anxiety Disorder; WS=Williams Syndrome; HC=Healthy Controls

Figure 3.

Common and distinct patterns of brain activation during facial emotion processing in SAD and WS.



4. Discussion

This is the first study to examine the common and distinct neural correlates of facial emotion processing across two disorders that are on opposite extremes in the continuum of social fear.

We found evidence for common and distinct patterns of neural activation (see figure 3 for a summary). Our most relevant finding was the engagement of limbic regions during facial emotion processing for both SAD and WS, with opposite patterns of activation for each disorder. Compared to HC, SAD was characterized by

hyperactivation of limbic regions during facial emotion processing. WS showed the inverse pattern, with decreased activation of these regions when compared to controls. Differential activation in a number of regions specific to either condition was also identified: SAD individuals exhibited greater activity of the insula, putamen, the superior temporal gyrus, medial frontal regions and the cuneus, while WS subjects showed decreased activity in the inferior region of the parietal lobule.

4.1 The role of limbic regions across the continuum of social fear: SAD and WS.

SAD and WS were characterized by opposite patterns of activation in the amygdala, but also on the parahypocampal gyrus, and the globus pallidus. The implication of limbic regions and the pattern of activation found for each disorder supports evidence provided by previous systematic reviews and metaanalysis on SAD (25,27,28) and WS (5,26) implicating limbic regions during facial emotion processing. Indeed, our study compares for the first time the brain response to facial emotion processing between SAD and WS.

The amygdala is a complex structure comprising more than a dozen nuclei. It has been implicated in a variety of functions such as receiving input about faces, orchestrating emotional responses, modulating attention and perception and signaling about salient external stimuli (56,57). Evidence from human and animal studies has shown how damage within this structure results in diminished fear response and increased social approach behaviors (58–61). Based on animal studies of macaques with amygdala lesions, Amaral et al., (2006) (59) proposed a model in which the amygdala plays a modulatory role on social behavior through its primary role in evaluating the environment for potential dangers. Consistent with this notion, we observed that amygdala hypoactivation was positively associated to an increased tendency to approach strangers in WS, which is in agreement with findings from basic research that show a reduced ability to detect social threat signals in this population (19,20). By contrast, amygdala hyperactivity to threatening faces in SAD was positively correlated with clinical ratings of social anxiety severity.

Opposite patterns of activation were also observed in the parahipoccampal gyrus and the globus pallidus. These findings support previous reports on SAD (28), and extend available evidence on WS. The parahippocampal gyrus is believed to play a role in processing the context during fear conditioning (62). In the context of SAD, hyperactivation of this region has been interpreted as indicative of disruptions in this process and the inability to assign accurate saliency value to a stimulus. Thus, the involvement of this region as a common correlate is interesting, in view of the atypical patterns on the processing of social cues and threat-signals previously mentioned in both individuals with SAD (24) and WS (19,20)

Lastly, the globus pallidus was a common neural correlate between SAD and WS. In addition to its primary role in motor functions (63), there is evidence that supports the involvement of this region in emotional aspects of behavior (64). Specifically, the expression of type 1 receptors of the corticotropin-releasing factor (CRFR1), which are believed to mediate anxiety-like behaviors in mice, is particularly dense in the globus pallidus (64). Furthermore, this region is thought to serve as an integration site for different behaviorally relevant neuronal circuits, with pallidal neurons being involved in the encoding of several aspects, including movement and reward information (65).

Together, these results provide evidence of the implication of limbic regions during facial emotion processing in SAD and WS. The involvement of these regions as a common correlate and the pattern of activation found for each disorder may reflect the neural substrate of the fear component. Taken together, the results nicely reflect how opposite extremes on the continuum of the fear component which are evident in opposite behavioural phenotypes also appear reflected by inverse neural activity within the same regions.

4.2. Distinct neural activation in SAD and WS

Differential activation in a number of regions specific to either condition was also identified. SAD was associated with increased activity in the insula, putamen,

medial frontal regions, encompassing the anterior cingulated cortex, the superior temporal gyrus and the cuneus. This is the first meta-analysis to demonstrate that increased activation of the insula, the putamen, medial prefrontal regions and the cuneus are associated with SAD. The only previous meta-analysis of SAD that used an ALE approach (28), did not find this association. However, Hattingh et al's meta-analysis included studies that performed whole-brain analysis, and comprised a total of seven studies compared to the 17 studies included in the present review; this may account for the differences. The right anterior insula has been identified as an essential neural substrate of interceptive awareness and subjective emotional experience (66,67). Activity in this region correlates positively with awareness of bodily responses and with subjective negative emotional experience, suggesting that this region mediates the awareness of visceral responses and its representation as a subjective feeling (66,67). The pattern of hyperactivation within this region observed in SAD, but not WS, may reflect subject's enhanced attention to internal bodily states and/or an enhanced awareness of their emotional experience (67). This is consistent with the observation that anxiety-prone individuals focus strongly on bodily states, and provides support for models involving this region in anxiety (68). Taken together, the findings suggest that the involvement of this region may be more characteristic of anxiety disorders such as SAD, perhaps, reflecting the subjective negative emotional experience in response to threat-related facial expressions.

Individuals with SAD also expressed increased activation in the putamen. Increased activation of this region during emotion processing has also been observed in other psychiatric populations (69) and in HC (70). This may reflect either greater facial mimicry or a greater amplification of the sensorimotor processing of facial affect, given the involvement of this region in sensorimotor processing, which is thought to contribute to the motor production of facial expressions during affect recognition (70,71).

We observed a pattern of hyperactivity in medial frontal regions in subjects with SAD. This finding is interesting, since increased activation in these regions also coexisted with limbic hyperactivity. Together with the ACC, medial prefrontal regions

are thought to be involved in several aspects of emotion processing, including appraisal and expression of negative emotions and regulation of this response (72). Moreover, neuroimaging studies support the notion that limbic-prefrontal circuitry is centrally involved in enabling representations of stimulus emotional salience and, importantly, in top-down control mechanisms (73,74). Thus, the coactivation of limbic-prefrontal regions may reflect the influence of cortical areas on this response, perhaps, in an attempt to regulate the limbic response.

Additionally, hyperactivity of the superior temporal gyrus, -a region that has been involved in social perception and gaze processing- (75,76), and the cuneus was observed in SAD. Enhancement of activity of primary visual cortex during the processing of emotional stimuli has been previously reported (77) and may be related to rapid detection and perceptual processing of emotionally salient stimuli. Thus, the hyperactivation pattern within this region in SAD may reflect rapid detection of potential threatening stimuli at a perceptual level. Our findings are in accordance with previous reports in SAD using other paradigms (78), with proposals of the involvement of visual cortex in emotional arousal (79,80), and fits the pattern of early hypervigilance to facial expressions observed in SAD (24).

Lastly, WS was specifically associated with decreased activity in the right inferior parietal lobule. This region is involved in the ventral/dorsal stream and plays an important role with various aspects of attention, including maintaining attentive control on current task goals and responding to salient new information or alerting to stimuli in the environment (81). Evidence of deficits in this region are consistent with structural and functional brain imaging evidence of abnormalities in both inferior and superior parietal areas, which may be related to the frequently severe deficits in visuospatial cognition observed in individuals with WS (82).

4.3 Limitations

Although ALE represents a powerful approach for the meta-analytic treatment of neuroimaging data, a number of factors should be considered in the interpretation

of the current findings. First, our study provides an estimate of the probability that activity in particular brain regions may differ between SAD and WS when compared to controls. We did not directly compare brain activity in SAD and WS and conclusions in this study are based on inferences from these results. Second, although the studies of SAD included yielded a substantial number of subjects and an acceptable number of *foci* recommended for this approach (<100) (83) the relatively small body of studies on WS available yielded a reduced number of subjects and *foci*. Third, the inclusion of studies using a ROI approach may have influenced the resulting activation patterns and may potentially have biased the results in favour of certain regions. Lastly, although we assume that some core symptoms of SAD and WS are at the opposite ends of a continuum and we interpret a set of our findings as a common neural correlate, we do not suggest that SAD and WS constitute a common entity. In fact, there are clear differences between the two conditions -including cognitive capacities, genetic weight and neurodevelopment trajectory- and the nature of the social symptoms is probably different for each disorder (56).

4.4 Conclusions

Our study provides evidence of common and distinct neural correlates during facial emotion processing in SAD and WS. The identification of limbic structures as a shared correlate may reflect the neural substrate of the fear component. The pattern of hyper/hypoactivation observed within limbic structures may contribute to explain the pattern of exaggerated/diminished fear response to social cues that characterizes SAD and WS respectively. We believe that insights from WS and the inclusion of this syndrome as a control group in future experimental studies may improve our understanding of the neurobiology of social behaviour in general and of SAD in particular. Future studies with direct comparison between both disorders seems to be desirable and opportune.

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Estudio 3(b). Neural correlates during facial emotion processing in Social Anxiety Disorder and Williams Syndrome: a fMRI study.

RESUMEN

OBJETIVO: Estudiar la actividad cerebral mediante resonancia magnética funcional (RMf) durante la tarea de procesamiento emocional a través de la expresión facial en sujetos con TAS y sujetos con SW y una muestra de sujetos controles sanos.

MÉTODO: Veinte sujetos con TAS, 20 con SW y 20 controles sanos de ambos sexos y edades comprendidas entre 18 y 30 años emparejados por sexo, edad y lateralidad fueron incluidos en el estudio. Los participantes con TAS y los controles sanos fueron seleccionados de la muestra caso-control del Estudio 2. La muestra de sujetos con SW se obtuvo en colaboración con la Unidad de Genética de la Universidad Pompeu-Fabra y la Asociación Española de SW. El diagnóstico de TAS se estableció mediante los criterios diagnósticos del DSM-IV (APA, 2000) y la administración de la Entrevista Neuropsiquiátrica MINI (Ferrendo, Bobes, & Gilbert, 1999). Se excluyeron pacientes con enfermedades médicas o neurológicas relevantes, abuso/dependencia de sustancias y otras enfermedades psiquiátricas. El diagnóstico de SW se estableció mediante los criterios fenotípicos establecidos por la Academia Americana de Pediatría (AAP, 2001) y la confirmación genética mediante la técnica FISH (prueba de hibridación por fluorescencia in situ para el gen de la elastina situado en el cromosoma 7). En el caso de los controles sanos, se administró la entrevista psiquiátrica MINI para confirmar ausencia de patología psiquiátrica. Todos los sujetos (SAD, SW y controles sanos) realizaron un chequeo físico completo; carecían de antecedentes de dependencia de sustancias o cumplían criterios de abuso de sustancias actual; y obtuvieron resultados negativos en la prueba de toxicidad en orina. Todos los participantes eran diestros. El ser portador de prótesis o marcapasos metálicos era un criterio de exclusión común a los tres grupos.

La evaluación clínica para los 3 grupos incluyó: (i) La versión española de la Escala de Ansiedad Social de Liebowitz (LSAS) (Bobes et al., 1999); (ii) el Inventario de Ansiedad Rasgo-Estado (STAI) (Spielberger, 1983); (iii) una Escala Visuo-Analógica de Ansiedad (VAS); y la adaptación española del Inventario de Carácter y Temperamento TCI (Gutierrez et al., 2001). En el caso de los participantes con SW, todos los instumentos

se administraron de forma heteroaplicada para asegurar su correcto entendimiento. La versión del TCI utilizada para este grupo fue la versión reducida de 56 items (Adan, Serra-Grabulosa, Caci, & Natale, 2009).

Durante la realización de la RMf los sujetos realizaron una versión de la tarea de procesamiento emocional a través de la facies (Hariri et al., 2002) con un diseño en bloque. Los sujetos debían emparejar dos caras, de las tres que se presentaban (una situada en la parte central superior; y dos opciones situadas en los extremos derecho e izquierdo inferiores) con el objetivo que coincidiera la expresión emocional de dichas caras (temor, alegría o enfado). Durante la tarea control los sujetos debían emparejar formas geométricas. La RMf se realizó mediante un imán de 1.5 Tesla (General Electric Medical Systems, Milwaukee, WI). Los datos de imagen se transfirieron y procesaron en un programa de MATLAB versión 7 mediante una plataforma de Windows Microsoft (The Math-Works Inc, Natick Massachussets). El análisis de las imágenes se procesó y analizó con el software Statistical Parametric Mapping (SPM8). Se realizó un análisis individual para identificar la diferencia entre el procesamiento de estímulos emocionales y la tarea control y un análisis de segundo nivel para la comparación de grupos. Con el objetivo de estudiar si existía una asociación entre las variables clínicas de interés (puntuaciones en la escala LSAS; y dimensiones del TCI HA/NS) y la activación durante la tarea se llevó a cabo un análisis de correlación "voxel-wise" con el LSAS y las dimensiones *HA* y *NS* como variables regresoras.

RESULTADOS: Los resultados del estudio reflejaron que: (i) en comparación a sujetos con TAS y controles sanos, la tarea de emparejar caras (vs. emparejar formas) produjo en los participantes con SW menor activación en la zona posterior del área visual primaria y ausencia de activación en la región lateral occipital derecha correspondiente al área comúnmente denominada "*Occipital Face Area" (OFA)* (Gauthier et al., 2000). Aunque no se observaron diferencias significativas entre grupos en zonas límbicas, el análisis intra-grupo reveló que en los participantes con SW, emparejar caras de temor o enfado no produjo la activación significativa de la amígdala, pero si produjo la activación significativa de esta región ante caras de alegría; (ii) en comparación a sujetos con SW y controles sanos, los participantes con TAS mostraron una hipoactivación en regiones corticales prefrontales, y una menor activación a nivel bilateral en el giro fusiforme en comparación a sujetos controles sanos; (iii) la

comparación entre los sujetos con TAS y SW reveló diferencias significativas en la activación en el giro temporal superior derecho. El análisis de correlaciones no reveló una asociación entre las puntuaciones del LSAS o TCI-*HA* y la activación cerebral durante la tarea. La dimensión del TCI-*NS* (*Novelty Seeking*) se asoció a la activación en el giro fusiforme, aunque con un patrón de correlación inverso para cada grupo (correlación positiva para el TAS; correlación negativa para el SW*). (*NOTA: Los resultados de la correlación se muestran en el Anexo 3(c)).

(Manuscrito en corrección)

"Facial emotion processing in Social Anxiety Disorder and Williams Syndrome: an fMRI study"

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1. Introduction

Social Anxiety Disorder (SAD) is a highly prevalent psychiatric disorder with estimated 12-month prevalence of 7.4% in general population (1). The core feature of the disorders is a marked and persistent fear of social situations in which the person is exposed to unfamiliar people or possible scrutiny by others (2). Excessive fear and behavioural avoidance typical of SAD can lead to impaired functioning in educational, occupational, and interpersonal domains (3).

A condition of great interest in the study of SAD is Williams-Beuren Syndrome (WS), a rare neurodevelopment disorder caused by a hemizygous deletion of 25-28 on chromosome band 7q11.23 (4). Although the existence of some major differences between both conditions –including development trajectory and cognitive profile-, there are some clinical features of the WS social phenotype that are to some extent, contrary to those of SAD. The WS social phenotype is characterized by increased social drive, a lack of social fearless, and the tendency to engage in social interactions (5,6). Whereas people with SAD are typically shy and withdrawn to unfamiliar people and social settings, (7), individuals with WS display outgoing, friendly, hypersocial behaviour and exhibit an unusual attraction to unfamiliar people (5,8–10). People with SAD typically fear and avoid eye contact (11), whereas people with WS exhibit an unusual attention and fixation to faces and eyes (12,13). Of note that this pattern of social fearless coexists with high levels of non-social anxiety (14,15).

Available evidence suggests that both SAD and WS process emotions atypically. Evidence has shown that people with WS show reduced ability to detect social threat signals, such as perceiving negative emotions through facial expressions and voices (16) or detecting angry faces (17), but show a positive bias toward processing happy

faces (18). In contrast, people with SAD are typically hypervigilant to facial expressions, and rapidly avoid facial stimuli percieved as threatening (19). Evidence from neuroimaging studies suggest that the alteration in the threat-detecting system may underlie the exaggerated fear response typical of SAD, and may be an important factor related to the tendency to approach strangers in WS (20,21). From the WS perspective, prior studies reported diminished amygdala response to negative facial expressions (22–24) and heightened amygdala response to happy faces (23). From the SAD perspective, the hyperactivation of the amygdala and other limbic regions has been a widely replicated finding across studies (20). Abnormal functioning of cortical prefrontal regions involved the top-down modulation of anxiety has also been proposed to be a core deficit of SAD (25–28) and might contribute to abnormal regulation of the amygdala in WS (22).

To identify common and specific neural correlates during facial emotion processing in SAD and WS, the present fMRI study compared for the first time, the neural response during a facial emotion processing paradigm in adults with SAD and WS using a healthy control (HC) group of subjects. We predicted that major differences in the activation of brain regions involved in the fear response would emerge between groups, including limbic regions such as the amygdala, and in cortical prefrontal regions involved in the top-down regulation of this response.

2. Material and methods

2.1 Participants

Twenty subjects with SAD, 20 subjects with WS and 20 HC from both genders and ages comprised between 18-30 years old participated in the study. Participants were matched by chronological age, gender, and laterality. Participants with SAD were recruited through poster advertisement. Participants contacted the study center by email and then a clinical researcher performed a preliminary interview by telephone. A screening visit was performed thereafter to confirm inclusion/exclusion criteria and good physical health by a complete physical examination. Inclusion criteria were: (a)

out-patients with a primary psychiatric diagnosis of generalized SAD according to DSM-IVTR criteria (2) in conjunction with the Mini-International-Neuropsychiatric-Interview (MINI) (29), (b) a Liebowitz Social Anxiety Scale (LSAS) (30) score >50, and (c) age between 18 and 60 years. Patients with relevant medical or neurological disorders, or other DSM-IV Axis I disorders were not considered for inclusion. In addition, subjects receiving any current psychotherapy or pharmacological treatment were not included. The finally selected sample represents a notably homogeneous SAD group of generalized type (no cases showing only performance related SAD were included) with childhood onset of symptoms and significant distress and interference in the patient's life, but with no current treatment that could confound the study results. Participants with WS were recruited from the Genetic Unit of the Pompeu-Fabra University (Barcelona), in collaboration with the Spanish Association of WS. The diagnosis of WS was confirmed by FISH (fluorescence in situ hybridization probes for the elastin gene on chromosome 7). Participants with WS were evaluated with the MINI psychiatric interview to confirm absence of SAD (29). Mean intelligence quotient (IQ) for the WS group was (Total IQ=55; CIV=62; CIM=57). Healthy controls were evaluated with the MINI psychiatric interview to ensure absence of psychiatric conditions and a complete psychical examination. Moreover, all HC had a LSAS score <30. All subjects (SAD, WS, HC) were free of any history of substance dependence or current substance abuse, and all provided negative urine toxicity and breathe alcohol screen. All participants were right-handed. The existence of prosthesis or metal pacemaker was an exclusion criterion common to all three groups.

Detailed behavioral assessments included the Spanish version of the LSAS (30,31) for social anxiety, the State–Trait Anxiety Inventory (STAI) (32) for general anxiety, the 0–100-mm visual analogue scales (VAS) as ratings of state anxiety, the Hamilton Rating Scale for Depression (HAMD) (33), and the Temperament and Character Inventory (TCI) (34). Written informed consent was obtained from all participants. For the WS group written informed consent was obtained also from parents. The study was approved by the local ethics committee (CEIC-IMAS, CEIC-H.Clínic, Barcelona) and was in compliance with the Declaration of Helsinki.

2.2 Emotion face assessment task

Subjects were assessed using a slightly modified version of the emotional face-processing task developed by Hariri et al. (2002) (35). Our task was identical to the paradigm described in Paulus et al. (2005) (36). During each 5-s trial, subjects were presented with a target face (center top) and two probe faces (bottom left and right) and were instructed to match the probe expressing the same emotion to the target by pressing a button in either their left or their right hand. A block consisted of six consecutive trials in which the target face was either happy, fearful or angry and the probe faces included two out of three possible emotional faces (happy, fearful and angry). During the control (shape) condition, subjects were presented with 5-s trials of ovals or circles in an analogous configuration and were instructed to match the shape of the probe to the target. A total of nine 30-s blocks of faces (three happy, three fearful and three angry) and three 30-s blocks of the control condition were presented interleaved in a pseudo-randomized order. A fixation cross was interspersed between each block (15s duration). For each trial, response accuracy and response latency (reaction time) were obtained. The paradigm was presented visually on a laptop computer running presentation software (www.neurobehavioralsystems.com). MRI-compatible high resolution goggles (VisuaStim Digital System, Resonance Technology Inc., Northridge, CA, USA) were used to display the stimuli. Subjects' responses were registered using a right- and a left-hand response device based on optical fiber transmission (Nordic NeuroLaboratories, Bergen, Norway).

2.3 fMRI acquisition

A 1.5-T Signa Excite system (General Electric, Milwaukee, WI, USA) equipped with an eight-channel phased-array head coil and single-shot echoplanar imaging (EPI) software was used. Functional sequences consisted of gradient recalled acquisition in the steady state [time of repetition (TR) 2000 ms; time of echo (TE) 50 ms; pulse angle 90 degrees] within a field of view of 24 cm, with a 64x64-pixel matrix, and with a slice thickness of 4 mm (plus interslice gap 1 mm). Twenty-two interleaved slices, parallel to

the anterior–posterior commissure line, were acquired to cover the whole brain. The functional time series consisted of 270 consecutive image sets obtained over 9 min. An anatomical three-dimensional (3-D) fast spoiled gradient (SPGR) inversion-recuperation prepared sequence with 130 contiguous slices (TR 11.8 ms; TE4.2 ms; flip angle 15x; field of view 30 cm; acquisition matrix 256X256 pixels; slice thickness 1.2 mm) was also acquired for each individual.

2.4 Image processing and statistical analysis

A Microsoft Windows platform running MATLAB version 7 (The MathWorks Inc., Natick, MA, USA) and Statistical Parametric Mapping software (SPM8; The Wellcome Department of Imaging Neuroscience, London, UK) was used. Image preprocessing involved motion correction, spatial normalization and smoothing using a Gaussian filter (full-width, half-maximum, 8 mm). Data were normalized to the standard SPM EPI template and resliced to 2 mm isotropic resolution in Montreal Neurological Institute (MNI) space. High quality functional images were obtained in all cases.

First-level (single-subject) SPM contrast-images were estimated for the following task effects of interest; (1) all faces>shapes; (2) fearful>shapes; (3) angry>shapes; (4) happy>shapes. For each subject, primary task regressors were created by specifying the onset and duration of each task block and applying a 4-s delay to account for the hemodynamic response delay. A high-pass filter was used to remove low-frequency noise (1/128 Hz). The resulting first-level contrast images for each subject were then carried forward to second-level random-effects (group) analyses. One-sample and 2-sample t test were used to estimate significant within- and between-group activation effects. In addition, SPM maps were generated showing the correlation between brain activation and individual LSAS scores in SAD and WS. All SPM results were thresholded using a false discovery rate correction of P_{FDR} <0.05 across the whole-brain volume with a minimum cluster extent of 10 contiguous voxels (KE, > 10 voxels).

3. Results

Table 1 shows sample characteristics. Compared to participants with WS and HC, SAD cases showed higher anxiety trait scores (STAI-T). State-anxiety scores before the fMRI session (both STAI-S and VAS), denoting anticipatory anxiety were higher in participants with SAD and WS compared to HC. After the experimental session state-anxiety scores were almost normalized in the WS, but remained at higher levels for the the SAD group. Harm Avoidance and Novelty Seeking temperament dimension scores differ between groups. Those with SAD showed the highest and the lowest scores in the HA and NS dimensions respectively. Participants with WS and HC showed similar scores in these dimensions.

3.1 Sample characteristics and clinical measures

Table 1	**Social Anxiety Disorder (n=20)**	**Williams Syndrome (n=20)**	**Healthy Controls (n=20)**
Age	25.05 (5.25)	25.42 (5.3)	25.65 (6.31)
Gender (M/F)	14/6	11/9	12/8
LSAS Total Score, mean (SD)	75.8 (14.7)	14.3 (9.2)	13.1 (8.6)
STAI-Trait Total Score, mean (SD)	33.1 (11.4)	19.5 (12.3)	11.7 (7.4)
STAI-State Total Score, mean (SD):			
Before fMRI session	32.1 (7.2)	21.9 (14.4)	9.6 (6.4)
After fMRI session	24.6 (6.4)	9.3 (8.1)	9.4 (8.3)
VAS State anxiety, mean (SD):			
Before fMRI session	49.2 (21.4)	33.6 (30)	8.3 (22.2)
After fMRI session	35.4 (27.4)	5 (9)	7.6 (12.5)
HAMD, mean (SD)	5.0 (4.4)	2.6 (3.9)	------
TCI Harm Avoidance (HA)	+ 1.5 SD	+ 0.5 SD	+ 0.6
TCI Novelty Seeking (NS)	- 0.4 SD	+ 1 SD	+ 0.8

LSAS – Liebowits Social Anxiety Scale; STAI - State-Trait Anxiety Inventory; VAS - Visuo-Analogue Anxiety Scale; TCI HA/NS – Temperament and Character Inventory. TCI HA and NS scores are expressed in standard deviations above/below the mean score of the population of reference.

3.1 fMRI results during Hariri task

3.1.1 Williams Syndrome

In the one-sample analysis, matching all faces (angry, fear, happy) compared to the control shape condition revealed significant activation in the visual cortex, the right fusiform gyrus, the lateral temporal cortex, the prefrontal cortex, and the anterior cingulate cortex (ACC) (Table 2). Specific analysis for happy, angry and fearful condition showed similar patterns of activation involving the five regions. Matching happy faces however, produced significant activation in the right amygdala (MNI 18 0 -14; cluster size 15007; t value= 4.77) and left amygdala (MNI -14 -2 -14; cluster size 15007; t value= 5.62). No activation on the amygdala was observed under the angry or fear condition. (Table S1).

Relative to SAD and HC, participants with WS showed significantly less activation in the posterior region of the primary visual cortex (occipital pole) and absence of activation in the right inferior occipital area for all conditions (Figure 1; Table 3).

3.1.2 Social Anxiety Disorder

In the one-sample analysis, matching all faces (angry, fear, happy) compared with the control shape condition revealed significant activation in the visual cortex, right lateral occipital area, fusiform gyrus, lateral temporal cortex, superior temporal gyrus, bilateral amygdala and the prefrontal cortex, and significant deactivation in the right anterior cingulate cortex (ACC) (Table 2). Specific analysis for happy, angry and fearful condition showed similar patterns of activation involving the six regions. (Table S1).

Relative to WS and HC, SAD cases showed significantly less activation in the prefrontal cortex and the lateral temporal cortex for all four conditions. Compared to HC subjects, SAD cases showed less activation the bilateral fusiform gyrus, left precuneus and the cerebellum. Specific analysis for the angry condition showed

additional decreased activation in the left amygdala in SAD relative to HC (MNI -10 -4 20; cluster size 1235; t value 4.23) (Table S1). Compared to WS subjects, SAD cases showed decreased activation in the right superior temporal gyrus and the ACC for all four conditions (Figure 2; Table 3).

Correlation of brain activation with LSAS scores.

Correlational analyses showed that there were no significant positive or negative correlations between LSAS scores and brain activation in any of the four conditions.

Table 2. Regions showing significant activation during the processing of emotional faces (all faces vs. shapes).

		Social Anxiety Disorder (n=20)			Williams Syndrome (n=20)			Healthy Controls (n=20)		
Brain Region		x y z (MNI)	Cluster size	t	x y z (MNI)	Cluster size	t	x y z (MNI)	Cluster size	t
Visual Cortex	R	18 -98 6	78658	12.32	36 -98 -8	13566	7.06	30 -94 -4	37467	16.89
	L	-14 -98 6	78658	10.23	-38 -94 -10	13566	7.02	-26 -96 -6	37467	15.51
Lateral Occipital area	R	44 -78 -2	78658	7.06				42 -84 -6	37467	11.37
	L									
Fusiform gyrus	R	38 -52 -26	78658	10.75	40 -48 -20	13566	5.46	40 -50 -22	37467	11.17
	L	-42 -60 24	78658	10.24				-38 -54 22	37467	10.49
Lateral temporal cortex	R	66 -24 18*	3216*	4.53*	54 -12 -18	4122	4.15			
	L				-52 -4 -22	252	3.9			
Superior temporal gyrus	R	58 -24 8*	3216*	3.68*						
	L	-58 -30 14*	2869*	4.16*				-54 -14 0*	2028*	3.71*
Amygdala	R	30 4 -28	4122	5.28				-16 -2 -24	238	5.44
	L	-28 -2 -22	4122	3.9						
Prefrontal Cortex	R	52 12 28	7865	9.66	44 22 3	5376	5.06	48 18 28	1651	5.97
	L									
Anterior cingulate cortex	R	0 28 32*	2115*	4.82*	12 18 42	5376	5.22	2 -26 44*	1125*	4.28*
	L	-48 8 30	7865	7.11	-40 24 24	5376	5.33	-42 24 24	9755	6.73

Intergroup analysis shown for each group.; R = right hemisphere; L = hemisphere; Cluster size express number of voxels.; Stereotactic coordinates from MNI (Monreal Atlas Neurological Institute); * Represent deactivations.

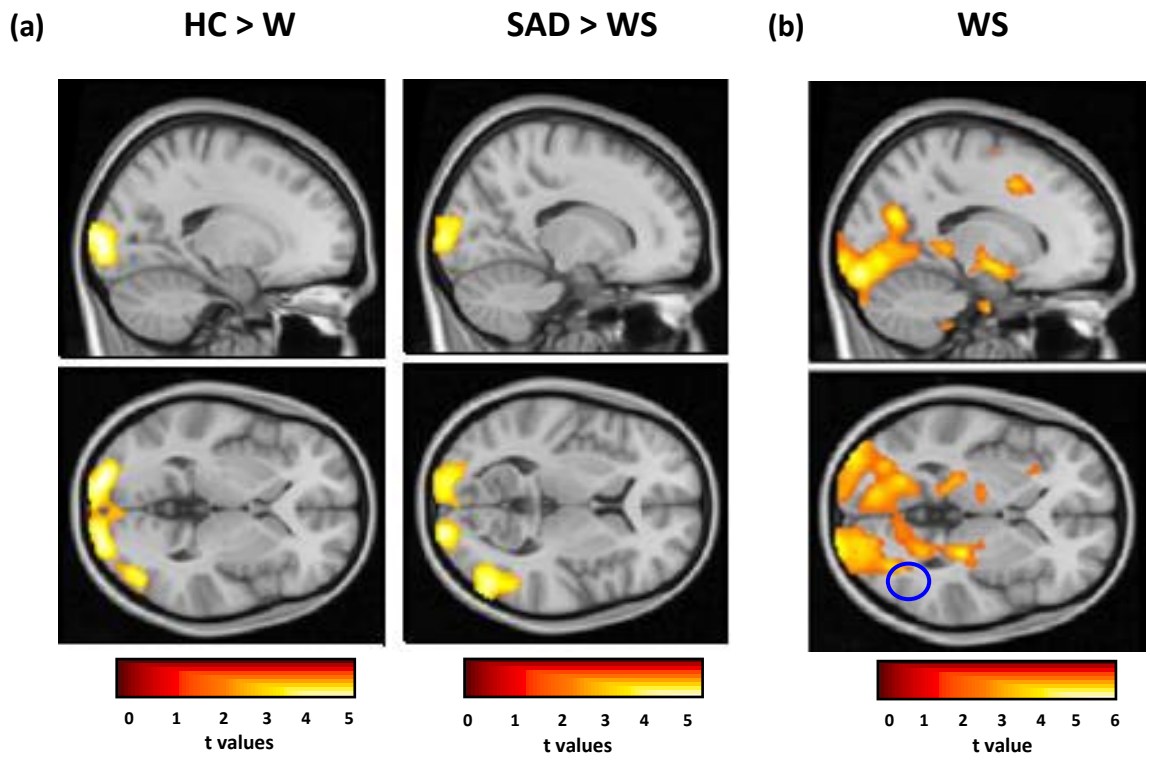
Table 3. Between-group analysis for brain activation during the processing of emotional faces (all faces vs. shapes)

	Cluster size	MNI Coordinates	T
SAD > HC			

SAD < HC			
Left medial prefrontal cortex	310	-6 18 54	4.14
Left lateral prefrontal cortex	1122	-44 24 22	4.39
Right fusiform gyrus	624	32 -72 -32	4.03
Left fusiform gyrus	495	-28 -74 -10	3.99
Left precuneus	1922	-4 -68 42	3.99
Right lateral temporal cortex	184	68 -30 -10	4.29
Left lateral temporal cortex	296	-62 -44 -14	3.62
Cerebellum	447	12 -56 -46	4.13
HC > WS			
Right primary visual cortex	1673	22 -98 4	5.10
Left primary visual cortex	1036	-18 -98 0	5.06
Right lateral occipital area	1673	50 -72 10	4.34
HC < WS			
Right temporal operaculum	832	56 -28 14	4.53
Right supplementary motor area	1430	18 -24 74	4.32
SAD > WS			
Right primary visual cortex	546	20 -100 4	4.87
Left primary visual cortex	779	-16 -100 8	3.97
Right lateral occipital area	487	48 -70 2	4.74
SAD < WS			
Medial prefrontal cortex/ACC	1565	-8 50 12	4.52
Right dorsal prefrontal cortex	220	28 24 34	4.38
Left dorsal prefrontal cortex	470	-20 26 42	4.83
Right superior temporal gyrus	779	38 -18 8	4.44
Right lateral temporal cortex	903	66 -22 -16	5.48
Left lateral temporal cortex	490	-66 -52 -8	4.62

SAD – Social Anxiety Disorder; WS – Williams Syndrome; Cluster size express number of voxels.

Figure 1.



(a) Between-group differences for matching emotional faces (all faces) compared with control shape condition displayed at p<0.01. (b) Within-group map showing significant activation for the WS group for the same contrast. The blue circle reflects the lateral occipital area, with no activation in the WS group.

Figure 2.

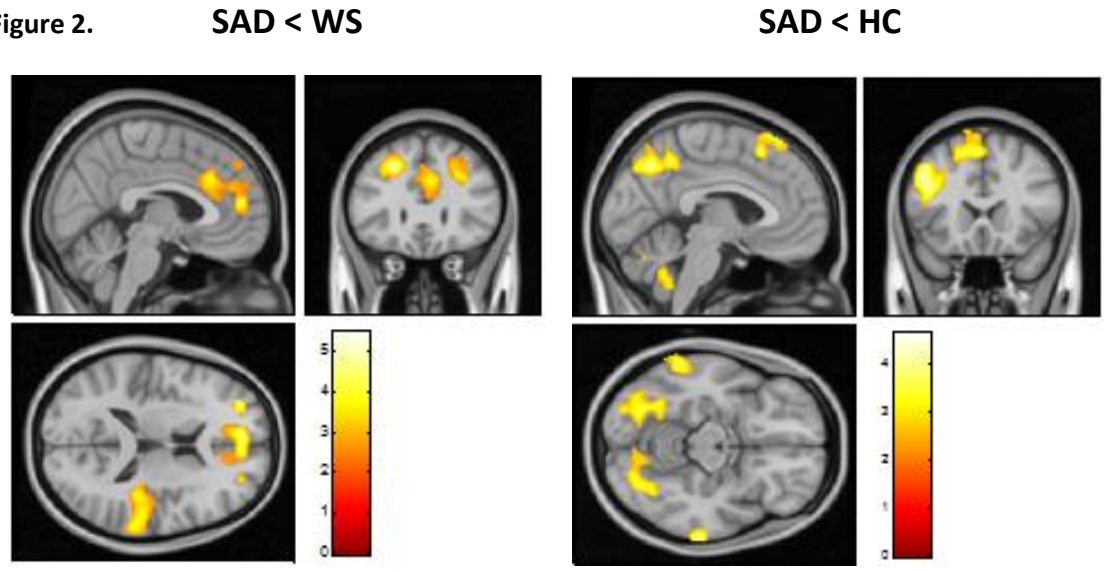


Figure 2. (a) Between-group analysis maps show differences in brain activation in response to matching emotional faces (all faces) and control shape condition.

4. Discussion

Using fMRI, the present study examined for the first time, common and differential patterns of brain activation during a facial emotion matching task between SAD patients, WS patients and a HC group. Contrary to our expectations, limbic activity did not differ between groups. Indeed, we observed that major differences between groups emerged in early visual areas of the face processing network (37) for WS, and in cortical prefrontal regions involved in the top-down regulation of anxiety (25,38) and the fusiform gyrus for SAD. Interestingly, we found that SAD and WS differed in the pattern of activation in the right superior temporal gyrus (STG), a region that has been linked to gaze-processing (39,40).

WS - specific findings

In the context of the WS literature, prior studies reported diminished amygdala response to negative facial expressions (22–24) and heightened amygdala response to happy faces (23). Unlike these studies, we did not observe significant differences on amygdala activation between WS and SAD or HC. It is noteworthy, however, that even though significant between-group differences did not emerge, inter-group analysis revealed that matching angry or fearful faces did not produced amygdala activation in the WS group, but did produced significant activation of bilateral amygdala under the happy condition. These latter findings resembles those reported by previous studies (22–24), which are thought to contribute to the social phenotype and the fearlessly approach towards strangers typical of subjects with WS (21).

Indeed, we observed that relative to SAD and HC, matching faces (vs. matching shapes) produced significant less activation in the posterior region of the primary visual cortex corresponding to the foveal (central) visual field (41), which is responsible for visual acuity and processing of features and fine details through high-spatial-frequency information (42). Furthermore, in comparison to both SAD and HC, participants with WS did not activate the right lateral inferior occipital cortex, a region that might correspond to the so-called occipital face area (OFA) (43) see (44) for a review). Human lesion studies (45) and transcranial magnetic stimulation (TMS) studies

have provided strong evidence that right OFA plays a major role in face processing (44,46,47). Particularly, it has been established that activity in this region reflects the processing of face parts (48,49). Traditional hierarchical feedforward models of visual processing (37) maintain that OFA's (or the inferior occipital area more generally) involvement in face processing is restricted to the initial feature-based analysis that is then fed forward to other higher order face-selective regions such as the fusiform face area (FFA) to process complex aspects (37,44). However, available data from brain-damaged patients (50) and fMRI (51) has challenged the notion that face processing occurs in a strictly hierarchical feedfoward manner. It has been observed that face-preferential activation in higher order visual regions of the right hemisphere such as the FFA, -as observed in the present study- can emerge in absence of activation in the OFA (52), and even in presence of structural damage of this region (50). Furthermore, evidence from TMS studies suggest that OFA might be involved in other higher-level perception abilities (46), such as the discrimination of facial expressions (53), identity (54), and judging the trustworthiness from faces (55). On this basis, Atkinson & Adolphs (2011) (46) pointed to a more interactive model in which higher-level face perception abilities rely on the interplay between functionally distinct neural regions that might depend on an intact OFA, whereas lower level categorization abilities, such as discriminating faces from objects, can be achieved without OFA. Other authors even support a non-hierarchical model of face processing in which the FFA is responsible for holistically early face detection, while OFA contributes to subsequent refinement through fine-grained analysis of face features (50,56). In support to these views, TMS delivered to the OFA does not affect participants' ability to categorize the stimulus as a face, but impairs recognition of face identity (54). The potential involvement of OFA in higher-perception abilities such as the discrimination of facial expressions (53), and judging the trustworthiness from faces (55) is interesting, in light of existing evidence that shows that individuals with WS has difficulties in identifying facial emotional expressions (16), tend to perceive unfamiliar faces abnormally positively (8), and show heightened approachability toward strangers (5).

In our study, individuals with WS showed hypoactivation in the posterior region of the primary visual cortex corresponding to foveal vision and absence of activation in the rOFA. Indeed, and similar to SAD and HC, participants with WS showed significant

activation in the right fusiform gyrus. Altogether, our results may suggest that individuals with WS fail to accurately process face features and fine-grained details, perhaps, in favor of a more coarse/holistic impression. This information might be critical for accurately processing of facial expressions (53), but also to detect threat-related signals such as fearful faces (57,58). In support to this notion, a recent study demonstrated that rapid detection of fearful faces is predominantly mediated by fine-grained high-spatial-frequency information (57). Deficient input from visual areas might also contribute to the absence of amygdala response to threat-related faces observed in our study. Interestingly, Sarpal et al., (2008) (59) reported significant reductions in the functional connectivity between the FFA and the amygdala during the presentation of threatening faces. Since a prior study in the same sample found diminished amygdala activation to threatening faces (22), the authors propose that input from facial stimuli from ventral stream areas might gain less access to amygdala and regulatory prefrontal regions, and contribute to the reduced amygdala activation, and associated lack of social fear of persons with WS (59). Together, our results extend previous findings by suggesting that deficient input from face-processing regions conveying fine-grained information important to accurately process facial expressions and detect threat signals might contribute to fearlessly social phenotype and difficulties in detecting threat-related signal typical of subjects with WS.

SAD – specific findings.

In the context of SAD, our major finding was that relative to WS and HC, participants with SAD showed no enchanced limbic response with decreased activation in medial/dorsal prefrontal regions and the anterior cingulate cortex. Furthermore, under the angry condition, SAD cases showed less activation of the left amygdala and surrounding regions relative to HC. Although several studies have reported exaggerated limbic response in SAD patients (eg. (60–64), others studies have failed to find limbic hyperactivity (25,26,28), or even found decreased amygdala response (65). Per example, Pujol et al., (2013) (28) used a paradigm in which subjects view pre-recorded videos of themselves performing a memory task in front of an audience, a

highly-distressing situation for SAD patients. The study found normal subcortical and limbic response with reduced activation in cortical prefrontal areas in SAD patients compared to HC; a pattern that is compatible with a failure in the cognitive control of anxiety. Consistent with the cognitive control notion, Ziv and colleagues (26) recently examined behavioral and brain responses using three distinct socio-emotional tasks in a large sample of subjects with SAD. The study found that negative emotion ratings were greater in the SAD group across all tasks, although there were no differences on brain responses in the amygdala and insula between SAD patients and HC in any of the three tasks. Indeed, differential brain responses between groups were observed in frontal, occipital and temporal regions. The authors explained these results by suggesting that ratings of negative emotion might be less tightly coupled with increased limbic activity than typically thought, and further proposed that deficits in higher cognitive processes implicated in emotion regulation may be a core deficit of SAD. Using the same tasks and the same sample, the authors then examined the neural response while participants were instructed to down-regulate negative emotion reactions using the reappraisal technique (27). The study found that, relative to controls, SAD patients showed reduced late brain responses in prefrontal regions, particularly, when reappraising harsh faces. In addition, they found that reduced late responses in the prefrontal cortex in patients with SAD were related to less reduction in negative emotion ratings when reappraising negative self-beliefs. Together, these studies support the notion that deficient cognitive regulation may be a core feature in SAD (25–28). In line with these studies, we found that SAD cases showed normal limbic activity -except for the angry condition, as detailed below-, with decreased activation in cortical prefrontal regions involved in the top-down mechanisms of emotion regulation (25,38). Our results extend previous findings by demonstrating abnormal prefrontal activity is SAD compared to a control group of WS and HC subjects.

On the other hand, we found that relative to HC subjects, SAD cases showed decreased activation in the bilateral fusiform gyrus for all contrasts. This result is in accordance with an earlier study in SAD that found fusiform hypoactivation in response to faces (66). However, other studies have reported fusiform hyperactivity (61,67,68), or did not report abnormal fusiform activation (60,62). Recently, Frick and colleagues (68) found increased reactivity in the bilateral fusiform gyrus in response to

fearful over neutral faces, and greater fusiform connectivity with right amygdala in SAD compared to HC. At first sight, it may seem that our results contradict those reported by Frick and colleagues (68). It should be noted however, that in our study, decreased fusiform activation was coupled with decreased amygdala reactivity under the angry condition in SAD relative to HC, precisely, in response to an expression that is particularly threatening to subjects with SAD. Interestingly, one previous study in a non-clinical sample of subjects with social anxiety found a modulation effect from the fusiform gyrus to the amygdala in response to emotional faces (69). In that study (69) social anxiety ratings were associated with amygdala response only after controlling for subject's level of activation in the fusiform gyrus. Furthermore, fusiform response to fearful faces showed a negative correlation only with those behavioral assessments related to avoidance behavior (69). Hypoactivation of the fusiform gyrus has also been reported by several studies on subjects with Autism-Spectrum-Disorder (ASD) (70), and in Fragile-X Syndrome (71), two conditions that shows relevant clinical overlap with SAD, including characteristic gaze avoidance. In the context of ASD and Fragile X, hypoactivation of the fusiform gyrus is thought to arise from diminished gaze fixation (70,71), and variations in eye-fixation modulates amygdala activation in subjects with ASD (70). Altogether, our findings suggest that fusiform hypoactivation may reflect the use of avoidance strategies and/or diminished gaze fixation to facial stimuli by SAD cases. This would further explain inconsistencies on fusiform reactivity between previous studies (61,66–68) and within the same study (61) that might vary depending on the use of avoidant strategies and the type of paradigm adopted by the study (61). Further studies using eye-tracking methodology are necessary to confirm this hypothesis. The pattern of fusiform hypoactivity coupled with decreased amygdala activation observed in participants with SAD relative to HC in response to angry faces, fits with previous findings that suggest a modulator effect from the fusiform gyrus to the amygdala activation in response to emotional faces, in particular those expressing threat (69).

Common finding: the role of eye-gaze

We found that relative to SAD cases, participants with WS showed greater activation the right STG. Note that both SAD and HC –but not WS- deactivated this

region and significant differences on brain activation for the STG only emerged for the SAD versus WS comparison. This is an interesting finding, since the STG region has been strongly implicated in eye-gaze processing (39,40), and lesions to the right STG produce important difficulties in gaze contact (72). This result seem to nicely fit with the pattern of gaze avoidance typical of SAD (11), and the increased attention and fixation to eyes and gaze characteristic of subjects with WS (12). However, these conclusions remain speculative, since no eye-tracking system was used in our study, and the paradigm we used may not be adequate to such purpose.

Further limitations should be mentioned. The face paradigm face paradigm adopted in our study is not intended to discriminate between the effects of different emotional expressions, as different emotions (target and probes) appear in each presented picture. Similarly, we did not control for the effect of neutral faces, which have been found to be related to an abnormal pattern of amygdala activation in SAD (73,74) and WS (75). The results of brain activation observed for the WS group are limited by the differences in cognitive capacities between participants with WS and the SAD/HC groups. However, the specificity of the findings suggests that the pattern of brain activation observed for this group is not a result differential cognitive capacities. Furthermore, previous studies reported abnormal patterns of brain activation to both fearful and happy faces in samples of subjects with WS with a similar IQ as our participants, compared to both typically developing and delay-developing controls (23,24).

Conclusions

This study compared for the first time, the neural response in SAD and WS, two conditions that are to some extent, on the opposite extreme on some clinical features, including social approach, processing of emotional and social cues and gaze behavior. Contrary to our expectations, SAD and WS did not differ in the pattern of activation in limbic regions. Indeed, we observed that major differences emerged on visual areas of the face processing network and distal cognitive areas involved in the top-down control of anxiety. Interestingly, we found that relative to SAD, participants with WS

showed greater activation in the right STG, a region that has been related to gaze-processing. Together, our results highlight the importance of other cortical regions beyond the amygdala during facial emotion processing.

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Supplementary Table 1(a). Regions showing significant activation during the processing happy faces vs. shapes

Happy vs. Shapes	Cluster size (Number of voxels)	MNI coordinates	T
WS			
Activation			
Left visual cortex	*15007	-36 -78 -12	6.69
Right visual cortex	*15007	36 -74 -8	6.46
Left fusiform gyrus	*15007	-40 -62 -18	5.13
Right fusiform gyrus	*15007	38 -50 -20	6.04
Left prefrontal cortex	213	-40 22 24	5.31
Right prefrontal cortex	654	38 30 18	4.83
Left amygdala	*15007	-14 -2 -14	5.62
Right amygdala	*15007	18 0 -14	4.77
Left lateral temporal cortex	327	-52 -6 -24	3.52
Right lateral temporal cortex	286	62 -18 -12	3.53
Desactivation			

SAD			
Activation			
Left visual cortex	*12596	-24 -98 -6	10.19
Right visual cortex	*12596	18 -100 4	12.87
Right lateral occipital cortex	*12596	42-80 -4	6.5
Left fusiform gyrus	*12596	-40 -56 -20	6.47
Right fusiform gyrus	*12596	40 -50 -24	7.36
Right prefrontal cortex	290	46 18 24	3.96
Desactivation			
Left anterior cingulate cortex	*1521	-10 46 12	3.72
Right anterior cingulate cortex	*1521	0 38 24	3.6
Right superior temporal gyrus	491	58 -28 12	3.39
Right lateral temporal cortex	582	64 -26 -14	4.71
HC			
Activation			
Left visual cortex	*27322	-20 -98 2	13.32
Right visual cortex	*27322	22 -98 4	14.38
Right lateral occipital cortex	*27322	42 -84 -6	10.33
Còrtex prefrontal esquerre	2307	-38 20 26	4.99
Còrtex prefrontal dret	522	48 18 28	4.2
Desactivation			
Right temporal operaculum/insula	*512	50 -30 18	3.92
Gir temporal superior dret	*512	60 -28 14	3.01

*same cluster
MNI - Montreal Neurological Institute

Supplementary Table 1(b). Regions showing significant activation during the processing angry faces vs. shapes

Angry vs. Shapes	Cluster size (Number of voxels)	MNI Coordinates	T
WS			
Activation			
Left visual cortex	3964	-36 -96 -10	6.25
Right visual cortex	*3021	36 -98 -8	6.36
Right fusiform gyrus	*3021	40 -48 -20	4.07
Left prefrontal cortex	729	-38 24 28	4.06
Right prefrontal cortex	557	42 22 32	4.33
Right anterior cingulate cortex	640	12 16 46	6.08
Left temporal cortex	201	-58 -38 -14	3.83
Right temporal cortex	362	52 -12 -18	3.98
Desactivation			

SAD			
Activation			
Left visual cortex	*17057	-18 -104 10	11.1
Right visual cortex	*17057	22 -100 -4	10.46
Right lateral occipital cortex	*17057	46 -76 0	6.64
Left fusiform gyrus	*17057	-38 -68 -22	5.99
Right fusiform gyrus	*17057	36 -56 -22	6.42
Right prefrontal cortex	367	48 18 28	3.85
Desactivation			
Left prefrontal cortex	632	-22 30 40	5.1
Right prefrontal cortex	*2033	28 30 40	3.8
Anterior cingulate cortex	*2033	0 28 32	4.69
Left temporal cortex	*2267	-58 -30 -16	5.08
Right temporal cortex	*3471	64 -26 -18	4.44
Left superior temporal gyrus	*2267	-62 -30 8	4.63
Right superior temporal gyrus	*3471	52 -28 12	4.58
HC			
Activation			
Left visual cortex	*35878	-26 -94 -6	15.58
Right visual cortex	*35878	16 -102 0	12.17
Right lateral occipital cortex	*35878	42 -84 -6	10.44
Left fusiform gyrus	*35878	-42 -52 18	5.73
Right fusiform gyrus	*35878	44 -42 12	3.79
Left amygdala	*11781	-14 -2 -22	5.06
Còrtex prefrontal esquerre	*11781	-40 10 26	6.13
Còrtex prefrontal dret	1744	50 22 26	5.68
Desactivation			
Gir temporal superior dret	*778	60 -24 10	3.62

*same cluster
MNI - Montreal Neurological Institute

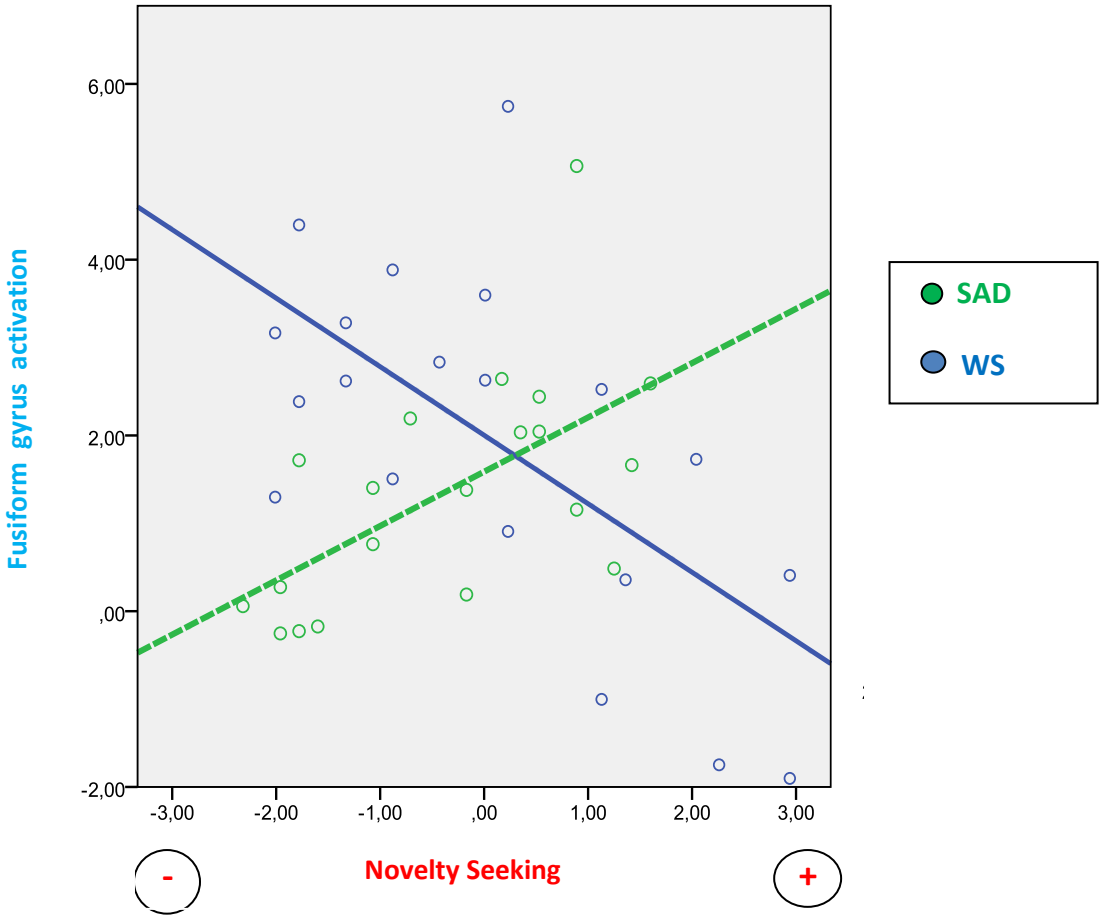
Supplementary Table 1(c). Regions showing significant activation during the processing fear faces vs. shapes

Fear vs. Shapes	Cluster size (Number of voxels)	MNI coordinates	T
WS			
Activation			
Left visual cortex	*17063	-38 -90 -12	7.29
Right visual cortex	*17063	20 -88 -4	5.49
Left fusiform gyrus	*17063	-38 -54 -12	5.4
Right fusiform gyrus	*17063	40 -46 -20	5.55
Left prefrontal cortex	*3495	-38 28 32	4.54
Right prefrontal cortex	2487	46 24 26	4.73
Left anterior cingulate cortex	*914	12 18 42	4.28
Right anterior cingulate cortex	*914	-10 20 44	3.9
Left temporal operaculum/insula	*3495	-38 14 10	4.16
Right temporal cortex	1765	60 -20 -10	3.18
Desactivation			

SAD			
Activation			
Left visual cortex	*26441	-24 -98 -4	11.86
Right visual cortex	*26441	24 -100 2	15.35
Right lateral occipital cortex	*26441	46 -76 0	7.12
Left fusiform gyrus	*26441	-38 -68 -22	6.99
Right fusiform gyrus	*26441	38-54 -24	8.99
Left prefrontal cortex	*11168	-46 24 22	5.63
Right prefrontal cortex	*11168	46 16 26	6.68
Desactivation			
Left prefrontal cortex	637	-24 30 40	5.06
Right prefrontal cortex	346	20 42 36	4.15
Right anterior cingulate cortex	1896	0 32 20	5.36
Left posterior cingulate cortex	1410	-2 -34 40	4.5
Left temporal operaculum/insula	4342	-50 -28 18	5.24
Right temporal operaculum/insula	4705	66 -26 18	5.01
Left superior temporal gyrus	2828	-50 -30 16	5.03
Right superior temporal gyrus	2261	56 -6 0	4.17
HC			
Activation			
Left visual cortex	*34826	-30 -92 -8	10.65
Right visual cortex	*34826	16 -92 -10	9.01
Right lateral occipital cortex	*34826	42 -80 -6	8.83
Left prefrontal cortex	10533	-48 20 32	7.73
Right prefrontal cortex	2260	48 20 26	6.2
Desactivation			
Right anterior cingulate cortex	*14763	10 -6 48	6.5
Right posterior cingulate cortex	*14763	6 -26 40	4.76
Left temporal operaculum/insula	6359	-56 -18 10	6.65
Right temporal operaculum/insula	*14763	56 -20 10	6.02
Left superior temporal gyrus	4739	-56 -26 12	5.9
Right superior temporal gyrus	8372	62 -24 8	5.69

*same cluster
MNI - Montreal Neurological Institute

Anexo 3(c) Correlation of brain activation with Novelty Seeking scores during facial emotion processing (All faces vs. Shapes).



Correlation analysis of brain activation and NS scores showed a clear tendency to differ between groups:

For the SAD group, NS was positively correlated with brain activation in the fusiform gyrus. Those participants with low-NS-scores (the majority of SAD participants) showed reduced activation in the fusiform gyrus; but increases in NS were positevily associated to increases in fusiform activation (R^2=0.359; p=0.01 uncorrected).

For the WS group, NS was negatively associated with brain activation in the fusiform gyrus. Those participants with low-NS-scores showed increased fusiform activation; and increases in NS were negatively associated to fusiform activation (R^2 = 0.44; p=0.01 uncorrected).

Discusión

6. Discusión General

En este proyecto propusimos una aproximación al estudio de la ansiedad social desde tres perspectivas: el estudio de los AVEs, el estudio de la personalidad y la heterogeneidad, y el estudio las bases neurales del trastorno. Numerosos hallazgos se desprenden de los trabajos realizados, algunos de ellos, de gran relevancia en el contexto de la literatura vigente. Mediante el primer estudio, demostramos que la violencia familiar se asocia a la presencia de ansiedad social en la vida adulta y que un alto porcentaje de estudiantes universitarios sufre de síntomas de ansiedad social; mediante el segundo estudio, demostramos que no todos los sujetos con un TAS presentan el perfil de personalidad prototípico inhibido-evitativo, y que al menos un subgrupo de sujetos muestra alta búsqueda de novedad y conductas del espectro impulsivo. Y por último, mediante el tercer trabajo profundizamos en el estudio de las bases neurales del TAS y el SW, y realizamos el primer estudio comparativo entre ambos trastornos. Los resultados de la comparación directa de sujetos con TAS y SW mientras realizaban una tarea de procesamiento emocional a través de la expresión facial revelaron diferencias significativas entre ambos trastornos en la activación del giro temporal superior, una región involucrada en el procesamiento de la mirada. Los resultados del estudio revelaron interesantes hallazgos para ambos grupos en la activación de regiones visuales involucradas en el procesamiento de los rostros, y la implicación de regiones corticales pre-frontales involucradas en los mecanismos de regulación *top-down* de la ansiedad en sujetos con TAS. A pesar de que una discusión detallada de cada uno de estos trabajos ha sido incluida en los apartados previos, se incluye a continuación, una discusión general de los aspectos más relevantes de cada uno de estos trabajos y la implicación de estos hallazgos en la literatura vigente.

6.1 Acontecimientos vitales negativos

En el primer estudio, evaluamos la asociación de cinco AVEs durante la infancia y la ansiedad social en la edad adulta en una muestra epidemiológica de adultos jóvenes universitarios. Dos importantes conclusiones se desprenden de este estudio.

La primera, se relaciona con los resultados obtenidos sobre la asociación entre la violencia familiar y la ansiedad social. En nuestro estudio, la violencia familiar se asoció a la presencia de ansiedad social, incluso, después de controlar por el efecto de la edad, el sexo y los antecedentes familiares psiquiátricos. Estos resultados están en coherencia con un trabajo previo (Magee, 1999) que encontró que la agresión verbal entre los progenitores -una forma de violencia familiar- se asociaba al TAS, y con la evidencia proporcionada por dos grandes estudios epidemiológicos (Green et al., 2010; McLaughlin et al., 2010a, 2010b*)* que han puesto de manifiesto que las disfunciones del ámbito familiar -incluida la violencia-, tienen un fuerte impacto en el desarrollo, persistencia y deterioro asociado a los trastornos psiquiátricos en general y los trastornos de ansiedad en particular. La importante cuestión de si la violencia familiar -y otras formas de AVEs- se asocian de forma específica a la ansiedad social o son un factor de riesgo general es una pregunta que nuestro estudio no puede responder. En este sentido, un estudio reciente basado en una muestra epidemiológica de más de 34,000 sujetos (Blanco et al., 2014), concluye que las disfunciones familiares, entre otras variables, son un factor de riesgo común para diferentes trastornos de ansiedad y la depresión mayor. Por el contrario, en nuestro estudio, ninguno de los restantes AVEs, incluido el abuso emocional, -el AVEs que ha recibido mayor atención en el campo de la ansiedad social- (Gibb et al., 2007; Kuo et al., 2011; Simon et al., 2009), se asoció a la presencia de ansiedad social. No obstante, cabe destacar, que junto con la violencia familiar, el abuso emocional fue el AVE más frecuente entre los sujetos con ansiedad social elevada (LSAS>60). Por otra parte, debe considerarse que nuestro estudio no tuvo en cuenta el de impacto de la severidad, persistencia e impacto subjetivo de los AVEs, y que los estudios previos que encontraron dicha asociación fueron realizados en muestra clínicas de sujetos con un diagnóstico clínico de TAS (Gibb et al., 2007; Kuo et al., 2011; Simon et al., 2009), lo que sugeriría que la asociación con esta forma de abuso podría limitarse a poblaciones clínicas de mayor gravedad o a aquellos casos de mayor impacto, persistencia y/o severdidad de abuso.

La segunda conclusión se relaciona con la prevalencia de la ansiedad social en la población universitaria. En nuestro estudio, casi un 20% de los participantes presentó una puntuación <60 en la escala de ansiedad social (LSAS), un dato significativo si

tenemos en cuenta que este punto de corte ha demostrado alta sensibilidad para detectar sujetos con el trastorno (Rytwinski et al., 2009). Aunque a priori esta prevalencia podría parecer elevada, datos en población universitaria en otros países han arrojado cifran similares (Baptista et al., 2012; Filho et al., 2010; Tillfors & Furmark, 2007), reforzando la noción de que se trata de un trastorno frecuente, aunque poco visible. Cierto es que el método de selección de participantes (carteles distribuidos por el campus universitario en el que se invitaba a participar a aquellas personas que se identificaban -o no- con las características de la ansiedad social) pudo haber producido un sesgo y aumentado la prevalencia a favor de un mayor número de ansiosos detectados. Aunque, en el contexto de un trastorno donde la característica nuclear es el temor y la evitación de situaciones no-familiares esto parece poco probable. También es posible que algunos de los sujetos con ansiedad social decidieran participar en el estudio con la expectativa de obtener ayuda o diagnóstico. En cualquiera de estos escenarios los resultados tienen una importante implicación clínica y sugieren que la población y el contexto universitario pueden ser un espacio particularmente adecuado para realizar la detección y el tratamiento precoz del trastorno. No debemos olvidar que se trata de una población en la que por rango de edad, el TAS se habrá desarrollado en el 80% de los casos (Stein & Stein, 2008). Sin embargo, para muchos sujetos, el trastorno estará probablemente en los primeros años de evolución, y por tanto, con una menor probabilidad de presentar comorbilidad y deterioro asociado (Filho et al., 2010). Facilitar la accesibilidad al tratamiento puede ser de gran importancia en el contexto de un trastorno en el que la detección suele fracasar en un alto porcentaje de casos (Crippa, 2009; Wagner et al., 2006), y en el que las personas afectadas tardan una media de más de 10 años en buscar ayuda profesional (Wagner et al., 2006).

6.2 Personalidad y heterogeneidad en el TAS

En el segundo estudio, propusimos a través de un estudio caso-control, una aproximación al estudio de la personalidad y la heterogeneidad en el TAS en base a dos dimensiones temperamentales, *HA* y *NS*, y la configuración de dos perfiles: HAns y

HANS. Los resultados del estudio confirmaron nuestra hipótesis y proporcionan nueva evidencia sobre la presencia de heterogeneidad en el TAS y la tendencia de un subgrupo de sujetos con elevada ansiedad social a mostrar alta búsqueda de novedad y conductas del espectro impulsivo/de riesgo (Kashdan & Hoffman, 2008; Kashdan et al., 2009). En coherencia con nuestra hipótesis, el perfil HAns caracterizó a la mayoría de los sujetos con el trastorno, mientras que el HANS caracterizó un subgrupo más reducido de sujetos. Los perfiles no mostraron diferencias en cuanto a la gravedad de los síntomas de ansiedad social aunque sí lo hicieron a nivel de correlatos clínicos. Mientras que el perfil HAns se asoció a un mayor consumo de alcohol, el HANS se asoció un mayor número de tentativas autolíticas previas y un mayor uso de sustancias con perfil estimulante (cocaína, anfetaminas, éxtasis, y alucinógenos), un hallazgo interesante, que encaja bien con los perfiles propuestos y da fuerza a los resultados. Aunque no se encontraron diferencias significativas en los polimorfismos estudiados, se observó una tendencia en sujetos con el perfil HAns a mostrar una mayor frecuencia del genotipo SS/SL 5HTTLRP, lo que sugiere que ambos perfiles no solo presentan un fenotipo clínico diferenciado, sino que podrían tener un *background* genético diferente. Ambos perfiles se asociaron a la presencia del TAS después de controlar por el efecto variables clínicas y genéticas. Estos hallazgos dan soporte y extienden la evidencia proporcionada por Kashdan y colaboradores (Kashdan & Hoffman, 2008; Kashdan et al., 2009) sobre la dimensión *NS* en el TAS y la propuesta de que no todos los *ansiosos sociales* tienen un perfil inhibido-evitativo. Los autores no encontraron diferencias en la gravedad de los síntomas de ansiedad, aunque sí lo hicieron en la gravedad del consumo de sustancias, un hallazgo que es parcialmente replicado por nuestro estudio, ya que a pesar de que los casos con un perfil HAns presentaron un mayor consumo de sustancias con perfil estimulante, en conjunto, el grupo de casos con TAS presentó una tasa de consumo de sustancias más bajo que los controles sanos. Este dato es *a priori* sorprendente, considerando la numerosa evidencia que demuestra que en comparación a sujetos de población general, las personas TAS consumen y presentan más trastornos relacionados con el uso de sustancias (Buckner et al., 2013). Sin embargo, debe tenerse en cuenta que la mayoría de los casos eran sujetos en la veintena de edad, en la que probablemente el consumo problemático de sustancias no se había iniciado aún. Ello, refuerza lo previamente comentado y la

noción de que las estrategias de prevención y tratamiento precoz pueden ser especialmente adecuadas en la población universitaria.

Estos resultados tienen dos importantes implicaciones desde un punto de vista clínico. La primera se relaciona con la detección del trastorno en la práctica clínica: si en condiciones típicas la detección primaria del TAS ya fracasa en un alto porcentaje de casos (Wagner et al., 2006), la existencia de casos con un perfil atípico podría amplificar esta situación y contribuir a que un número de casos no fueran correctamente diagnosticados. En segundo lugar, la adaptación de algunos componentes del tratamiento podría ser adecuado para este subgrupo de sujetos, teniendo en cuenta que los tratamientos estándar recomendados para esta población centran una parte importante del trabajo en las conductas evitativas (Pilling et al., 2013).

6.3 Correlatos neurales en el TAS

En el tercer estudio, propusimos una aproximación original al estudio de las bases neurales del TAS no realizada hasta la fecha. Para ello, realizamos una revisión sistemática y meetanálisis comparativo de los hallazgos disponibles hasta la fecha de RMf utilizando el paradigma del procesamiento emocional a través de la expresión facial en el TAS y el SW, y llevamos a cabo el primer estudio de neuroimagen en el que se comparó de forma directa a estos dos trastornos.

Desde la perspectiva del TAS, podemos afirmar que hasta la fecha, el hallazgo más consistente y replicado ha sido la hiperactividad de la amígdala -aunque también de otras regiones paralímbicas como la ínsula o el giro parahipocampal- durante el procesamiento emocional; un hallazgo que ha ido en parte ligado al claro foco de una generación de estudios por la amígdala y las áreas límbicas, y que ha desembocado en que muchos de estos estudios seleccionaran *a prior* a la amígdala como la región de interés, o que utilizaran un criterio de significación relativamente liberal en algunos casos (Straube et al.,2005). En este sentido, los resultados de la revisión dejan reflejado como al ampliar el foco de estudio a otras áreas se observan alteraciones en

otras regiones importantes en la regulación de la respuesta de miedo y el procesamiento de la *facies*, incluidas algunas regiones temporales, prefrontales, y occipitales. Desde la perspectiva del SW, la revisión de la literatura refleja que una doble disociación en la activación de la amígdala durante el procesamiento emocional, -hipoactivación frente a caras de temor; hiperactivación frente a caras de alegría- podría contribuir a explicar el fenotipo social caracterizado por el escaso temor social, la hipersociabilidad y la tendencia a aproximarse a extraños típicos de esta población.

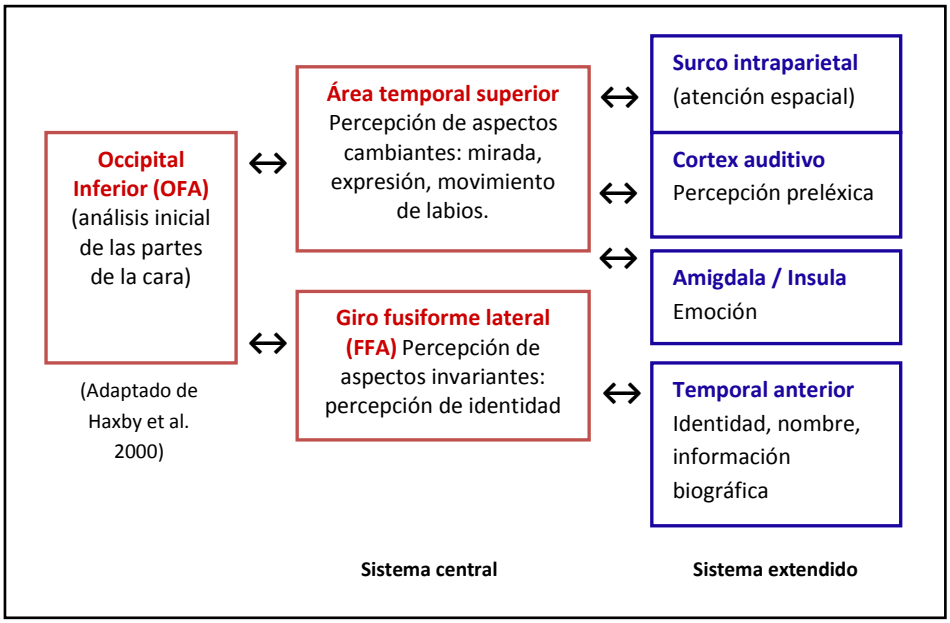
Sin embargo, la comparación directa de sujetos con TAS, sujetos con SW y sujetos controles sanos mientras realizaban una tarea de procesamiento emocional a través de la expresión facial (Estudio 3.b) no reflejó diferencias significativas en regiones límbicas entre grupos; unos resultados que contradicen nuestras predicciones y la evidencia proporcionada por estudios previos, y que como se discute a continuación, podría relacionarse con el patrón de activación observado en otras regiones. Debe puntualizarse sin embargo, que para el grupo con SW, el análisis intra-grupo reveló que emparejar caras de temor o enfado no produjo la activación significativa en la amígdala, mientras que emparejar caras de alegría sí produjo la activación significativa de esta región a nivel bilateral; unos hallazgos que se aproximan y encajan bien con los estudios previos en muestras con SW (Haas et al., 2009; Meyer-Lindenberg et al., 2005; Mimura et al., 2010; Paul et al., 2009).

Por el contrario, los resultados de nuestro estudio pusieron de relieve la implicación e importancia de algunas regiones visuales involucradas en el procesamiento de la cara, y de regiones corticales prefrontales importantes para regular la respuesta de miedo. Estos resultados sugerirían un modelo más complejo, en el que la alteración *en*, y *entre* algunas regiones visuales, límbicas y prefrontales subyacería a las alteraciones observadas durante el procesamiento emocional en el TAS y el SW y podrían contribuir a explicar el fenotipo social característico de cada trastorno.

En sujetos con SW, los resultados del estudio demostraron un correlato neural específico implicando a regiones involucradas en el procesamiento de la cara, que sugeriría que parte del proceso podría estar alterado y contribuir a que las personas

con éste síndrome no perciban o integren adecuadamente información del rostro necesaria para discriminar correctamente la expresión facial y detectar señales de amenaza. De forma específica, observamos que la tarea de emparejar caras (*vs*. emparejar formas), produjo en sujetos con SW una hipoactivación en la región posterior del área visual primaria correspondiente a la visión foveal (central) (Lavidor & Walsh, 2004) -es decir, la visión que proporciona agudeza visual y permite procesar detalles a través de información de alta frecuencia- y ausencia de activación en la región lateral occipital derecha, o también denominada, "Área Occipital de las Caras" ("*Occipital Face Area*"; *OFA*) (Gauthier et al., 2000). Se trata de una región quizás menos conocida que la ampliamente-estudiada "Área Fusiforme de las Caras" *("Fusiform Face Area; FFA) (*Kanwisher, McDermott, & Chun*, 1997)*, pero que ha demostrado jugar un rol central en el procesamiento de la cara, en particular, la región derecha (Atkinson & Adolphs, 2011; Pitcher, Walsh, & Duchaine, 2011; Rossion, Hanseeuw, & Dricot, 2012). Buen reflejo de ello es la evidencia proporcionada por numerosos estudios de estimulación magnética transcraneal (EMT) (Pitcher et al., 2011) y un metaanálisis realizado en pacientes prosopagnósicos, -una afección que afecta al reconocimiento de la cara- que demuestró que la mayoría de pacientes presentaban lesiones en el territorio de la región *OFA* derecha (Bouvier & Engel, 2006). En particular, se ha demostrado que la región *OFA* está involucrada en el procesamiento de las diferentes partes de la cara (Liu, Harris, & Kanwisher, 2009; Pitcher, Walsh, Yovel, & Duchaine, 2007). Aunque la importancia de esta región ha quedado bien demostrada en numerosos estudios, la dinámica temporal en la que el OFA participa con el resto de regiones involucradas en el procesamiento de la cara es un tema aún un tema de debate (Atkinson & Adolphs, 2011; Pitcher, Walsh, & Duchaine, 2011; Rossion, Hanseeuw, & Dricot, 2012). Desde los modelos tradicionales jerárquicos de procesamiento visual (Ej. Haxby, Hoffman, & Gobbini, 2000) se sostiene que la participación de esta región se limita al análisis inicial de las partes; y que el *OFA* alimentaría a otras regiones como la *FFA* que luego se encargarían de procesar y analizar aspectos más complejos (Figura 2) (Haxby et al., 2000; Pitcher et al., 2011).

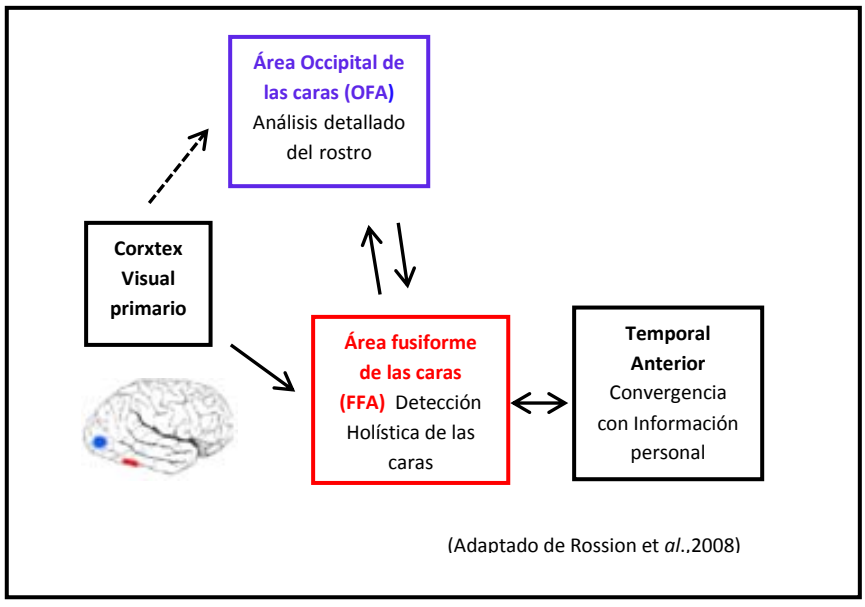
Figura 2. Esquema de procesamiento visual según modelos jerárquicos.



Sin embargo, tal como se discute en el tercer trabajo (Estudio 3b), algunos hallazgos provenientes de estudios de EMT, o RMf (Jiang et al., 2011) y estudios en pacientes con daño cerebral (Rossion et al., 2003; Steeves et al., 2009) han desafiado la noción que este procesamiento sea estrictamente jerárquico. Por ejemplo, se ha demostrado que la activación neural preferencial hacia las caras (frente a otro tipo de estímulos) en regiones visuales de orden superior como la *FFA*, -y tal como se observa en nuestro estudio- puede producirse en ausencia de activación en la región *OFA (*Rossion, Dricot, Goebel, & Busigny, 2011*),* e incluso, en presencia de daños estructurales de esta región (Rossion et al., 2003; Steeves et al., 2009), lo que sugeriría la existencia de una vía alterativa desde áreas visuales tempranas (o incluso desde regiones subcorticales) a la *FFA* que no pasarían por el *OFA (*Rossion et al., 2003; Steeves et al., 2006*).* En buena coherencia con estos resultados, un estudio reciente de EMT en sujetos neurológicamente sanos encontró que la estimulación transcraneal aplicada al *OFA* (lo cual inhibe temporalmente la funcionalidad en dicha región) no afectaba la capacidad de los participantes de categorizar un estímulo como una cara pero si afectaba su capacidad para determinar la identidad de la misma (Solomon-Harris, Mullin, & Steeves, 2013). Otros estudios han demostrado que la aplicación de EMT a la región del *OFA* afecta la percepción de la expresión facial (Pitcher, Garrido,

Walsh, & Duchaine, 2008), la ejecución cuando se procesa de forma combinada la identidad y la expresión facial (Kadosh, Walsh, & Kadosh, 2011), y que incluso podría participar en el proceso de juzgar la confianza a través del rostro (Dzhelyova, Ellison, & Atkinson2011); unos hallazgos interesantes en el contexto de la literatura del SW que han demostrado que las personas con el síndrome tienen dificultades para detectar expresiones faciales de temor (Plesa-Skwerer et al., 2006), y tienden percibir rostros desconocidos como anormalmente positivos (Bellugi et al., 1999). En base a esta evidencia, otros autores proponen un modelo más interactivo, de manera que las habilidades básicas como categorizar una cara podrían realizarse sin el *OFA* (probablemente mediante las supuestas conexiones entre áreas visuales tempranas y la *FFA*) mientras que las habilidades más complejas, -como determinar la identidad, la emoción o la confianza de una cara- dependerían del buen funcionamiento de todo el conjunto de regiones implicadas en este proceso, incluyendo un *OFA* intacto (Atkinson & Adolphs, 2011). Rossion y su grupo (Rossion, 2008; Rossion et al., 2003) proponen un modelo en el que la *FFA* realizaría un análisis holístico/grueso inicial de la cara, mientras que el *OFA* contribuiría a un análisis fino/detallado posterior que permitiría el análisis de aspectos más complejos (Figura 3). Se trata de un modelo que contempla la posibilidad de conexiones reentrantes entre el *OFA* y otras regiones como la *FFA*.

Figura 3. Esquema del procesamiento de la cara según modelo no-jerárquico desarrollado por Rossion y *cols.*



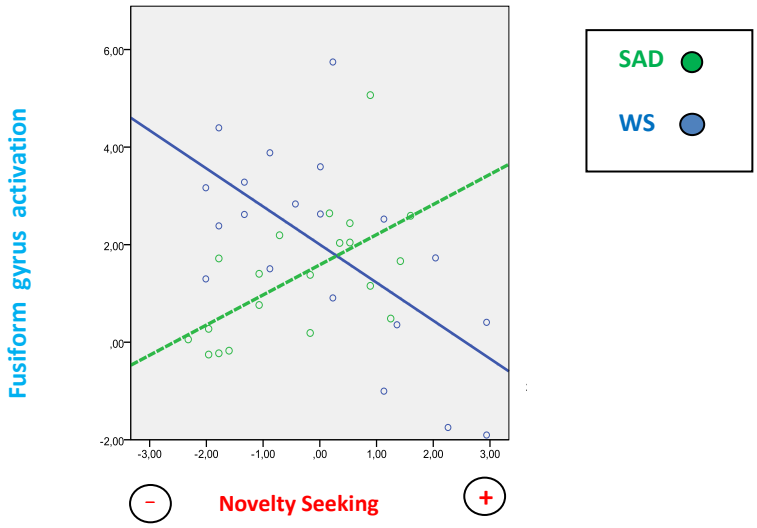
Estas últimas propuestas son interesantes desde el punto de vista de nuestro trabajo dado el patrón de activación observado en las áreas visuales en los participantes con SW: ausencia de activación en la región *OFA* y activación significativa en la región fusiforme derecha; unos resultados que parecen encajar bien con las propuestas no-jerárquicas (Atkinson & Adolphs, 2011; Rossion et al., 2003). La activación significativa del giro fusiforme derecho, -siendo la región derecha la dominante en el procesamiento de las caras-, sugeriría que efectivamente, los participantes con SW son capaces de discriminar y percibir las caras. Sin embargo, la ausencia de activación *OFA* sugeriría que parte de este proceso está alterado y que los sujetos con SW podrían no procesar o integrar adecuadamente la información sobre las partes y/o los detalles-finos. El patrón de hipoactivación observado en el grupo con SW en la región posterior visual primaria correspondiente a la visión foveal reforzaría esta noción. Por otra parte, se ha sugerido que la región *OFA* (al igual que la región foveal) contiene campos receptivos pequeños (Rossion et al. 2008; Smith, Singh, Williams, & Greenlee, 2001), que a diferencia de los campos receptivos de mayor tamaño, procesarían información de frecuencia-espacial-alta, es decir, información detallada-fina. Esta información no solo es necesaria para el adecuado procesamiento de la expresión facial (Pitcher et al., 2008), sino que ha demostrado ser necesaria para detectar señales de amenaza (Pessoa & Adolphs, 2010; Stein, Seymour, Hebart, & Sterzer, 2014). En apoyo a esta noción, un estudio reciente demostró que la detección rápida de caras de miedo está mediada mayoritariamente por información detallada de frecuencia-espacial-alta (Stein et al., 2014). Un *input* deficiente desde la región visual podría contribuir a explicar la ausencia en la respuesta de la amígdala observada en nuestro estudio para las caras que expresan amenaza. En buena coherencia con esta noción, Sarpal y sus colaboradores (Sarpal et al., 2008) encontraron una disminución significativa en la conectividad funcional entre la *FFA* y la amígdala en sujetos con SW durante la presentación de caras que expresaban temor. Dado que un estudio previo en la misma muestra de sujetos (Meyer-Lindenberg et al., 2005) encontró una disminución en la activación de la amígdala frente a las caras de temor, los autores propusieron que el *input* desde regiones visuales podría tener un menor acceso a la amígdala y las regiones prefrontales y contribuir al escaso temor social típico de personas con SW (Sarpal et al., 2008).

Desde la perspectiva del TAS los resultados del estudio reflejaron que en comparación a los sujetos con SW y sujetos controles sanos, los casos con TAS mostraron una menor activación en regiones corticales prefrontales involucradas en la regulación *top-down* de la ansiedad (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006; Ochsner & Gross, 2005); un hallazgo interesante en el contexto de la literatura vigente en el que crece el interés por la implicación de estas regiones en el trastorno. Estos hallazgos estarían a favor de las propuestas actuales que sostienen que el núcleo central del trastorno estaría asociado a un déficit en los mecanismos corticales implicados en la regulación emocional, y no tanto en un aumento de la actividad límbica como se ha mantenido tradicionalmente (Goldin, Manber, et al., 2009; Ziv et al., 2013a, 2013b) . De hecho, a pesar de que numerosos estudios han demostrado una respuesta límbica exagerada en el TAS (Ej. Blair et al., 2008; Klumpp, Angstadt, Nathan, & Phan, 2010; Phan, Fitzgerald, Nathan, & Tancer, 2006; Stein, Goldin, Sareen, Zorrilla, & Brown, 2002; Straube, Kolassa, Glauer, Mentzel, & Miltner, 2004) otros estudios no han encontrado una hiperactividad en esta región (Goldin, Manber, et al., 2009; Pujol et al., 2013; Ziv et al., 2013b), o incluso, han encontrado una hipoactivación de la amígdala (Kilts et al., 2006). En coherencia con estos hallazgos, en nuestro estudio, el grupo de casos con TAS mostró una respuesta límbica normal en la mayoría de contrastes con una excepción: las caras de enfado. Para este contraste, los sujetos con TAS (frente a los controles sanos) mostraron un patrón de hipoactivación límbica; un hallazgo sorprendente si se tiene en cuenta que se trata de la expresión facial que generalmente mayor temor genera en sujetos con TAS; pero que como se discute a continuación, vaya probablemente ligado al patrón de activación en el giro fusiforme. Al igual que en el grupo de participantes con SW, los resultados del estudio reflejaron hallazgos interesantes en regiones visuales para este grupo. Así, en comparación con sujetos controles sanos, los participantes con TAS mostraron una hipoactivación en el giro fusiforme a nivel bilateral. Este resultado está en coherencia con un estudio previo que encontró una hipoactivación de esta región frente a la exposición a caras (Gentili et al., 2008), pero contradice sin embargo, a dos estudios previos que encontraron una hiperactividad en esta región (Frick, Howner, Fischer, Kristiansson, & Furmark, 2013; Straube et al., 2004, 2005). En uno de estos estudios, (Frick et al., 2013), los autores encontraron que en comparación a sujetos controles, los casos con TAS mostraron una

mayor reactividad en el giro fusiforme bilateral en respuesta a expresiones de temor y una mayor conectividad funcional entre el fusiforme y la amígdala derecha. Aunque a priori podría parecer que nuestros resultados contradicen los hallazgos de Frick y colaboradores (Frick et al., 2013) es importante destacar que en nuestro estudio, la disminución en la activación fusiforme coexistió con hipoactivación amigdalar en respuesta a caras que expresaban enfado. Curiosamente, un estudio realizado en una muestra no-clínica de sujetos con ansiedad social (Pujol et al., 2009), encontró un efecto modulador del giro fusiforme en la activación de la amígdala en respuesta a caras emocionales. En el citado estudio, las puntuaciones de ansiedad social se asociaron a la activación de la amígdala sólo después de controlar por el nivel activación en el giro fusiforme (Pujol et al., 2009). La hipoactivación del giro fusiforme ha sido también un hallazgo encontrado por numerosos estudios en sujetos con Trastornos del Espectro Autista (TEA) (Dalton et al., 2005); y en sujetos con Síndrome X-Frágil (Garrett et al., 2004), dos trastornos que muestran algunos correlatos clínicos similares al TAS, incluyendo la evitación de la mirada. En el contexto del TEA y el Síndrome X-Frágil, se ha propuesto que la hipoactivación del giro fusiforme se relaciona con la evitación de la mirada (Dalton et al., 2005; Garrett et al., 2004), y que variaciones en la fijación de la mirada modulan la activación de la amígdala (Dalton et al., 2005). En conjunto, nuestros resultados sugieren que la hipoactivación fusiforme podría reflejar la evitación o diminución en la fijación de la mirada hacia las caras por parte de los casos con TAS. Ello explicaría las inconsistencias entre estudios previos (Frick et al., 2013; Gentili et al., 2008; Straube et al., 2004, 2005), y dentro del mismo estudio en función del tipo de tarea utilizado (Straube et al., 2004), que podría variar en función de la utilización de estrategias de evitación y el tipo de paradigma adoptado. Futuros estudios que incorporen métodos de monitorización ocular son necesarios para confirmar esta hipótesis. El patrón de hipoactividad fusiforme y la disminución en la activación amígdalar observada en los participantes con TAS frente a controles sanos en respuesta a caras de enfado, encajaría con hallazgos previos que sugieren un efecto modulador del giro fusiforme en la activación de la amígdala en respuesta a las caras emocionales, en particular, a aquellas que expresan amenaza (Pujol et al., 2009).

De gran interés es la correlación observada entre la activación entre el giro fusiforme y la dimensión del TCI-NS (Figura 4); una dimensión que como hemos comentado anteriormente, se relaciona con la exploración y la búsqueda de novedad. La comparación entre sujetos con TAS y SW reveló un patrón claramente opuesto.

Figura 4. Correlación entre las dimension del temperament Novelity Seeking y la activación en el giro fusiforme durante el procesamiento emocional a través de la expresión facial (*all faces vs. shapes)*



En el caso del TAS, la dimensión NS se asoció positivamente a la activación en el giro fusiforme, de manera que aquellos sujetos con bajas puntuaciones en la dimensión NS (aquellos sujetos más evitativos y que menos exploran, y la mayoría de casos con TAS) mostraron menor activación fusiforme; un hallazgo que encajaría bien con el patrón de hipoactivación observado en nuestro estudio RMf en el grupo TAS y con el perfil inhibido-evitativo característico de sujetos con el trastorno. Estos resultados están en coherencia con un estudio previo que encontró una correlación negativa entre la activación fusiforme y dos dimensiones que miden aspectos de evitación conductual (Pujol et al., 2009). Sin embargo, el análisis de correlaciones reveló que a medida que aumentaba la puntuación en esta dimensión (es decir, en aquellos sujetos menos inhibidos y con más tendencia a explorar) aumentaba la activación fusiforme. Este es un hallazgo interesante en el contexto de nuestro trabajo. Por un lado, estos resultados replican y extienden los resultados obtenidos en el estudio de personalidad (Estudio 2) que sugieren la existencia de un perfil de ansiosos

con tendencia a explorar y a ser más impulsivos. En el tercer estudio (Estudio 3b) nuevamente observamos que un subgrupo de sujetos presentó puntuaciones elevadas en dimensión *NS*; y demostramos que mayores puntuaciones en la dimensión *NS* asociadas a este perfil se asocian a mayor activación fusiforme; en otras palabras, aquellos sujetos menos evitativos y con más tendencia a explorar presentan mayor activación en el giro fusiforme. Esto sugeriría que los perfiles propuestos en el Estudio de Personalidad (Estudio 2) no solo se diferenciarían por la tendencia exploratoria y en el fenotipo clínico sino también por la respuesta neural durante el procesamiento emocional.

En el caso del SW, el patrón de correlación observado fue claramente el opuesto: la dimensión *NS* se asoció negativamente a la activación en el giro fusiforme. Aquellos sujetos con puntuaciones bajas en la dimensión *NS* mostraron una mayor activación fusiforme; y aumentos en las puntuaciones del *NS* se correlacionaron con una activación fusiforme a la baja. La interpretación de estos resultados parece menos clara que en el TAS y resulta en parte contraintuitiva, ya que el fenotipo de hipersociablidad y de acercamiento a extraños típica del SW a priori parecería encajar mejor con el patrón opuesto. Nótese sin embargo, que la exploración típica del SW se limita en gran parte al aspecto social, y que la dimensión NS evalúa aspectos más amplios. De hecho, una gran parte de sujetos en este grupo obtuvo puntuaciones bajas en esta dimensión. En conjunto, lo que sí parece claro que la dimensión *NS* y la activación fusiforme presentan un comportamiento diferente en cada trastorno.

Por último, los resultados de la comparación entre el TAS y el SW reflejaron diferencias significativas en la activación en el giro temporal superior derecho (mayor activación para el SW, menor activación para el TAS); un hallazgo interesante dada la evidencia disponible que demuestra la implicación de esta región en el procesamiento de la mirada (Itier & Batty, 2009; Zilbovicius et al., 2006) , tales que lesiones derechas en esta región producen importantes dificultados en el contacto visual (Akiyama et al., 2006). Este hallazgo encajaría bien con el patrón de atracción y fijación en la mirada característico de los sujetos con SW y con el patrón de evitación de la mirada típico del TAS y refleja un sustrato neural común a ambos trastornos.

Limitaciones

El proyecto cuenta por supuesto, con varias limitaciones que deben enumerarse. En el estudio de los AVEs (Estudio 1) no se tuvo en cuenta el impacto de la severidad, la persistencia y el impacto subjetivo de los AVEs, un factor que podría haber afectado a los resultados. La presencia de AVEs se evaluó de forma retrospectiva mediante preguntas cerradas y podría estar afectada por sesgos en el recuerdo. Sin embargo, la evidencia sugiere que en sujetos que sufrieron maltrato en la infancia es más habitual el informe *a-la-baja* de estos hechos (Hardt et al., 2004). El diseño del estudio no permite hacer inferencias sobre la causalidad. En cuanto al estudio de la Personalidad (Estudio 2) es importante destacar, que a pesar de la fuerte asociación observada entre la personalidad y el TAS, el diseño del estudio no permite realizar conclusiones sobre la dirección de esta asociación y el posible solapamiento entre los síntomas del TAS y los síntomas asociados a los rasgos de personalidad. Por otra parte, el estudio se centra en las dimensiones *HA* y *NS* y no tiene en cuenta el posible impacto del resto de dimensiones del temperamento y el carácter. La inclusión de muestras de estudiantes universitarios limita la generalización de resultados a otras poblaciones. El estudio de neuroimagen funcional comparativo entre el TAS y el SW (Estudio 3b) las conclusiones referentes al grupo con SW están limitadas y podrían atribuirse a las diferencias en las capacidades cognitivas existentes entre los sujetos con SW y los sujetos controles sanos y con TAS, aunque la especificidad de los hallazgos encontrados apunta a que las diferencias no se deben a unas capacidades cognitivas comprometidas. Por otra parte, estudios previos en en el que se comparó a muestras de sujetos con SW con un nivel cognitivo similar al de nuestros participantes, con sujetos controles con capacidades cognitivas en el rango de la normalidad (Haas et al. 2009; Mimura 2010) también encontraron alteraciones en la activación cerebral frente a caras emocionales. Los cuestionarios administrados a la muestra de SW no están validados para esta población. El paradigma de caras utilizado en nuestro estudio no permite discriminar adecuadamente el efecto entre diferentes expresiones emocionales, dado que la tarea se basa en un diseño de presentación en el que caras con diferentes emociones (una cara objetivo; dos caras de sondeo) aparecen simultáneamente en cada presentación. Del mismo modo, no controlamos el efecto de

caras neutrales, que se ha relacionado con un patrón de activación anormal en sujetos con TAS (Cooney, Atlas, Joormann, Eugène, & Gotlib, 2006; Straube et al., 2005) y SW (Paul et al., 2009).

Líneas de investigación futuras

El estudio de los AVEs y la violencia familiar en sujetos con un diagnóstico de TAS confirmarían el posible rol de esta forma de estresor en sujetos con un diagnóstico clínico de TAS; un estudio que actualmente se está llevando a cabo por parte del equipo investigador. La ampliación del estudio de la heterogeneidad en el TAS y la existencia de un perfil con tendencia a explorar y mostrar conductas del espectro impulsivo parece oportuna. Algunos de los resultados observados a lo largo de este trabajo apuntarían a que este subgrupo de sujetos podría tener unos correlatos diferenciados desde un punto de vista biológico. Las investigaciones en este campo contribuirían a delimitar las diferencias entre ambos fenotipos. En cuanto al estudio del TAS y el SW, el estudio de la conectividad cerebral entre regiones visuales (en particular de la región OFA y el giro fusiforme) con áreas límbicas como la amígdala permitiría confirmar algunas de las hipótesis propuestas en este trabajo y contribuir a extender a nuestro conocimiento de las bases neurales del TAS y el SW. La inclusión de métodos de registro de movimientos oculares y medidas fisiológicas (ej. Frecuencia cardíaca) permitiría confirmar algunas de las hipótesis planteadas durante el trabajo y obtener una medida objetiva de la respuesta de ansiedad frente a las caras.

Consideraciones finales

En un mundo eminentemente social en el que las habilidades y las competencias sociales representan un valor cultural fundamental y en el que la interacción social en sí representa un aspecto humano básico, la presencia de ansiedad social en su forma más extrema lleva implícita, la afectación e interferencia de algunas áreas fundamentales en la vida de un individuo. La importante pregunta de *por qué* esta forma de ansiedad evoluciona de un estado adaptativo a una forma de patología,

es a fecha de hoy una pregunta sin resolver. Como en la mayoría de trastornos psiquiátricos, la respuesta parece recaer en la interacción compleja de factores biológicos, psicológicos y ambientales. Mediante el presente trabajo hemos contribuido a profundizar en algunas piezas clave que podrían contribuir al origen y mantenimiento del TAS, con algunas aportaciones novedosas y relevantes en el contexto de la literatura vigente. Estas aportaciones no se han limitado a la literatura del TAS sino que se extiende al campo uno de los trastornos de mayor importancia en el campo de las neurociencias en la actualidad: el SW. Quedan aún muchas preguntas sin resolver y a pesar de su elevada prevalencia, el TAS ha sido -y continúa siendo- uno de los trastornos de ansiedad menos estudiados. Esperamos que los años puedan revertir esta situación. Lo que si parece cierto es que el TAS se enfrenta a tiempo de cambios. La forma y los medios mediante los cuales nos relacionamos socialmente han experimentado y continúan experimentando una profunda transformación. Con la galopante llegada de las nuevas tecnologías, muchas de nuestras interacciones han pasado del tradicional *cara-a-cara* a ser eminentemente virtuales; y aquellas descripciones que Marks y Geler realizarían en los años 70 en el que la ansiedad social tomaba forma de temor a ruborizarse, a ir a bailes y fiestas, comer y beber, o hablar delante de otras personas (Marks, 1970) podrían tomar una forma completamente diferente dentro de 20 años. En cualquier caso y tal como postulan Stanley & Adolphs (Stanley & Adolphs, 2013), con la emergencia de nuevos y complejos campos de investigación y a través de la colaboración entre científicos de diferentes campos, los próximos 25 años serán determinantes y nos ofrecerán la oportunidad de mejorar nuestro entendimiento sobre la naturaleza de algunas de las capacidades humanas fundamentales y de los trastornos psiquiátricos en general. Unos años que probablemente conllevaran importantes avances en el campo de la investigación psiquiátrica, psicológica y de las neurociencias, y que contribuirán también a mejorar nuestro entendimiento sobre la naturaleza del TAS.

Conclusiones

7. Conclusiones

Se detallan a continuación, las conclusiones en relación a los objetivos planteados al inicio de trabajo:

Objetivo 1: *Estudiar la asociación entre cinco AVEs experimentado en la infancia y/o adolescencia y la ansiedad social en la edad adulta en una muestra epidemiológica de adultos jóvenes universitarios.*

Los resultados del primer estudio permiten concluir que:

- La violencia familiar sufrida antes de los 18 años se asocia a la presencia de ansiedad social en adultos jóvenes universitarios.
- Un alto porcentaje de estudiantes universitarios presenta síntomas de ansiedad social.
- La población y el contexto universitario pueden ser particularmente adecuados para realizar la detección y tratamiento precoz del TAS y facilitar el acceso al tratamiento.

Objetivo 2: *Estudiar la personalidad y la heterogeneidad en base a las dimensiones del temperamento del TCI "Evitación del Daño" y "Búsqueda de novedad" en sujetos con un diagnóstico clínico de TAS y sujetos controles sanos.*

- Existe heterogeneidad en el TAS y no todos los sujetos con el trastorno presentan un perfil de personalidad prototípico caracterizado por la inhibición y la evitación. Al menos un subgrupo de sujetos muestra alta búsqueda de novedad y conductas del espectro impulsivo/de riesgo.
- Los perfiles basados en las dimensiones del temperamento *HA* y *NS* (HAns y HANS) discriminan adecuadamente estos perfiles.

- Los perfiles HAns y HANS muestran correlatos clínicos específicos, podrían tener un *background* genético diferente, y asociarse a una respuesta neural diferenciada.

Objetivo 3: *Profundizar en las bases neurales del TAS mediante una perspectiva comparativa con el SW.*

Los resultados de la revisión sistematizada de la literatura vigente y la comparación directa de sujetos con TAS y sujetos con SW en un estudio de resonancia magnética funcional (RMf) mientras realizaban la tarea de procesamiento emocional a través de la expresión facial de Hariri nos permiten concluir que:

- La revisión de los estudios de RMf examinando el procesamiento emocional a través de la expresión facial disponibles hasta la fecha reflejan que el hallazgo más consistente y replicado ha sido la hiperactivación de la amígdala en sujetos con TAS, y la hipoactivación de esta región en sujetos con SW frente a expresiones faciales de temor.

- La comparación directa de sujetos con TAS y SW mientras realizaban la tarea de Hariri (estudio de RMf) no reprodujo estos resultados. No se encontraron diferencias significativas en la actividad cerebral entre grupos a nivel límbico.

- Durante la realización de dicha tarea, los sujetos con TAS y SW se diferenciaron por la activación cerebral en el giro temporal superior derecho, una región involucrada en el procesamiento de la mirada.

- Los resultados de estudio de RMf pusieron de relieve la relevancia de regiones visuales involucradas en el procesamiento de la cara y de regiones corticales prefrontales importantes para regular la respuesta de miedo.

- Para el grupo con SW, los resultados del estudio demostraron un correlato neural específico de hipoactivación en la región posterior del área visual primaria y ausencia de activación de la región *OFA* durante la realización del paradigma de procesamiento emocional a través de la Hariri. Esto sugeriría que

a pesar de que los sujetos con SW son capaces de discriminar rostros, parte del proceso está alterado.

- Las alteraciones observadas en el grupo de participantes con SW sugieren que los sujetos con SW podrían no percibir o procesar adecuadamente información del rostro necesaria para discriminar adecuadamente la expresión facial y detectar señales de amenaza.

- La existencia de *inputs* deficientes desde regiones visuales involucradas en el procesamiento del rostro podrían contribuir a explicar la ausencia de respuesta en la amígdala frente a expresiones de temor observada en nuestro estudio y contribuirían a explicar el fenotipo social de escaso temor-social típico de estos sujetos.

- Para el TAS, los resultados del estudio demostraron un correlato neural específico de hipoactivación en regiones corticales prefrontales importantes para regular la respuesta de ansiedad. Este resultado apoya las propuestas actuales que postulan que un déficit en los mecanismos cognitivos implicados en la regulación de la ansiedad -y no la hiperactividad límbica- serían el déficit principal del trastorno.

- La hipoactivación en el giro fusiforme observada en los casos con TAS podría reflejar el uso de estrategias evitativas y la evitación de la mirada típica del trastorno durante la realización de la tarea. Esto explicaría las inconsistencias existentes entre estudios previos, y el patrón de hipoactivación de la amígdala observado en estos sujetos frente a caras de enfado en nuestro estudio; un patrón que sugeriría también un efecto modulador desde el giro fusiforme a regiones límbicas.

- En conjunto, estos resultados sugieren un modelo complejo en el que alteraciones *en,* y *entre* regiones visuales, límbicas y prefrontales podrían contribuir a explicar las alteraciones en el procesamiento emocional observadas en el TAS y el SW, y el fenotipo social característico de cada trastorno.

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